

Single Technology Appraisal

Efgartigimod for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Efgartigimod for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Contents:

The following documents are made available to stakeholders:

[Access the **final scope** and **final stakeholder list** on the NICE website.](#)

1. **Company submission** from Argenx BV
2. **Company summary of information for patients (SIP)** from Argenx BV
3. **Clarification questions and company responses**
 - a. Clarification follow-up
4. **Patient group, professional group and NHS organisation submissions** from:
 - a. Inflammatory Neuropathies UK
 - b. Association of British Neurologists
5. **Expert personal perspectives** from:
 - a. Dr Aisling Carr, Consultant Neurologist – clinical expert, nominated by Argenx BV
 - b. Dr Chinar Osman, Consultant Neurologist – clinical expert, nominated by Association of British Neurologists
 - c. Ms Nadia Mulliner – patient expert, nominated by Inflammatory Neuropathies UK
 - d. Mr Richard Gedge – patient expert, nominated by Inflammatory Neuropathies UK
6. **External Assessment Report** prepared by BMJ Technology Assessment Group
7. **External Assessment Report – factual accuracy check**
8. **Managed access committee briefing**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Company evidence submission

October 2025

File name	Version	Contains confidential information	Date
ID6409_efgartigimod CIDP_dossier_redacted	V1	No	17 October 2025

Company evidence submission template for efgartigimod with recombinant human
hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Contents

LIST OF FIGURES	4
LIST OF TABLES.....	4
ABBREVIATIONS	7
1. DECISION PROBLEM, DESCRIPTION OF THE TECHNOLOGY AND CLINICAL CARE PATHWAY	10
1.1. Decision problem	11
1.2. Description of the technology being evaluated	17
1.3. Health condition and position of the technology in the treatment pathway.....	18
1.3.1. Disease overview	18
1.3.2. Pathophysiology	19
1.3.3. Classification and diagnosis	19
1.3.4. Epidemiology	22
1.3.5. Clinical burden.....	23
1.3.6. Humanistic burden	25
1.3.7. Caregiver burden.....	29
1.3.8. Economic burden	30
1.3.9. Current treatment	31
1.4 Equality considerations	43
2. CLINICAL EFFECTIVENESS.....	44
2.1 Identification and selection of relevant studies	45
2.2 List of clinical effectiveness evidence	45
2.3 Summary of methodology of the relevant clinical effectiveness evidence	47
2.3.1. ADHERE	50
2.3.1 ADHERE+	55
2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence	55
2.4.1 ADHERE	58
2.4.2 ADHERE+	59
2.5. Critical appraisal of the relevant clinical effectiveness evidence	59
2.6. Clinical effectiveness results of the relevant studies.....	59
2.6.1. ADHERE	59
2.6.2 ADHERE+	72
2.7 Subsequent treatments used in the relevant studies	74
2.8 Subpopulation analysis	74
2.9 Meta-analysis	76
2.10 Indirect and mixed treatment comparisons	77
2.10.1 Background and objectives	77
2.10.2 SLR to inform the ITC	77
2.10.3 ITC feasibility assessment	77
2.10.4 ITC Results.....	81
2.10.5 Strengths and limitations	81
2.10.6 ITC conclusions	81
2.11 Adverse reactions	82
2.11.1 ADHERE	82
2.11.3 ADHERE+	85
2.12 Ongoing studies	86
2.13 Interpretation of clinical effectiveness and safety evidence	87
3. COST-EFFECTIVENESS	90
3.1. Published cost-effectiveness studies	92
3.2 Economic analysis	92
3.2.1 Patient population.....	93
3.2.2 Treatment pathways.....	94
3.2.3 Model health states	97
3.2.4 Model structure.....	101
3.2.5 Features of the economic analysis.....	104

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

3.2.6	Intervention technology and comparators	105
3.3	Clinical parameters and variables	105
3.3.1	Response rate	105
3.3.2	Probability to enter remission and relapse	106
3.3.3	Transition probabilities	107
3.4	Measurement and valuation of health effects	122
3.4.1	Health-related quality-of-life data from clinical trials	122
3.4.2	Mapping	122
3.4.3	Health-related quality-of-life studies	122
3.4.4	Health-related quality-of-life data used in the cost-effectiveness analysis	123
3.4.5	Adverse events	124
3.4.6	Adverse event utility decrements	127
3.4.7	Disutilities associated with complications related to intravenous access	128
3.4.8	Disutilities associated with drug administration	129
3.4.9	Caregiver disutilities	130
3.5	Cost and healthcare resource use identification, measurement and valuation	130
3.5.1	Intervention and comparators' costs and resource use	130
3.5.2	Health-state unit costs and resource use	137
3.5.3	Adverse reaction unit costs and resource use	139
3.5.4	Miscellaneous unit costs and resource use	141
3.6	Severity	141
3.7	Uncertainty	141
3.8	Managed access proposal	141
3.9	Summary of base case analysis inputs and assumptions	142
3.9.1	Summary of base case analysis inputs	142
3.9.2	Assumptions	142
3.10	Base case results	147
3.10.1	Base case incremental cost-effectiveness analysis results	147
3.11	Exploring uncertainty	148
3.11.1	Probabilistic sensitivity analysis	148
3.11.2	Deterministic sensitivity analysis	149
3.11.3	Scenario analysis	151
3.12	Subpopulation analysis	156
3.12.1	Subpopulation 1 – patients on Ig maintenance	156
3.12.2	Subpopulation 2 – Ig dependent patients	156
3.12.3	Subpopulation 3 – patients dependent on ultra-high dose of Ig	157
3.13	Benefits not captured in the QALY calculation	157
3.14	Validation	158
3.14.1	Validation of cost-effectiveness analysis	158
3.15	Interpretation and conclusions of economic evidence	158
4.	REFERENCES	160

List of figures

Figure 1: Most bothersome CIDP symptoms at the time of starting medication	28
Figure 2: Current UK treatment pathway (without efgartigimod)	33
Figure 3: Current UK treatment pathway (including efgartigimod)	42
Figure 4: ADHERE and ADHERE+ – study design	54
Figure 5: ADHERE Stage A – Kaplan–Meier plot of the time to initial confirmed ECI in participants treated with open-label efgartigimod (Stage A safety analysis set)	63
Figure 6: ADHERE Stage B – Kaplan–Meier analysis of the relative risk of CIDP relapse based on time to first aINCAT deterioration in participants treated with efgartigimod or placebo (mITT analysis set)	66
Figure 7: ADHERE Stage B – Kaplan–Meier plot of the time to clinical deterioration, sensitivity analysis (per protocol analysis set)	67
Figure 8: ADHERE Stage B – Kaplan–Meier analysis of time to I-RODS deterioration in participants treated with efgartigimod or placebo (mITT analysis set)	68
Figure 9: ADHERE – longitudinal mean aINCAT scores of Stage A responders from run-in baseline to last assessment in Stage B (post-hoc analysis; run-in and mITT analysis sets)	70
Figure 10: ADHERE+ substudy – Kaplan–Meier analysis of time to clinical deterioration during q2w dosing regimen (efficacy analysis set)	73
Figure 11: ADHERE+ substudy – Kaplan–Meier time to restabilisation on q1w after clinical deterioration during q2w dosing	74
Figure 12: ADHERE Stage A – Forest plot of a post-hoc analysis of confirmed ECI responders (primary endpoint) by subpopulation of participants treated with open-label efgartigimod	75
Figure 13: ADHERE Stage B – Forest plot of the time to first occurrence of clinical deterioration, overall and by stratification factors (mITT analysis set)	76
Figure 14: Treatment pathway in the intervention arm, proportion of cohort on treatment with Ig before simulation start	95
Figure 15: Treatment pathway in the intervention arm, proportion of Ig intolerant and Ig refractory cohort	96
Figure 16: Treatment pathway in the comparator arm, proportion of cohort on treatment with Ig maintenance before simulation start	96
Figure 17: Health state EQ-5D values	100
Figure 18: Model structure	102
Figure 19: Time on Treatment on efgartigimod maintenance	120
Figure 20: Distribution of results of PSA simulations in the cost-effectiveness plane	149
Figure 21: Cost-effectiveness acceptability curve	149
Figure 22: Results of the OWSA	151

List of tables

Table 1: The decision problem.....	12
Table 2: Technology being evaluated	17
Table 3: UK HTA recommendations and national commissioning policies	31
Table 4: Comparison of current treatment options for CIDP.....	36
Table 5: Clinical effectiveness evidence	45
Table 6: Summary of study methodology	47
Table 7: ADHERE – Summary of statistical analyses	55
Table 8: ADHERE – Analysis sets	58
Table 9: ADHERE – Baseline characteristics (safety population)	60
Table 10: ADHERE Stage A – confirmed ECI responders (primary endpoint) by prior CIDP therapy (Stage A safety analysis set).....	61

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 11: ADHERE Stage A – confirmed ECI responders (primary endpoint) by prior CIDP therapy in a sensitivity analysis (Stage A safety analysis set excluding participants ongoing in Stage A at the 88th relapse event in Stage B).....	62
Table 12: ADHERE Stage A – change from Stage A baseline in aINCAT score, I-RODS score, MGS score, MRC sum score, TUG test score and EQ-5D-5L VAS at Stage A last assessment (Stage A safety analysis set).....	63
Table 13: ADHERE Stage A – change from Stage A baseline in aINCAT score, I-RODS score and MGS score at Stage A last assessment (Stage A safety analysis set, post-hoc analysis)	64
Table 14: ADHERE Stage A – change from Stage A baseline in exploratory endpoints in participants treated with open-label efgartigimod (Stage A safety analysis set).....	65
Table 15: ADHERE Stage B – summary of secondary endpoint results of participants treated with efgartigimod or placebo.....	68
Table 16: ADHERE Stage B – summary of exploratory endpoint results in participants treated with efgartigimod or placebo.....	70
Table 17: Baseline characteristics in ADHERE and ADHERE+	72
Table 18: Overview of treatments, design and population in studies identified as eligible for inclusion in the ITC feasibility assessment following completion of the study selection process and endpoint heterogeneity assessment	79
Table 19: MAIC results for change in aINCAT from baseline for efgartigimod compared with HyQvia at the last assessment up to 32 Weeks ^a	81
Table 20: ADHERE Overview of AEs (Stage A)	82
Table 21: Most common TEAEs in Stage A (reported in ≥5 participants) (secondary analysis; safety population).....	83
Table 22: ADHERE Overview of AEs (Stage B)	84
Table 23: Most common TEAEs in Stage B (reported in ≥3 participants in either arm) (secondary analysis; safety population).....	84
Table 24: Safety and tolerability outcomes in ADHERE and ADHERE+ (safety population).....	86
Table 25: Baseline model cohort characteristics	94
Table 26: Distribution across treatments after efgartigimod discontinuation	94
Table 27: Distribution across treatments after Ig discontinuation	95
Table 28: Cohort distribution across Ig products	97
Table 29: Functional impairment associated with each level of the aINCAT disability score ⁵⁶	99
Table 30: Definitions of model health states	100
Table 31: Utility associated with each health state	101
Table 32: Distribution of the cohort at baseline (intervention and comparator arms).....	103
Table 33: Distribution of the cohort at baseline (Ig-refractory).....	103
Table 34: Distribution of the cohort after response to efgartigimod	103
Table 35: Features of economic analysis	104
Table 36: Inputs to inform cycle probability of entering remission and returning to active disease....	107
Table 37: Efgartigimod maintenance, cycle 1	109
Table 38: Efgartigimod maintenance, cycle 2	109
Table 39: Efgartigimod maintenance, cycle 3.....	110
Table 40: Efgartigimod maintenance, cycle 4	110
Table 41: Efgartigimod maintenance, cycle 5 onwards	111
Table 42: Cohort distribution at cycle 4 in the Comparator arm (active disease only)	113
Table 43: Intervention arm, first cycle after efgartigimod discontinuation.....	113
Table 44: Ig maintenance, cycle 1	116
Table 45: Ig maintenance, cycle 2	117
Table 46: Ig maintenance, cycle 3	118
Table 47: Ig maintenance, cycle 4	118
Table 48: Ig maintenance, cycle 5 onwards.....	119
Table 49: Fitting of the parametric curves on the Time on Treatment data from pooled ADHERE and ADHERE+	120
Table 50: Unplanned discontinuation of Ig maintenance	121
Table 51: Risk of hospitalisation without ICU admission	122
Table 52: Risk of hospitalisation with ICU admission	122
Table 53: Utility by health state	123

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 54: Incidence of AEs per cycle for efgartigimod arm (affecting at least 5% of patients in the full safety population).....	124
Table 55: HR for AEs at different IVIg doses	124
Table 56: Per-cycle probability of AE in Ig maintenance	125
Table 57: Per-cycle probability of AE in PLEX maintenance	125
Table 58: Per-cycle probability of AE with corticosteroids	126
Table 59: Per-cycle probability of AE with immunosuppressants	126
Table 60: Complications related to intravenous access	126
Table 61: Duration of AEs	127
Table 62: AE disutilities.....	128
Table 63: Disutilities related to intravenous access.....	129
Table 64: Per-cycle disutilities associated with IVIg administration.....	129
Table 65: Caregiver disutility per cycle	130
Table 66: Efgartigimod drug acquisition cost during induction	131
Table 67: Inputs used to inform the drug administration costs for efgartigimod	131
Table 68: Proportion of cohort eligible for q2w efgartigimod maintenance.....	132
Table 69: Costs per cycle for efgartigimod maintenance.....	132
Table 70: Distribution of the cohort across different Ig maintenance doses.....	133
Table 71: Average time between IVIg treatment cycles	133
Table 72: Drug acquisition costs.....	134
Table 73: Inputs used to inform the drug administration costs for Ig	135
Table 74: Drug administration costs per-cycle.....	136
Table 75: Disease monitoring - healthcare resource use per model cycle.....	137
Table 76: Disease monitoring - unit cost per healthcare professional.....	138
Table 77: Professional caregiving - consumption and cost	138
Table 78: Mobility aids	138
Table 79: Length of hospitalisation event	139
Table 80: Cost per day of hospitalisation event.....	139
Table 81: Costs associated with AEs.....	140
Table 82: Costs of complications related to intravenous access	140
Table 83: Assumptions.....	142
Table 84: Base-case results at PAS price	147
Table 85: Net health benefit at PAS price.....	147
Table 86: Base case probabilistic incremental cost-effectiveness results	148
Table 87: Percentage change in ICER in base case results following lower and upper variation in parameters	150
Table 88: Alternative inputs for distribution of Ig cohort across different posology's.....	153
Table 89: Alternative inputs for average dose per Ig-treatment cycle	153
Table 90: Alternative inputs for average time between Ig-treatment cycles	153
Table 91: Alternative distributions across treatments post-Ig discontinuation	154
Table 92: Alternative distributions across treatments post-efgartigimod discontinuation	154
Table 93: Results of the scenario analyses	155
Table 94: Subpopulation 1 - Results.....	156
Table 95: Subpopulation 2 - Results.....	157
Table 96: Subpopulation 3 – Results	157

Abbreviations

40-MWT	40-metre walk test
6-SST	6-spot step test
A&E	Accident and emergency
ADL	Activity of daily living
AE	Adverse event
AIC	Aikake information criterion
aINCAT	Adjusted Inflammatory Neuropathy Cause and Treatment score
BPI-SF	Brief Pain Inventory – Short Form
BIC	Bayesian information criterion
BNF	British National Formulary
CDAS	CIDP Disease Activity Status
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
CVC	Central venous catheter
DSA	Deterministic sensitivity analysis
EAN/PNS	European Academy of Neurology/Peripheral Nerve Society
ECI	Evidence of clinical improvement
ECMD	Evidence of clinically meaningful deterioration
EFNS/PNS	European Federation of Neurological Societies/Peripheral Nerve Society
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimension
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EQ-5D-5L-VAS	EuroQol 5-Dimension 5-Level Visual Analogue Scale
ESS	Effective sample size
FcRn	Neonatal Fc receptor
GBP	Great British Pounds
GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare professional
HCRU	Healthcare resource utilisation
HR	Hazard ratio
HRG	Healthcare Resource Groups
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
Ig	Immunoglobulin
IgG	Immunoglobulin G
INCAT	Inflammatory Neuropathy Cause and Treatment
INUK	Inflammatory Neuropathies UK

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

I-RODS	Inflammatory Rasch-built Overall Disability Scale
ISR	Injection site reaction
ITC	Indirect treatment comparison
IV	Intravenous
IVIg	Intravenous immunoglobulin
KM	Kaplan-Meier
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MGS	Mean grip strength
mITT	Modified intent to treat
MRC	Medical Research Council
MS	Multiple sclerosis
NC	Not calculated
NHB	Net health benefit
NHS	National Health Service
NHSPS	National Health Service Payment Scheme
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
PAS	Patient Access Scheme
PFS	Pre-filled syringe
PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity
PICC	Peripherally inserted central catheter
PLEX	Plasma exchange
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
q1w	Every week
q2w	Every two weeks
QALY	Quality-adjusted life year
rHuPH20	Recombinant human hyaluronidase PH20
RT-FSS	Rasch-transformed Fatigue Severity Scale
SAE	Serious adverse event
SC	Subcutaneous
SCIg	Subcutaneous immunoglobulin
SD	Standard deviation
SE	Standard error
SEE	Structured expert elicitation
SF-36	36-Item Short Form Health Survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TLR	Targeted literature review

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

TP	Transition probabilities
TSQM-9	9-item Treatment Satisfaction Questionnaire for Medication
TUG	Timed up and Go
UK	United Kingdom
US	United States
WTP	Willingness-to-pay

1. Decision problem, description of the technology and clinical care pathway

Overview

- Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare, debilitating, acquired immune-mediated neuropathy characterised by chronic inflammatory demyelination of peripheral nerve fibres and a motor-predominant peripheral neuropathy that causes muscle weakness and sensory disturbances, which result in fatigue, pain, and disability.¹⁻⁵
- Based on an estimated prevalence of six cases per 100,000 people⁶ and an England population estimate of 58.6 million (2024),⁷ a total of 3,517 people are estimated to be living with CIDP in England.
- CIDP manifests through multiple pathophysiological mechanisms, leading to a complex range of impairments that affect patients' functional capabilities and quality of life. Symptoms often accumulate over time and further constrain daily functioning, and the severity of clinical impairment can be considerable over the full disease course of CIDP. Functional dependence (e.g., assistance with personal or domestic activities) is common in clinical practice.⁸
- Resource pressures are evident across healthcare services, with persistent symptoms despite treatment, reliance on immunoglobulin (Ig) and practical limits on delivery models that can delay or constrain access to care. Switching and cessation attempts further compound demand, with about 30% of patients having multiple failed cessation attempts and around 10% of relapsing patients presenting to accident and emergency (A&E) departments, requiring substantial nurse time for reassessment, re-titration and monitoring.⁹
- Caregiver support in CIDP is common and time-intensive, and overall burden escalates as disability progresses, meaning that prolonged reliance on informal care is likely to become harder to sustain as disease courses evolve and households age, with measurable consequences for caregiver wellbeing and stability.¹⁰
- Healthcare resource use in CIDP is closely linked to treatment patterns, with Ig therapy the primary driver of direct medical costs.¹¹⁻¹⁴ Beyond direct medical costs, the economic impact on patients living with CIDP includes substantial productivity losses and personal expenditure.¹⁵
- CIDP imposes a substantial humanistic burden marked by pain, fatigue, functional dependence, and curtailed participation, and these impacts often persist despite maintenance treatment.¹⁵ The pattern underscores an unmet need for therapies that are both more effective and more convenient, with the potential to reduce patient suffering and ease pressures on healthcare services.
- In CIDP, the choice of initiation treatment and options for long-term maintenance treatment present three major challenges: inadequate response to the treatment options currently available, practical limitations of current therapies, and long-term management concerns.
- Efgartigimod is a novel treatment for patients living with CIDP, supplied as a co-formulation of efgartigimod with recombinant human hyaluronidase PH20

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

(rHuPH20) in a pre-filled syringe for subcutaneous administration that can be self-administered at home (20-30 seconds in a total volume of 5 ml).² At-home use is expected to reduce hospital visits and reduce demand for NHS infusion services.

- Efgartigimod addresses the unmet need by offering an alternative for patients with unsatisfactory treatment with Igs.¹⁶ Its self-administered subcutaneous dosing can reduce reliance on hospital-based infusions and aligns with the NHS priority to shift care closer to home.^{17,18} This is particularly pertinent given ongoing Ig supply constraints in England.¹⁹⁻²¹

Whilst some residual uncertainty is inherent given the rarity of CIDP and limitations in the available evidence base, the Company has taken structured and transparent steps to mitigate this. A number of complementary evidence-generation activities were specifically commissioned to build upon the existing clinical trial evidence, strengthen the real-world UK understanding of CIDP and to address data gaps identified during early engagement with NICE. These include clinician workshops and structured expert elicitation to validate key model assumptions, a multi-site retrospective patient chart review to characterise real-world treatment patterns, patient and caregiver cross-sectional surveys exploring burden and quality of life in collaboration with Inflammatory Neuropathies UK, and targeted nurse and clinician engagement exercises to validate service delivery assumptions. Together, these studies form a programme of commissioned evidence that enhances the robustness of the clinical and economic case. Further details of these complementary studies, including objectives, design and publication status, are presented in **Appendix K**.

1.1. Decision problem

Efgartigimod (Vyvgart®) is anticipated to be licensed as a monotherapy for the treatment of adult patients with progressive or relapsing active chronic inflammatory demyelinating polyneuropathy (CIDP) after prior treatment with corticosteroids or immunoglobulins (Igs).

The submission focuses on the part of the population expected in the marketing authorisation for efgartigimod, specifically for patients with unsatisfactory treatment with Igs (intravenous immunoglobulin [IVIg] or subcutaneous immunoglobulin [SCIg]). This proposed population is an optimised population that represents CIDP patients with the greatest disease burden and unmet need, while supporting efficient use of National Health Service (NHS) resources. The clinical relevance and suitability of this population have been confirmed and validated by UK clinical experts.^{9,16,16,17,22}

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
Population	Adults with CIDP.	Adults with CIDP after prior treatment with immunoglobulin (IVIg or SCIg).	The target population proposed by the Company is based on those who would receive treatment with efgartigimod in clinical practice and reflects an optimised population of the planned UK marketing authorisation. This definition has been validated by clinical expert opinion, ensuring it is representative of patients who would be treated in NHS practice.^{9,16,16,17,22} Given the heterogeneity of CIDP and variability in individual response to Ig, treatment decisions should be made through shared decision-making between physician and patient to ensure the most appropriate care pathway. Efgartigimod should be considered for patients with CIDP who have a confirmed diagnosis according to EAN/PNS guidelines¹ but for whom Ig treatment is unsatisfactory. Unsatisfactory Ig treatment may be defined by at least one of the following criteria: 1. High burden of Ig treatment: patients who have received at least 6 months of treatment with Igs (IVIg or SCIg for whom ongoing Ig infusions or injections significantly impact daily life, work, or caregiving responsibilities). This category includes patients who remain symptomatic or require high doses or frequency of Ig to maintain benefit and avoid peri-dose fluctuations. 2. Patients who are intolerant or refractory to Ig: patients unable to continue Ig due to adverse events, safety concerns (e.g.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID640

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
			thromboembolism and heart failure), or relevant comorbidities. Criteria 1 has been validated by two sources. Based on data obtained from a Company market research survey with nine clinicians, it was estimated that within the proportion of Ig responders, around 30% experience continued symptom burden and side effects, falling into this category of unsatisfactory treatment.¹⁷ This is further supported by an advisory board of five specialist nurses from UK neuromuscular centres, which reported that 20-40% of their current CIDP patients would fall into the "high burden" category.⁹ Criteria 2 has been validated by clinicians through structured expert elicitation and through an Ig chart review.^{16,23} This demonstrates that around 5% of CIDP patients would fall into this category.^{16,23} This population is represented in the Company cost-effectiveness model as three subpopulation patients who receive stable Ig maintenance dose, patients who are intolerant to Ig, patients who are refractory to Ig.
Intervention	Efgartigimod with recombinant human hyaluronidase PH20.	Efgartigimod with recombinant human hyaluronidase PH20.	Not applicable.
Comparator(s)	Established clinical management without efgartigimod with recombinant human hyaluronidase PH20, including but not limited to: corticosteroids Igs (IVIg or SCIg)	Established clinical management without efgartigimod with recombinant human hyaluronidase PH20, including but not limited to: corticosteroids Igs (IVIg or SCIg)	Based on the target population, the Company considers Ig (IVIg or SCIg) to be the primary comparator, which has been validated by five neurologists who currently manage CIDP patients across different geographical regions in England to ensure representation of NHS clinical practice. ¹⁶ This reflects the point in the treatment pathway where

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID640

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
	plasma exchange (PLEX) immunosuppressive therapies	plasma exchange (PLEX) immunosuppressive therapies	patients who would currently be receiving maintenance Ig therapy may be considered for treatment with efgartigimod. To reflect the broader population eligible for treatment with efgartigimod (including patients who are intolerant or refractory to Ig) and the CIDP treatment pathway, other treatment options (PLEX, corticosteroids, and immunosuppressants) are grouped into a basket of alternative treatments. PLEX remains available as a treatment option within the broader pathway, but clinical experts emphasised that it is rarely used for long-term maintenance due to its invasive nature and associated risks.^{17,24} As such, PLEX is generally reserved for patients with severe or refractory disease after other options have failed and would not typically be used before considering efgartigimod.^{17,24} Corticosteroids are commonly used as an initiation therapy, provided there are no contraindications, but are not typically maintained long-term in patients with progressive or relapsing CIDP due to risk of iatrogenic conditions, side effect profile and limited durability of effect.^{17,24}
Outcomes	Physical function change from baseline Disease progression Hospitalisations Adverse effects of treatment HRQoL	Physical function change from baseline Disease progression Hospitalisations Adverse effects of treatment HRQoL	Not applicable.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID640

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	A de-novo Markov model was developed in Microsoft Excel. The model adopts a lifetime time horizon to reflect the chronic nature of CIDP, where disease progression and symptoms may persist throughout a patient's life. A 6-month cycle length is applied, consistent with routine clinical practice in which patients are typically assessed biannually for changes in disease status. The economic analysis is appropriate and consistent with the NICE reference case.	Not applicable.
Subpopulations to be considered	No subpopulations identified.	No subpopulations identified.	No difference. However, as noted above, the Company submission focuses on patients with unsatisfactory treatment with Ig. The Company's cost-effectiveness model distinguishes between the subpopulations eligible for efgartigimod (those with high burden of Ig treatment and those intolerant or refractory to Ig), with each population linked to a specific treatment pathway. Within each population, patients transition through the model and are distributed across treatment options based on clinical expert input, with patients who are refractory or intolerant to Ig receiving only treatments included in the basket of alternative treatments. Alternative scenario analyses have been considered for these treatment pathways.
Special considerations	Guidance will only be issued in accordance with the marketing	The draft remit and scope have been reviewed against equality	Not applicable.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID640

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
including issues related to equity or equality	authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	considerations, and no aspects have been identified that could lead to unlawful discrimination or differential access for groups with protected characteristics. While it is recognised that there is a disproportionate male gender distribution in the prevalence of this condition, this reflects the natural epidemiology of the disease rather than any discriminatory aspect of the proposed scope or technology evaluation process. No additional evidence gathering is considered necessary for equality impact assessment, as the proposed scope already enables comprehensive consideration of the relevant patient populations and their characteristics.	

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; HRQoL: Health-related quality of life; Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; PLEX: Plasma exchange; SCIg: Subcutaneous immunoglobulin.

1.2. Description of the technology being evaluated

Table 2 presents a brief description of efgartigimod for the treatment of CIDP. The draft Summary of Product Characteristics (SmPC) can be found in **Appendix A**.

Table 2: Technology being evaluated

UK approved name and brand name	Generic name: Efgartigimod Brand name: Vyvgart® ▼
Mechanism of action	Efgartigimod is a coformulation of efgartigimod and rHuPH20.² The mechanism of action of efgartigimod in CIDP centres on its interaction with FcRn.²⁵ In CIDP, both T cells and B cells contribute to the disease process through an immune-mediated attack that leads to demyelination of peripheral nerves.²⁶ Efgartigimod works by targeting the FcRn system that normally protects IgG antibodies from degradation.^{25,26} Efgartigimod is a humanised IgG1 Fc fragment that has been engineered with specific modifications to increase its binding affinity for FcRn at both neutral and acidic pH levels.²⁵ When administered, it competitively binds to FcRn, preventing this receptor from carrying out its normal function of rescuing IgG antibodies from cellular degradation pathways.^{25,26} By blocking FcRn's protective recycling mechanism, efgartigimod causes a reduction in circulating IgG levels, including the pathogenic autoantibodies that contribute to nerve damage in CIDP.²⁵ Importantly, this effect is selective for IgG – efgartigimod does not significantly impact levels of other immunoglobulins, or other proteins recycled by FcRn: albumin or cholesterol.²⁵ The reduction in IgG levels is also reversible, with levels typically returning to baseline after treatment cessation.²⁵ It is co-formulated with rHuPH20, which helps to facilitate rapid subcutaneous delivery and dispersion of efgartigimod.^{27,28}
Marketing authorisation	An application for UK MHRA marketing authorisation was submitted on 15 September 2025, via the International Recognition Procedure (IRP). Anticipated date of UK MHRA marketing authorisation is February 2026. Efgartigimod was granted orphan designation from the European Medicines Agency (EMA) in January 2022 and received EMA approval on 19 June 2025.^{2,29} Efgartigimod was also granted Promising Innovative Medicine (PIM) status by the UK MHRA for CIDP on 20 November 2024.²⁹
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Efgartigimod is indicated as monotherapy for the treatment of adult patients with progressive or relapsing active CIDP after prior treatment with corticosteroids or immunoglobulins. ²
Method of administration and dosage	The recommended dose is 1,000 mg administered via a pre-filled syringe for subcutaneous administration that can

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

	be self-administered at home (20-30 seconds in a total volume of 5 ml).² The first 4 injections must be administered either by or under the supervision of a healthcare professional. Subsequent injections should be administered by a healthcare professional or may be administered at home by a patient or caregiver after adequate training in the subcutaneous injection technique. Treatment is initiated with a weekly dose regimen and may be adjusted to every 2 weeks based on clinical evaluation. In case of worsening symptoms with administration every 2 weeks, once-weekly injections should be resumed.²
Additional tests or investigations	There are no specific laboratory tests or diagnostic investigations required by the prescribing information for initiating or maintaining treatment with efgartigimod. Routine clinical monitoring, including vigilance for infection and hypersensitivity reactions, remains standard.²
List price and average cost of a course of treatment	The list price of efgartigimod is £15,307.47 (per pre-filled syringe containing 1,000 mg of efgartigimod in 5 ml [200 mg/mL]) has been submitted to the Department of Health and Social Care. The cost for a course of treatment at the anticipated list price in the first 6 months including initial induction is £183,690, with an annual cost of £735,103 in Year 1. This is followed by an annual cost of £703,466 thereafter. These calculations assume that [REDACTED] % of patients receive weekly dosing, with [REDACTED] % of patients receiving bi-weekly dosing.
Patient Access Scheme (if applicable)	A simple fixed discount PAS has been submitted to NHS England with this initial evidence submission to NICE. This is to ensure enough time for full consideration in advance of the committee meeting. This PAS discount price (£[REDACTED]) has been included in the economic analyses in this submission.

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; Fc: Fragment crystallisable; FcRn: Neonatal Fc receptor; IgG: Immunoglobulin G; IRP: International recognition procedure; MHRA: Medicines and Healthcare products Regulatory Agency; PAS: Patient Access Scheme; PFS: pre-filled syringe; rHuPH20: Recombinant human hyaluronidase PH20.

1.3. Health condition and position of the technology in the treatment pathway

1.3.1. Disease overview

CIDP is a rare, debilitating, acquired immune-mediated neuropathy that causes muscle weakness and sensory disturbances, which result in fatigue, pain, and disability.²⁻⁵ In the UK, it is estimated that up to 650 people are diagnosed with CIDP each year.³⁰

CIDP is characterised by the targeted inflammatory-mediated demyelination of nerve fibres. Nerve fibres with the most myelin (such as motor and proprioceptive fibres) are most affected, whilst nerve fibres with little or no myelin (autonomic and sensory fibres) are largely unaffected.^{31,32}

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

CIDP is clinically heterogeneous, with typical and variant phenotypes.³³ In addition to this phenotypic variation, CIDP is described by clinical course “progressive” and “relapsing–remitting”, which are descriptors of the temporal pattern of disease rather than distinct patient subpopulations requiring different treatments.³⁴ Patients with CIDP may present with either a progressing or a relapsing–remitting course³⁴ and while monophasic courses are recognised, they are less common.³⁵

Importantly, all adults with active CIDP (progressive or relapsing) are considered part of a single treatment population, irrespective of disease course. Progressive CIDP denotes gradual neurological worsening developing over at least eight weeks, whereas relapsing–remitting CIDP denotes discrete relapses of neurological worsening separated by periods of improvement or stability; both patterns represent active disease requiring treatment.³⁴ For all forms of CIDP, symptoms must persist for at least eight weeks to establish the diagnosis.³⁶ These temporal patterns can change within an individual over time, reflecting variability of CIDP’s clinical course rather than defining separate populations.³⁷

1.3.2. Pathophysiology

Evidence demonstrates that the pathophysiology of CIDP involves humoral and T -cell-mediated mechanisms, which lead to the targeted degradation of myelin in the peripheral nervous system. While CIDP is primarily characterised by demyelination, secondary axonal degeneration is a common finding. The inflammatory demyelinating process leads to nerve hypertrophy, attributed to compensatory Schwann cell proliferation and overlapping around denuded axons.³⁶ This disruption of peripheral nerve function manifests clinically as progressive weakness, sensory loss, and fatigue, which significantly impair mobility and independence for patients.

Pathogenic autoantibodies, particularly immunoglobulin G (IgG), have been implicated in CIDP pathophysiology. The observed deposition of immunoglobulins and complements on myelinated nerve fibres in CIDP patients provides evidence of humoral immunity involvement.^{38–40} Furthermore, the transfer of CIDP patient sera or IgG into animals leads to the manifestation of CIDP symptoms.^{41,42} The therapeutic role of plasma exchange (PLEX)^{43–46} and immunoadsorption⁴⁷ also suggest a role of the humoral immune system.

1.3.3. Classification and diagnosis

1.3.3.1. Classification

CIDP is characterised by chronic inflammatory demyelination of peripheral nerve fibres and a motor-predominant peripheral neuropathy that typically affects both sides of the body equally, presenting with matched weakness and sensory deficits in corresponding distal and proximal muscle groups.¹ This section summarises diagnostic classification and is not intended to describe treatment subpopulations. When classifying CIDP during diagnosis, it is defined as typical CIDP and atypical CIDP (distal, multifocal, motor, and sensory variants).¹

Typical CIDP manifests as symmetrical, proximal and distal muscle weakness of the upper and lower limbs with sensory involvement in at least two limbs and absent or reduced tendon reflexes in all limbs; some patients may present with an acute onset where symptoms progress within four weeks.³³ Reported frequencies of typical versus atypical forms vary between studies because of differing definitions.⁴⁸ 31-48% of the CIDP patient population are initially diagnosed with one of the four variants of CIDP. However, it is common for symptomatology to evolve into a more typical CIDP presentation throughout the course of the disease.⁶

1.3.3.2. Diagnosis and monitoring

In the absence of UK-specific guidance, UK practice generally follows international standards, particularly the 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guideline, which combines clinical and electrodiagnostic evidence of demyelination with supportive criteria.^{1,22} Electrodiagnostic testing is mandatory; sensitivity can be increased by assessing more than four motor nerves and including proximal stimulation in the upper limbs.¹ If electrodiagnostic criteria are not initially met, a repeat study at a later date is recommended.¹ In addition to the EAN/PNS guidelines, UK clinicians may rely on an alternative diagnostic criteria from the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS).⁴⁹ Clinicians might choose to use the EFNS/PNS criteria because it offers higher sensitivity and specificity, as well as possibly aligning better in certain clinical practice situations.⁵⁰ A tabulated summary of the EAN/PNS CIDP diagnostic guidelines is provided within **Appendix J**.

Application of these criteria is iterative and informed by clinical course; if diagnostic criteria are not met initially or the clinical picture evolves, repeat evaluation including electrodiagnostic studies should be considered.¹ At this stage, some investigations are harder to interpret: IVIg can introduce exogenous antibodies that confound antibody/paraprotein tests and may transiently elevate cerebrospinal fluid protein and white cell counts.⁵¹ Where an alternative diagnosis cannot be established by other means, nerve biopsy may be considered in selected cases, particularly when CIDP is suspected but cannot be confirmed on clinical/electrodiagnostic grounds, or when there is little or no response to treatment and alternative diagnoses are being considered.¹

The CIDP Disease Activity Status (CDAS) classification provides a clinician-assessed, longitudinal framework to categorise current disease activity and treatment status over time (scores 1–5: cure, remission, stable active disease, improving, unstable active disease).⁵² CDAS can be applied to contextualise whether changes reflect clinically meaningful shifts in overall disease activity.⁵² A tabulated summary of CDAS categories, sub-classifications, and treatment status is provided in **Appendix J**.

1.3.3.3. Differential diagnosis and diagnostic challenges

Although criteria are established, diagnosis can be challenging in real-world settings because clinical presentations are heterogeneous and overlap with CIDP mimics. The literature describe a substantial potential for misdiagnosis and delay, with consequences for

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

treatment appropriateness and timing.^{6,50,53} Mimics include haematological malignancies, amyloid and hereditary neuropathies (e.g. hereditary neuropathy with liability to pressure palsy [HNPP], Charcot-Marie-Tooth Type 1 [CMT1]), metabolic conditions (e.g., diabetic or uraemic neuropathies), toxic neuropathies (e.g., amiodarone, ethylene glycol), systemic disorders (e.g., sarcoidosis, polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes [POEMS]), and autoimmune nodopathies (e.g., multifocal motor neuropathy [MMN], anti-myelin-associated-glycoprotein [MAG], nodal/paranodal antibody-associated nodopathies).⁶ At least 15 different diagnostic criteria sets have been developed to capture the full spectrum of CIDP presentations,⁵³ and over-reliance on subjective treatment responses rather than objective metrics (e.g., grip strength, I-RODS) can perpetuate diagnostic error.^{6,54}

Consistent with these diagnostic challenges, UK real-world evidence shows that misclassification and delay are common. In a cross-sectional survey of CIDP patients conducted in collaboration with the patient group, Inflammatory Neuropathies UK (INUK), 49.2% (n=31/63) reported an initial incorrect diagnosis (most often Guillain–Barré syndrome or multiple sclerosis), and while 57.1% (n=36/63) were diagnosed within six months of symptom onset, 17.4% (n=11/63) reported delays of at least three years; these experiences place emotional burden on patients and families and risk permanent nerve damage through delayed appropriate treatment.¹⁵ To address this risk within the evidence base, efgartigimod's clinical trial programme (ADHERE) required independent diagnostic confirmation by an expert CIDP Confirmation Committee; 28% (n=179/629) of screened patients were excluded for not meeting the diagnostic inclusion criteria, illustrating the extent of real-world diagnostic complexity while ensuring that only confirmed CIDP was studied.⁵⁵ In line with this, the submission positions efgartigimod only within the confirmed CIDP population, as reflected in both this trial design and UK treatment pathway mapping that was conducted by the Company (Section 1.3.9).

1.3.3.4. Outcome and monitoring tools

CIDP outcomes assessment spans clinician-rated and patient-reported measures to capture disability, impairment, and health-related quality of life (HRQoL). In routine practice and trials, commonly used disability measures include the Inflammatory Rasch-built Overall Disability Scale (I-RODS) and the Inflammatory Neuropathy Cause and Treatment scores (INCAT/aINCAT).^{56–64} Impairment is typically evaluated with Medical Research Council (MRC) muscle strength testing and the Timed Up and Go (TUG) test for balance/fall risk.^{65,66} HRQoL is frequently captured with the EuroQol 5-Dimension 5-Level (EQ-5D-5L), including the visual analogue scale (VAS).⁶⁷ Descriptions, strengths and weaknesses of the outcome and monitoring tools of I-RODS, INCAT/aINCAT, MRC, TUG, and EQ-5D-5L-VAS are provided in **Appendix J**. A schematic of the INCAT disability scale is also provided within **Appendix J** for reference.

The 2021 EAN/PNS guideline defines an objective response as improvement on at least one disability and one impairment scale.¹ In practice, I-RODS is a patient-reported outcome covering everyday activities and correlating with grip strength,^{64,68} while INCAT/aINCAT are clinician-rated disability scales sensitive to clinically meaningful change.^{56–63} MRC provides a Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

standardised strength assessment widely used in neuromuscular evaluation,^{32,65} TUG offers a pragmatic indicator of mobility and falls risk,⁶⁶ and EQ-5D-5L-VAS complements these by reflecting overall health status and HRQoL.⁶⁷

1.3.3.4.1. Interpreting response and residual burden

Consistent with the guideline definition of response, meeting minimum thresholds on these scales does not equate to meaningful functional recovery for all patients.^{34,69} In a 2024 UK cohort of 112 patients with CIDP at University Hospitals Birmingham, persistent disability among responders was common: 62/98 responders (63.3%) had partial responses, while only 36/112 (32.1%) achieved complete functional recovery ('complete response').⁶⁹ UK clinician insights similarly revealed a concerning gap, where despite high response rates (IVIg 87.8%, SCIg 92.9%), many patients treated with Igs continue to experience symptoms: clinicians estimate approximately 30% of Ig responders experience continued symptom burden and side effects despite treatment; This is further supported by an advisory board of five specialist nurses from UK neuromuscular centres which reported that 20-40% of their current CIDP patients would fall into the "high burden" category.^{9,17} This underscores a limitation of using only scale measures to assess response and highlights the importance of interpreting scale changes alongside clinical judgement and patient-centred outcomes.

Taken together, these findings indicate that responder definitions do not fully capture the extent of treatment benefit. Even among patients meeting responder criteria, many continue to experience residual disability and persistent symptoms.^{17,69} Moreover, continued treatment with IVIg does not necessarily imply disease control and many patients remain on long-term therapy despite only partial benefit, often in the absence of effective alternatives.¹⁷ This includes those on ongoing Ig treatment regimens where treatment burden is high, with adverse impacts on daily life, work and patients' caregivers.^{10,15}

1.3.4. Epidemiology

The estimated global prevalence of CIDP ranges from one to seven cases per 100,000 adults, though this is generally considered to be an underestimate.^{70,71} A systematic review and meta-analysis published in 2019 comprising studies conducted in Europe, Japan, Australia, and the United States estimated a crude prevalence rate of CIDP of 2.81 per 100,000 person-years.⁵³ In recognition of the rarity of the condition, efgartigimod was granted orphan designation by the European Medicines Agency (EMA) in 2022 for the treatment of generalised myasthenia gravis, and orphan designation was maintained for CIDP in 2025.⁷²

Based on an estimated prevalence of six cases per 100,000 people⁶ and an England population estimate of 58.6 million (2024),⁷ a total of 3,517 people are estimated to be living with CIDP in England, and an estimated 1,817 people with CIDP would be eligible for efgartigimod in England and in Year 1. Details are provided in the **Company budget impact analysis submission**.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

CIDP is a rare disorder that can affect any age group and begin during any decade of life. CIDP affects males twice as often as females and the mean age reported for all patients is 60 years of age, though the condition can also affect children.³⁶ In the UK, it is estimated that up to 650 people are diagnosed with CIDP each year.^{30,53,70,71} CIDP is not only a rare disorder but also one that places a disproportionate burden on NHS services due to its reliance on long-term Ig therapy. The NHS Immunoglobulin Database Annual Report for 2023/24 identified approximately 1,650 patients currently receiving Ig treatment for CIDP, representing 11% of all patients on Ig therapy (n=1,650/14,877).⁷³ Although CIDP patients comprise only 11% of all patients on Ig therapy, CIDP remains the largest single indication for Ig use nationally, accounting for about 25% of total Ig consumption.⁷³ This indicates that, on average, patients with CIDP require much higher volumes of Ig compared to the overall patient cohort.⁷³ This dependence on a constrained resource underscores the system-level impact of CIDP and the importance of accurately understanding its epidemiology. It also highlights the pressing need for alternative, effective treatment options that could reduce dependence on Ig, improve patient outcomes, and alleviate significant pressure on NHS capacity. Furthermore, supply of Ig remains an ongoing risk for the NHS and is further detailed in section 1.3.9.3.

1.3.5. Clinical burden

1.3.5.1. Patient Clinical Burden

CIDP confers a sustained and often severe clinical burden characterised by neurological impairment, treatment-related demands, and downstream effects on independence and safe mobility.^{4,11} These features may persist even when overt disease activity appears controlled and are consistent with the accumulation of residual deficits over time.⁴ Resource pressures are evident across services,⁹ with persistent symptoms despite treatment, reliance on immunoglobulin and practical limits on delivery models that can delay or constrain access to care.⁹ This context underscores a continuing unmet need for effective, durable disease control alongside treatment approaches that are feasible within NHS capacity.

CIDP manifests through multiple pathophysiological mechanisms, leading to a complex range of impairments that affect patients' functional capabilities and quality of life. The cornerstone symptoms are motor and sensory deficits. Motor impairments primarily present as muscle weakness affecting the extremities, and on the INCAT disability scale, one study reported a mean score of 3.3, consistent with moderate limitations in daily activities.¹¹ This level of disability typically means (see **Appendix J**) that many patients require a walking stick or crutch for longer distances or uneven terrain, alongside upper limb impairment that affects everyday tasks such as buttoning clothes or using a knife and fork. Sensory disruptions are equally prevalent, with one study reporting that 72–89% of patients experience numbness, paraesthesia, and diminished touch sensation.⁷⁴ These neurological impairments are closely linked to reduced mobility and poorer balance control, with evidence of increased trunk sway and slower gait that materially elevates fall risk and can manifest as difficulties with transfers, gait initiation, and safe ambulation.⁷⁵

Symptoms often accumulate over time and further constrain daily functioning. In one cohort, 17% of patients reported extreme pain, and many described profound fatigue that severely limited sustained activity.⁷⁶ The disease course contributes to this clinical burden. While a proportion of patients experience monophasic or treatment-free remission, more commonly, CIDP progresses slowly or in a relapsing manner over time.⁸ Despite available treatments, disease progression and residual disability remain concerns. Consistent with this, a Dutch registry of 112 patients found that 88% reported ongoing symptoms after treatment, including sensory disturbance, fatigue, weakness, and pain; fatigue and pain were especially prominent, indicating continued clinical burden in treated patients.⁴ Extending beyond the Netherlands, a multinational real-world survey reported that approximately 12% of treated patients rated their symptom control as poor and around 11% were dissatisfied with outcomes, despite approximately 82% being on maintenance therapy and more than half receiving immunoglobulins; this adds patient-reported evidence of residual burden during maintenance and aligns with insights reported by UK clinicians in Section 1.3.3.4.⁷⁷

The severity of clinical impairment can be considerable over the full disease course of CIDP. Historical series indicate that disability is often present at diagnosis and may be severe, with mean Rankin scores around 2.9 at presentation and peak Rankin 4-5 occurring in over half of patients during the disease course.⁸

Functional dependence is common in clinical practice. In a global survey, many patients reported requiring assistance with personal or domestic activities and expressed ongoing concerns about neurological progression.⁸ In multinational real-world data, nearly half of clinically diagnosed patients used mobility aids, most commonly a stick or cane, with walking frames, wheeled walkers, and wheelchairs also reported.⁷⁷ Health status measures also show marked heterogeneity, with EQ-5D-5L utilities spanning from negative values to near full health (−0.225 to 0.989) and a cohort mean around two-thirds of full health, reflecting variability in clinical impact at the individual level.⁷⁷

1.3.5.2. NHS Clinical burden

Specialist CIDP nurses are integral to the delivery and monitoring of Ig therapy, providing continuity of care, patient education, psychological support, and ongoing assessment across treatment cycles.⁹ Through their close and sustained contact with patients, they offer valuable real-world insight into the daily burden of disease, treatment challenges, and the wider impact on quality of life for patients and their caregivers.⁹ Insights from a dedicated advisory board of five specialist neuromuscular nurses from UK centres indicate that treatment logistics add to clinical load and healthcare resource use.⁹ Four of five had six to 10 years' CIDP experience, four of five currently manage 51–100 CIDP patients and one manages about 100; for three of five, CIDP accounts for 51–75% of workload and for one about 75%. Taken together, this reflects a high-volume, experienced UK perspective.⁹

Nurses reported that Ig is widely used, yet service capacity constraints are reflected in wait times for treatment access and appointments taking place within infusion suites (infusion suite wait times of four to six weeks, and as much as up to eight weeks), indicating system strain that can delay clinically necessary therapy.⁹ Although SCIg can reduce the reliance on Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

hospital infusion units, uptake in the UK has been limited as they introduce a significant training requirement, with initiation commonly involving structured home training sessions (two to six sessions and each session can last two to five hours).⁹ Even centres with CIDP specialist nurses struggle to commit to these training requirements, as they involve full days away from the hospital setting, limiting their ability to provide the training required to switch patients to SCIg.⁹ In addition, several centres reported that they are unable to transition CIDP patients to SCIg due to constraints with the preparations available through the national framework agreement.⁹ Under the current framework introduced in April 2025, awarded SCIg products include Cuvitru 20%, Xembify 20%, Cutaquig 16.5%, and facilitated HyQvia 10%.^{21,78} Of these, only HyQvia is licensed for maintenance treatment of CIDP.^{79–82} As the available lower concentration (although facilitated) SCIg requires larger total volumes, administration may involve longer infusions or more frequent and larger volumes, which can reduce practicality and patient acceptability at higher doses.⁸³ Consequentially, many centres continue to rely on IVIg despite recognising the potential logistical advantages of subcutaneous therapy.⁹

Resource demands are substantially compounded by treatment switching and cessation attempts, with approximately 30% of patients experiencing multiple failed cessation attempts, which necessitate significant nurse time by requiring additional clinical assessments, dose re-titration, and safety monitoring.⁹ The introduction of the new national tender has increased switching frequency, requiring extensive clinical management, including patient counselling, product familiarisation, and monitoring for tolerability issues. Cessation trials impose a particularly high burden on both patients and services: each attempt requires comprehensive patient counselling regarding relapse risk, implementation of home monitoring protocols, and vigilant surveillance for deterioration.⁹ Upon relapse services must coordinate rapid re-treatment, often complicated by limited infusion centre capacity requiring patients to wait for appointments while their condition deteriorates.⁹ Approximately 10% of relapsing patients present to secondary accident and emergency (A&E) departments, further straining acute services.⁹ This cycle of switching, cessation, relapse, and re-titration represents a substantial and often underestimated demand on specialist nursing time, infusion resources, and the broader healthcare system.

1.3.6. Humanistic burden

CIDP imposes a substantial humanistic burden marked by pain, fatigue, functional dependence, and curtailed participation, and these impacts often persist despite maintenance treatment.¹⁵ The pattern underscores an unmet need for therapies that are both more effective and more convenient, with the potential to reduce patient suffering and ease pressures on healthcare services. Patient testimonials describe persistent losses in autonomy, energy, and participation that can continue despite treatment. The testimonials below are drawn from the joint company-INUK UK patient survey and are included to supplement the literature evidence presented in this section:¹⁵

- *“CIDP robs you of your livelihood, independence, energy and at times enthusiasm for life... it imposes so many life-limiting restrictions upon you.”*

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

- *“Everything takes so much longer to do. Tiredness makes life difficult, as does pain. I hate being the one with the disability so I try not to talk about CIDP, but this is isolating.”*
- *“My whole world changed overnight. From being a fit active sociable 64-year-old I became an immobile dependent person living with constant pain.”*

In addition to the Company-commissioned patient survey with INUK, three anonymised patients provided testimonials describing the profound burden of CIDP and its treatment. Patients 1 and 2 highlighted the physical, psychological and logistical impact of IVIg, including frequent hospital attendance, painful cannulation, severe post-infusion malaise and, for Patient 1, a serious episode of aseptic meningitis. Both reported reduced independence, fatigue and constraints on work and social participation, with cyclical deterioration between infusions necessitating life to be planned around treatment and escalating venous access difficulties. Patient 3 emphasised the impact of mobility loss and the consequent strain on family life, with their partner retiring to provide care. Although IVIg initially improved symptoms, the extended four-day, five-hour infusions and lengthy travel added to the treatment burden. Transition to efgartigimod reduced time and frequency of hospital visits, eliminated headaches for this patient and enabled self-administration at home, supporting a return to everyday activities. Collectively, these accounts illustrate the heavy personal, social and practical toll of CIDP and the potential of more convenient, less invasive options to reduce the burden of treatment. A few selected quotes are provided below and the full testimonials are in **Appendix L**.

Patient 1

- *“I feel a shadow of my former self... CIDP has stripped me of my independence.”*
- *“I then [after IVIg treatment] spend that weekend in bed feeling like life is not worth living.”*
- *“I suffer with migraines, sickness and such overwhelming weakness and tiredness, I can barely function.”*

Patient 2

- *“My veins have also shrunk making cannulation much harder and it normally takes multiple attempts to get a successful insertion, and I no longer look forward to treatment despite the benefit I know I will get afterwards.”*
- *“We therefore try and organise our life such that we do most activities in the middle two weeks whilst avoiding the week before and after treatment, the rollercoaster lives on.”*

Patient 3

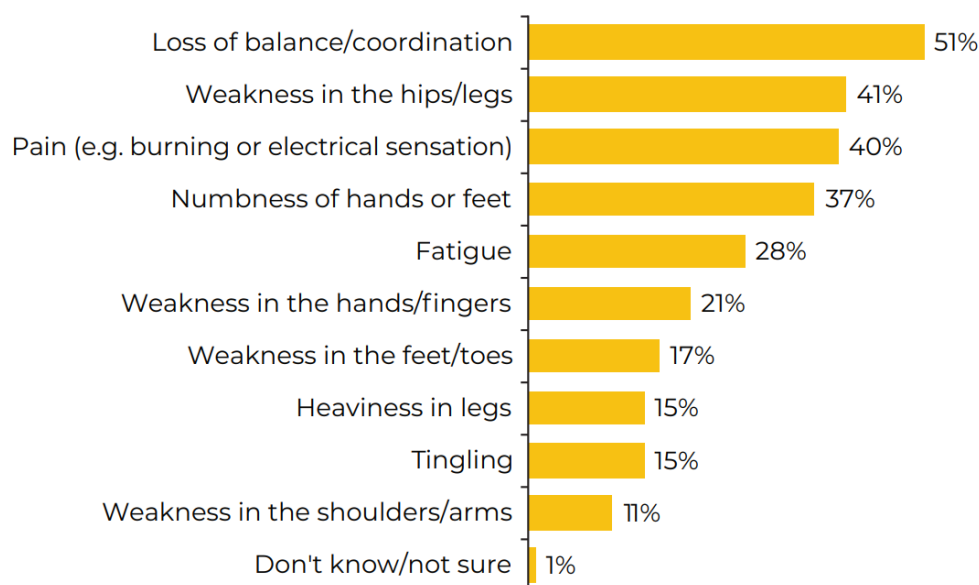
- *“I noticed straight away efgartigimod stopped my headaches... I am now able to administer the drug myself at home with my visit to hospital for checks reduced to every six weeks.”*
- *“The nearest treatment centre was 50 miles each way and the treatment would take five hours a day... this made me very tired and again my husband stepped in to take me to and from the hospital as I also suffered headaches....”*

Across multiple studies, patients report markedly lower HRQoL than age- and gender-matched controls, with physical function most affected.^{3,12,84–88} In line with this, UK and European cohorts demonstrate significant decrements on generic measures; for example, gait impairment correlates with lower EQ-5D-5L-VAS scores, with patients rating their health at around 65% of the level of healthy controls.⁸⁸

Pain and fatigue are central to the lived experience. A meta-analysis of 38 studies involving 991 patients found that 46% experience pain during the disease course.⁸⁹ In a Southeast England cohort, 73.8% reported at least moderate pain or discomfort whilst 40.5% experienced challenges with self-care; in the most severely affected patients, persistent pain and profound fatigue are prominent drivers of poor self-rated health and reduced participation.¹² These symptoms often track with lower 36-Item Short Form Health Survey (SF-36) scores, particularly in physical domains, reinforcing the tight linkage between symptom burden and reduced HRQoL.^{3,84,87}

At treatment initiation, approximately half of respondents in one study ranked loss of balance or coordination among their three most bothersome symptoms, with pain, weakness, and numbness also frequently cited (Figure 1).⁹⁰ These same domains reappear during maintenance Ig treatment, with patients most frequently selecting ‘regaining control/function of the arms and/or legs’ as their primary treatment goal in one study, alongside improving overall quality of life and balance/coordination.⁹¹ The recurrence of the same problems as both baseline priorities and ongoing goals indicates that these symptoms remain insufficiently controlled during treatment, evidencing residual burden that limits independence and quality of life; findings from the Company-commissioned UK patient survey conducted in collaboration with INUK are consistent with continued difficulties in hand function and walking support among treated individuals.¹⁵

Figure 1: Most bothersome CIDP symptoms at the time of starting medication



Source: Allen et al (2019)⁹⁰

Large real-world datasets confirm the breadth of humanistic burden and residual burden despite treatment.⁹² In one multinational study conducted across Europe, Japan, and the United States (N=310), half of patients reported ongoing moderate-to-severe symptoms despite treatment, and 56% required mobility aids or home modifications, most commonly canes or walking sticks.⁹² Employment was also commonly affected, with retirement, unemployment, or long-term sick leave attributed to CIDP by a notable proportion of respondents.⁹² The worst-affected subpopulation reported the greatest restrictions on daily activities and the lowest HRQoL, underscoring persistent unmet need even during maintenance therapy.⁹² Long-term functional outcomes are also often poor; a systematic review of 21 observational studies, encompassing 1,199 patients, found that less than half of patients (47%) achieve what clinicians consider a good functional outcome.⁹³

The burden of CIDP also extends into psychological well-being, with 38.1% of patients in the same Southeast England cohort reporting moderate anxiety or depression.¹² Several factors have been identified as predictors of worse health status, as measured by SF-36 scores, including higher INCAT motor scores (indicating greater disability), depression, employment status (being unemployed and/or retired), and shorter disease duration.⁸⁴

Recent UK-specific findings are consistent with this picture of humanistic burden.¹⁵ In a cross-sectional observational survey commissioned by the Company in collaboration with INUK (N=63), only 15.9% (n=10) reported no problems with hand function, while 52.4% (n=33) required walking support.¹⁵ Pain was a persistent issue, with 34.9% (n=22) reporting moderate pain or discomfort and 20.7% (n=13) severe or extreme pain.¹⁵ On the EQ-5D-VAS, mean health was rated at 56.0 (standard deviation [SD] 20.1; range 11.0–92.0), with a mean EQ-5D-5L utility of 0.595 (SD 0.234), confirming substantial and wide-ranging impact at the individual level.¹⁵

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

In summary, CIDP imposes a profound and sustained humanistic burden that extends well beyond loss of strength and sensation. Pain, fatigue, and functional dependence limit independence, participation, and emotional well-being, while continued disability persists even among patients receiving long-term Ig therapy. These impacts reverberate through daily life, restricting mobility, work, and social engagement, and contribute to psychological distress and carer strain.^{3,12,84–88} Real-world data and UK patient reports consistently demonstrate that current therapies often fail to restore meaningful function, leaving many individuals reliant on demanding, hospital-based treatment regimens.¹⁵ Together, these findings highlight an urgent unmet need for therapies that are both more effective in achieving sustained functional recovery, and more convenient and less burdensome to deliver, reducing patient suffering while alleviating pressure on NHS services.

1.3.7. Caregiver burden

Caregivers are an integral requirement for the day-to-day management in CIDP, where three-quarters of patients (74.6%, n=47) in the UK report receiving assistance to manage their CIDP symptoms.¹⁵ Given the sparsity of published literature on caregiver burden in this condition, UK evidence from a cross-sectional caregiver survey conducted by the Company in collaboration with INUK provides important context for both lived experience and quantitative impact. Drawn from that survey, the quotations below highlight the substantial personal impact on caregivers, most of whom provide informal support as partners or family members:¹⁰

- *“The illness is rare and there is no understanding or support. His medicines have caused other illnesses. We have no life. No one cares.”*
- *“It eats away at my ability to work normal hours. I then have to work late into the night to catch up but also have to maintain a balance with caring. I just don't have enough hours in the day to care and to work.”*
- *“It is exhausting, it's impacted my health. Helping him manage his struggle with CIDP and the effects on his mental health leaves me isolated, lonely, and confused.”*

In the same UK survey, caregiving was undertaken chiefly by women in mid to later adulthood, most often spouses or partners, and delivered predominantly as informal support.¹⁰ Among respondents who quantified their contribution, the median time commitment was 20 hours per week with a wide variation (four to 90 hours per week), indicating that a subpopulation of caregivers carry particularly intensive roles.¹⁰ Caregiving responsibilities are frequently balanced with employment and managing household tasks, which further increases the burden experienced by caregivers.¹⁰ The mean CarerQoL-7D index was 75.0, a score that reflects the coexistence of fulfilment with substantial difficulties.¹⁰ While many caregivers reported some satisfaction in their role, this coexisted with substantial personal impacts: 67% reported mental health problems, 81% physical health problems, and 43% financial strain.¹⁰

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Broader real-world data further reinforce a similar reliance on informal care within CIDP.⁹² In a multinational survey of 310 patients across Europe, Japan, and the United States, 29% reported requiring regular caregiver support, most commonly from a partner or spouse, with an average of more than four hours of help per day.⁹² The impact extends beyond the home, with a notable proportion citing CIDP as a contributing factor to early retirement, unemployment, or long-term sick leave.⁹²

These findings raise concerns about sustainability. Given that caregiver support in CIDP is common and time-intensive, and that overall burden escalates as disability progresses, prolonged reliance on informal care is likely to become harder to sustain as disease courses evolve and households age, with measurable consequences for caregiver wellbeing and stability. Approaches that strengthen support for carers and simplify treatment pathways to reduce hands-on care demands may help to mitigate this burden.

1.3.8. Economic burden

Healthcare resource use in CIDP is closely linked to treatment patterns, with Ig therapy the primary driver of direct medical costs.^{11–14} In large US claims datasets, Ig therapy accounts for the majority of total costs, and chronic Ig users accrue annual expenditures that are more than double those of the overall CIDP population.¹³ In the UK, 2023/24, total Ig drug spend was ~£397 million; applying CIDP's 26.1% share of total Ig grams (1,381,729/5,301,310) gives an estimated ~£104 million CIDP drug spend.⁷³ This cost concentration reflects the delivery model: hospital-based IVIg is typically administered in repeated cycles that can span multiple days per cycle, generating substantial infusion-unit, nursing, and pharmacy costs and compounding service capacity pressures.^{17,23} These patterns are consistent with UK clinical practice, where repeated infusions over several days per cycle add materially to health system costs.^{17,23}

Beyond direct medical costs, the economic impact on patients living with CIDP includes substantial productivity losses and personal expenditure.¹⁵ In the joint Company-INUK UK patient survey, on average, patients missed 25.4% (SD 39.7) of work time due to CIDP.¹⁵ While at work, they experienced a 19.3% (SD 27.4) impairment in productivity.¹⁵ Absenteeism was higher than presenteeism for patients living with CIDP, indicating that the condition is likely to lead patients to miss work entirely rather than continue to work at reduced capacity.¹⁵ The high standard deviations in the results further reflect the heterogeneity in how CIDP impacts patients.¹⁵ Some patients reported premature exit from the workforce, with a median 6.5 years earlier than planned among those affected.¹⁵ Out-of-pocket costs were heterogeneous but non-trivial for many, including purchases of over-the-counter medicines (mean £67.60 over three months among reporters) and spending on adjunctive therapies such as physiotherapy, where reported costs ranged widely and could be substantial for intensive courses (median £270 and mean £800 over three months among reporters, ranging up to £5,000).¹⁵ Travel to clinic also carried time and expense burdens, with some patients reporting journeys of at least an hour each way and a mean three-month travel spend of £64.80 among those providing data.¹⁵

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

The caregiving burden of CIDP also contributes materially to the societal cost.¹⁰ In the joint Company-INUK UK caregiver survey, overall work impairment amongst caregivers averaged 24.7% among employed caregivers, driven by high presenteeism (24.5%) despite low absenteeism (1.9%), and activity impairment across the full caregiver cohort averaged 42.4%.¹⁰ Employment consequences were mixed but meaningful for a minority, including job changes and stopping work before retirement age.¹⁰ These productivity losses sit alongside the substantial time required for informal care, with the median time commitment being 20 hours per week.¹⁰ The coexistence of fulfilment with measurable strain was reflected in caregiver outcomes, with many reporting mental, physical, and financial impacts.¹⁰

These substantial economic burdens persist despite available treatments, demonstrating that current therapies fail to eliminate significant direct and indirect costs. The health system costs associated with repeated, multi-day infusion cycles, combined with productivity losses and out-of-pocket expenses borne by patients and caregivers, underscore the need for treatment options that provide effective disease control while reducing delivery complexity and service dependence.^{10–16,23}

1.3.9. Current treatment

To date, there are no published positive reimbursement recommendations for treatments for CIDP from NICE. Table 3 summarises the key recommendations and guidelines from major UK health technology assessment and commissioning bodies regarding the management of CIDP.

Table 3: UK HTA recommendations and national commissioning policies

HTA or Commissioning body	Type	Recommendation
NICE	Guidelines	Suspected neurological conditions: recognition and referral [NG127]. ⁹⁴
	Guidelines	Neuropathic pain in adults: pharmacological management in non-specialist settings [CG173] ⁹⁵
	Quality standard	Suspected neurological conditions: recognition and referral [QS198]. ⁹⁶
	Single technology assessment	Efgartigimod: assessment in development [ID6409]. Expected publication date TBC. ⁹⁷
NHS England	Clinical commissioning policy	Rituximab is not recommended to be available as a routine commissioning treatment option [170026/P]. ⁹⁸
	Clinical commissioning policy	Therapeutic Igs are recommended to be available routinely for CIDP. ⁷⁸

Abbreviations: HTA: Health technology assessment; Ig: Immunoglobulin; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; TBC: To be confirmed.

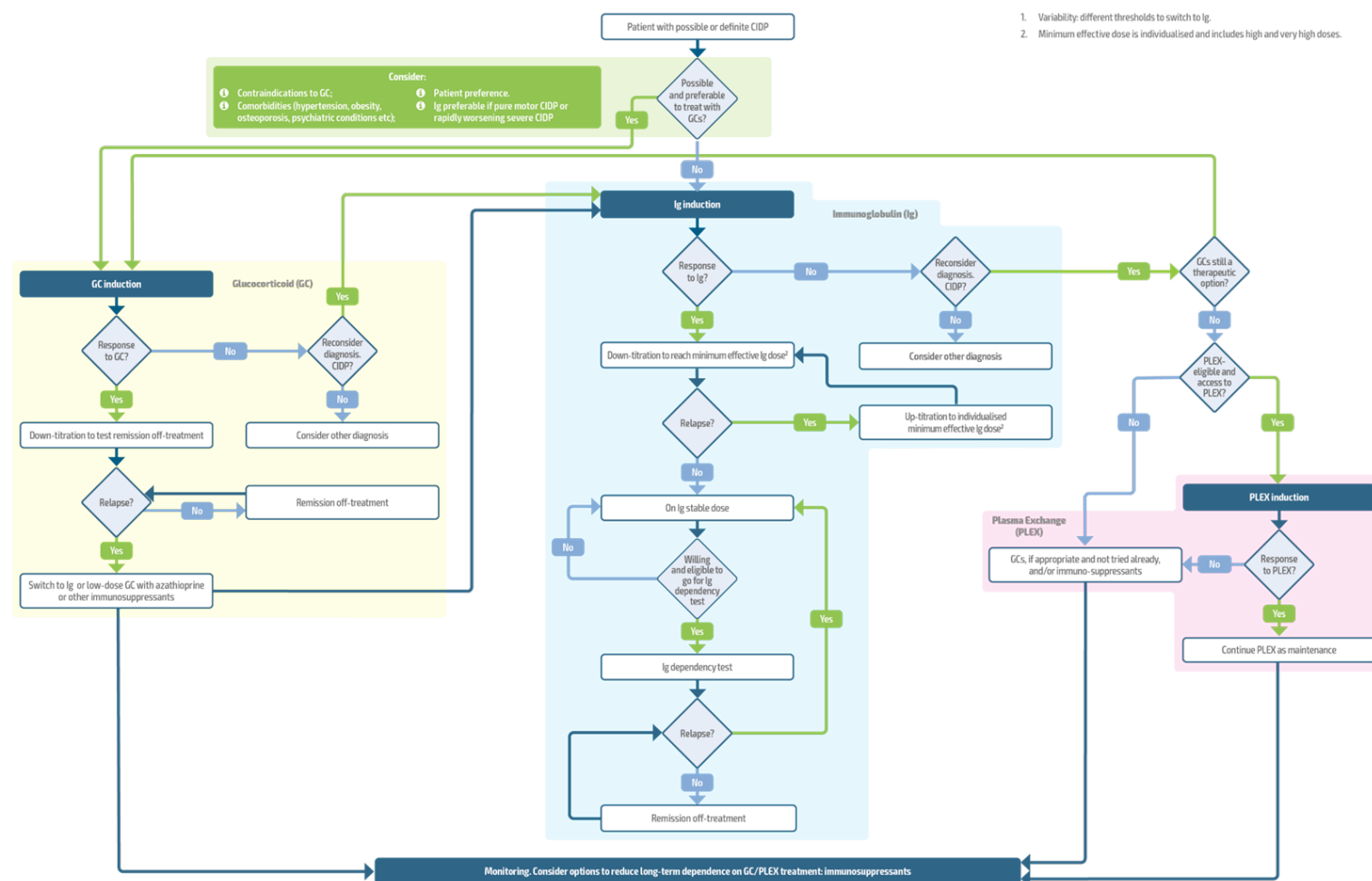
There are uncertainties surrounding the current treatment pathway for CIDP in the UK, as existing guidelines describe available treatment options but do not provide clear recommendations on how to sequence or select between them in practice.¹ Insights from a

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

clinician market research survey reported a large amount of variability in different dosing and administration schedules for Ig.¹⁷ To address this uncertainty, the Company collaborated with UK clinical experts to build a more detailed understanding of how CIDP is managed in routine NHS settings.^{16,17} To inform this, the Company first reviewed existing UK and international guidelines to draft a preliminary treatment pathway. A qualitative study was then undertaken with five consultant neurologists with substantive experience in CIDP management, from a geographically representative sample of neuromuscular centres across England, to validate the treatment pathway for CIDP.¹⁶ Insights from the study confirm variability in practice for CIDP, though a broadly agreed pathway for CIDP management has now been established by the Company for the UK.¹⁶ Decision-making depends heavily on clinician assessment, patient preference, disease presentation, and local service capacity, with CIDP specialist nurses playing a key role in coordinating care, supporting treatment decisions, and facilitating transitions between therapies.⁹

The current UK treatment pathway for CIDP, derived from the EAN/PNS guidelines and validated through qualitative and quantitative research, with UK clinical experts, is presented in Figure 2.¹⁶ For the first time, UK CIDP specialists have reached consensus on a nationally representative clinical pathway, an important milestone in aligning and standardising CIDP management across the NHS. While the pathway accommodates heterogeneity - reflecting variations in disease presentation, patient characteristics, induction therapies, and preferred clinical practice - it offers a clear and unified framework that accurately mirrors current UK practice and enables a clear and consistent - and physician-driven - positioning for efgartigimod (Figure 3).

Figure 2: Current UK treatment pathway (without efgartigimod)



Adapted from: Van den Bergh et al. (2021)¹ and validated via qualitative workshop activity¹⁶

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; CS: Corticosteroids; IVIg: Intravenous immunoglobulin; PLEX: Plasma exchange; SCIg: Subcutaneous immunoglobulin.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

1.3.9.1. Induction treatment

The purpose of induction treatment is to control disease activity rapidly and to confirm the diagnosis, since a clinical response to therapy is often used as supportive evidence for CIDP.¹ Induction treatment recommendations follow a differentiated approach based on CIDP presentation.¹ For typical CIDP, the guidelines recommend either IVIg (but not SCIg) or corticosteroids as induction therapy, with neither treatment preferred over the other.¹ However, in motor CIDP, IVIg is specifically recommended as the induction treatment, based on evidence showing patient deterioration following corticosteroid use in this phenotype.¹ In UK clinical practice, corticosteroids are used primarily for short-term induction; patients rarely remain on steroid therapy beyond the initial phase because of relapse on tapering and the risk of long-term adverse effects.^{1,99} Most patients who respond initially to corticosteroids transition to maintenance therapy with Ig once relapse occurs.¹⁷

While PLEX is effective, it is not recommended as an induction treatment due to its more complex administration compared to IVIg or corticosteroids.¹ The guidelines also advise against using SCIg for induction treatment based on the very low certainty evidence for using SCIg as induction treatment.¹ SCIg also typically requires larger volumes and multiple infusion sites compared to IVIg, which reduces practicality and also may reduce patient acceptability.⁸³

1.3.9.2. Maintenance treatment

The purpose of maintenance therapy is to sustain disease control, prevent relapse and optimise long-term functioning once induction therapy has achieved a clinical response. The approach to maintenance therapy emphasises individualisation and dose optimisation, whereby decisions on sequencing and combining therapies should be tailored to the individual, considering disease severity, comorbidities, and treatment availability.¹

Ig treatment (IVIg and SCIg):

- Ig is widely recognised as the most commonly used maintenance treatment, supported by the findings from a Company-commissioned clinician survey, which reports that 77% of patients receive IVIg (63%) or SCIg (14%) for their maintenance treatment.¹⁷ In an advisory board with UK clinicians, advisors stated that patients with CIDP are mainly treated with IVIg, which is favoured over steroids in patients with progressive CIDP due to its quick response time and the long-term adverse effects associated with high-dose steroids, and in patients with certain comorbidities where steroids are not appropriate.^{1,22,99}
- Both SCIg and IVIg are recommended as maintenance therapy for patients with active disease.¹ The choice is often influenced by patient preference, though SCIg is typically suitable for patients who are controlled on relatively low-dose or low-frequency IVIg.^{1,9} However, an advisory board of five specialist nurses from UK neuromuscular centres reported that uptake of SCIg remains low, mainly due to the complex training required for administration, patients' reluctance to switch to SCIg because of its frequency and volume of dosing, as well as the administrative and logistical challenges of arranging treatment switches.⁹ This is further supported by the Company-commissioned market

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

research survey with UK clinicians, which reports that around 14% of patients receive SCIg for their maintenance treatment.¹⁷

- Following initiation therapy, the guidelines recommend gradual dose tapering or extending administration intervals of Ig to identify the minimum effective maintenance dose.¹ The majority of patients (60%) receive 1.00-1.99 g/kg about once a month, which is in line with the reported UK average maintenance dose regimen for Ig (approximately 1.4 g/kg every 4.3 weeks).^{16,100} However, a small minority of patients with CIDP may require higher doses of Ig (>2g/kg/every 6 weeks) as maintenance treatment.⁷⁸ Research from the Company commissioned Structured Expert Elicitation (SEE) suggests that approximately 24% of patients with CIDP receive 2g/kg roughly once a month, which is considered higher than the UK average and are in the high dose category.^{16,100} Clinicians also noted that some patients continue Ig despite poor tolerability or response, highlighting the lack of viable alternatives and another area of unmet need.¹⁷
- Importantly, in the UK regular trials of cessation are attempted in stable patients to confirm disease activity and prevent over-treatment with Ig therapy.⁷⁸

Corticosteroids:

- Rarely corticosteroids can be used as maintenance therapies, with the choice guided by patient factors and treatment response.¹ Corticosteroids are not typically maintained long-term in patients with refractory or relapsing CIDP due to the risk of iatrogenic conditions, side effect profile and limited durability of effect.^{17,24} This aligns with findings from the Company-commissioned clinician market research survey, which showed that 3% of patients received daily corticosteroids for their maintenance therapy.¹⁷ This approach is consistent with wider clinical practice across immune-mediated and inflammatory diseases, where long-term corticosteroid use is generally avoided because of cumulative toxicity and loss of sustained efficacy.¹⁰¹

PLEX:

- While PLEX remains available as a treatment option within the broader pathway, clinical experts emphasised that it is rarely used for long-term maintenance due to its invasive nature and associated risks.^{17,24} As such, PLEX is generally reserved for patients with severe or refractory disease after other options have failed and is not typically used.^{17,24} PLEX was described as a last resort treatment due to its invasiveness, infection risk and logistical challenges; PLEX is only available at specialised apheresis units, with limited geographic accessibility across the UK, further restricting its utility as a treatment option.¹⁰² This aligns with the Company-commissioned clinician market research survey, which also found that fewer than 5% of patients on maintenance therapy receive PLEX.¹⁷

Table 4 provides an overview of the four main treatment approaches for CIDP, detailing their administration methods, efficacy considerations, and key limitations.

Table 4: Comparison of current treatment options for CIDP

Treatment	Administration and efficacy profile	Practical considerations and limitations
IVIg	Induction begins with a total dose of 2 g/kg divided over two to five days, with typical maintenance regimens of 1 g/kg every three weeks.^{1,103} Initial treatment occurs in hospital or day-facility settings; in current UK practice, most maintenance IVIg is delivered in hospital/day units, with home administration used selectively under monitoring.¹ Practical constraints include limited chair capacity and daytime operating hours across multi-day cycles, with reported scheduling issues; these are issues raised by infusion nurses in advisory feedback. Only 16% of patients achieve remission with a single course.¹⁰⁴ Treatment efficacy is impacted by a "wearing off" effect, where IVIg levels may decline as early as two weeks post-administration, necessitating personalised regimen adjustments.^{48,105}	Access challenges include limited infusion-suite capacity,¹⁰⁶ scheduling difficulties for working patients,⁹⁰ venous access problems (particularly in those with renal insufficiency or poor venous capacity),^{106,107} and supply shortages.¹⁰⁸ As CIDP represents the single largest indication for Ig use within the NHS, this population is particularly vulnerable to the effects of supply constraints and distribution pressures.^{73,108} Even short-term disruptions in supply may have a disproportionate impact on service delivery and treatment continuity for these patients. Common AEs associated with treatment include headache, nausea, malaise, fatigue, fever, and chills, primarily due to rapid infusion rates and high volumes.^{48,51,105,106,109} Headache and nausea can persist for days post-infusion; for headache, onset is often delayed and it can last between 24 and 72 hours which can materially affect quality of life and work productivity.⁵¹ More serious complications can include venous and arterial thromboembolic events,¹⁰⁵ requiring careful consideration particularly in patients with congestive heart failure.¹⁰⁵
SCIg	Utilised exclusively as a maintenance treatment option, particularly beneficial for patients experiencing venous access difficulties, systemic IVIg side effects, or the wearing off phenomenon with IVIg¹⁰⁵ or experiencing high treatment burden through intensive hospital visits that disrupt work, family life, and social activities. While sharing similar AEs with IVIg, these tend to be less frequent and severe.^{105,110}	Primary limitations include its restriction to use as maintenance therapy in those patients who are controlled on low dose IVIg only, the requirement for multiple days of training and equipment being stored in the house,⁹ more frequent infusions than IVIg,¹ and discomfort from repeated subcutaneous administrations; including issues with swelling and pain from high administration volumes which in turn may lead to adherence issues.¹⁰⁹
Corticosteroids	Corticosteroids are commonly used as an induction therapy, provided there are no contraindications, but are not used as a maintenance therapy in patients with progressive or relapsing CIDP due to the risk of iatrogenic conditions and their significant side effect profile with long-term use and limited durability of effect.^{1,99}	

Treatment	Administration and efficacy profile	Practical considerations and limitations
PLEX	PLEX remains available as a treatment option, but clinical experts emphasise that it is rarely used for long-term maintenance due to its invasive nature and associated risks. ^{17,24} Regimens are also intensive (for example, guidance describes schedules such as 2 sessions per week for 3 weeks followed by weekly for 3 weeks), and UK provision can be uneven. ^{9,34} The procedure can provide short-term benefit, with 33-66% of patients showing improvement in disability and nerve conduction, but relapse is common, occurring in around two-thirds of responders within 7-14 days. ^{43,46} Access is further limited by the need for specialised equipment and monitoring, and AEs are reported in 3–17% of procedures, mainly linked to venous access and haemodynamic changes. ⁴⁶ These drawbacks position PLEX as a less utilised option, generally reserved for severe or refractory cases after IVIg and corticosteroid failure.	

AE: Adverse event; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; IVIg: Intravenous immunoglobulin; NHS: National Health Service; PLEX: Plasma exchange; SCIg: Subcutaneous immunoglobulin.

1.3.9.3. Alternative treatments for highly refractory disease

When patients require high maintenance doses or have an inadequate response to Ig, the treatment strategy can be modified in several ways. If the initial choice of therapy results in significant side effects or inadequate response, clinicians should try alternative treatments before considering combination therapies.¹ For patients refractory to IVIg; corticosteroids, PLEX, cyclophosphamide, ciclosporin, or rituximab may be considered.¹

Immunosuppressant or immunomodulatory agents are sometimes added; azathioprine, mycophenolate mofetil, or ciclosporin may be used as immunoglobulin- or corticosteroid-sparing agents, although none is licensed and evidence is limited.¹ In refractory disease, cyclophosphamide, ciclosporin, or rituximab may be considered.¹ These unlicensed and unproven options are used only as a last resort, underscoring the need for effective, evidence-based therapeutic alternatives. This aligns with findings from the Company-commissioned clinician market research survey, which showed that fewer than 5% of patients on maintenance therapy receive immunosuppressants.¹⁷

The guidelines also emphasise comprehensive care beyond immunotherapy.¹ This includes addressing neuropathic pain according to established pain management guidelines and considering additional support such as physiotherapy, psychological care, or rehabilitation specialist referral based on individual patient needs.¹ Patient education through support groups is also recommended as part of the care strategy.¹

1.3.9.4 Immunoglobulin supply in England

In England, Ig supply for neurological use, including CIDP, is determined by the national Ig procurement framework.⁷⁸ As CIDP represents the single largest indication for Ig use within the NHS, this population is particularly vulnerable to the effects of supply constraints and distribution pressures.^{73,108} Under the current framework introduced in April 2025, the awarded IVIg brands available for NHS use are: Octagam 5%, Gamunex 10%, Intratect 10%, Kiovig 10%, Gamten 10%, and Panzyga 10%. The awarded SCIg products are: Xembify 20%, Cuvitru 20%, Cutaquig 16.5%, and facilitated HyQvia 10%. All IVIg products are licensed for CIDP.^{111–116} Of the SCIg products, only HyQvia holds a licence for

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

maintenance treatment in CIDP.^{79–82} Treatment guidelines state that there is no evidence of a difference in efficacy between different IVIg preparations for treating CIDP.¹ Furthermore, it is generally considered that the efficacy of IVIg and SCIg is comparable in CIDP. Although it is recognised that SCIg may offer some safety and quality of life advantages to some patients.¹¹⁰

1.3.9.5 Unmet needs of current treatment paradigm

In CIDP, the choice of initiation treatment and options for long-term maintenance treatment present numerous challenges. Nevertheless, administration of effective treatment is critical to limit irreversible axonal degeneration,¹¹⁷ to prevent or minimise long-term disability and avoid permanent weakness, sensory loss, pain, and imbalance.¹¹⁸ Unfortunately, there have been no innovative new treatments approved for CIDP in more than 30 years.¹¹⁹ This lack of therapeutic innovation contrasts sharply with other immune-mediated neurological and inflammatory disorders, where targeted biologic therapies have transformed long-term outcomes.¹²⁰ Efgartigimod has been granted Promising Innovative Medicine status by the UK MHRA for CIDP, signalling regulatory recognition of disease severity, unmet need and the medicine's potential to address it.²⁹

The existing treatment paradigm faces three major challenges: inadequate response to the treatment options currently available, practical limitations of current therapies, and long-term management concerns, with certain patient groups experiencing these pressures more acutely than others. In practice, many patients remain on therapy despite sub-optimal benefit because alternatives are limited, switching can be burdensome, and clinicians are cautious about withdrawal given the risk of deterioration (see Section 1.3.3.4 and 1.3.5).¹⁷ This results in a cycle of ongoing treatment dependency, including treatment-related adverse events (AEs),^{24,48,51,99,105,106,109} exposing patients to cumulative burden while placing sustained demand on infusion services and the Ig supply chain. There is also a substantial burden to patients and caregivers from current therapies, including transport costs, time away from work, and disruption to family schedules and dynamics.^{9,10,15}

Approximately 25% of patients cannot be stabilised with standard therapies (IVIg, corticosteroids and PLEX),¹²¹ with rates up to 30% reported in some series depending on definition and cohort.^{74,122–124} These patients represent a particularly vulnerable group, as their options become severely limited. Due to the lack of other viable options, lack of stabilisation does not necessarily result in discontinuation of Ig treatment, with only around 5% discontinuing. Those patients who discontinue may be prescribed immunosuppressants such as cyclophosphamide, ciclosporin or rituximab. These are used off-label and supported only by very limited evidence from case series in refractory CIDP.¹ This subpopulation therefore represents a critical population with the highest unmet need, who either persist with suboptimal Ig treatment, or resort to empirical, off-label escalation rather than evidence-based options.

The practical implementation of current therapies presents another significant challenge, particularly impacting specific patient subpopulations. Patients with renal insufficiency or poor venous capacity face additional hurdles with IVIg treatment,^{106,107} while those with certain comorbidities (diabetes, osteoporosis, glaucoma, and congestive heart failure) are

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

often unable to receive corticosteroids.^{125,126} IVIg treatment, while effective, is complicated by a "wearing-off" effect, with levels declining as early as two weeks post-administration,¹⁰⁵ requiring constant regimen adjustments to maintain efficacy.⁴⁸

Long-term management poses particular challenges for patients requiring high maintenance doses of therapy. When high maintenance doses of IVIg, SCIg, or corticosteroids are needed, patients face increased risk of side effects and complications.¹ These patients often require the addition of immunosuppressant or immunomodulatory medications, further complicating their treatment regimen. Even among those who initially respond to treatment, many continue to experience residual neurological impairment and disability, along with symptom fluctuations related to treatment timing.^{52,85,127,128}

In the Company-commissioned clinician market research survey carried out in January 2025, the moderate clinician-reported satisfaction scores for IVIg and SCIg highlight areas where improvements could be made, particularly in reducing the logistical burden of frequent hospital visits.¹⁷ All nine clinicians reported that treatment dissatisfaction related to IVIg treatment was driven by the inconvenience of hospital visits.¹⁷ One clinician noted that alternative models of care, such as home-based administration of therapies, could significantly improve patient satisfaction and adherence.¹⁷

The NHS 10 Year Health Plan emphasises a fundamental shift "from hospital to community", with the core preventative principle that care should happen "as locally as it can, digitally by default, in a patient's home if possible, in a neighbourhood health centre when needed, in a hospital if necessary".¹⁸ To achieve this transformation, the plan commits that "over the course of this plan, the share of expenditure on hospital care will fall, with proportionally greater investment in out-of-hospital care", with this shift in investment to be delivered over the next three to four years.¹⁸

The urgency of this transition is further underscored by ongoing supply constraints affecting IVIg. The EMA has notified healthcare providers of human normal Ig shortages expected to continue until June 2026,²⁰ whilst the Office of Health Economics has emphasised in its submission to parliamentary inquiries on UK drug shortages that such supply constraints necessitate the availability of effective alternative treatments to ensure continuity of patient care.¹²⁹ These systemic pressures make it increasingly critical to identify treatment options that can reduce reliance on hospital-based infusion services.

The current reality for many patients remains heavily hospital-dependent, creating particular challenges for those with significant disability due to symptoms and who require swift and reliable treatment responses. While IVIg can provide rapid improvement, the logistical challenges of regular infusions, combined with potential AEs and wearing-off effects, can significantly impact treatment effectiveness and patient quality of life; and these patients may also face greater challenges with treatment alternatives as previously described.¹⁵

The Company-commissioned patient survey conducted in collaboration with INUK also highlighted the logistical burden associated with treatment access.¹⁵ Nearly all IVIg users 96.7% (n=29/30) received infusions in hospital.¹⁵ Travel was frequently substantial: 30.2% (n=19/63) reported journeys of at least 60 minutes for appointments, and 27.0% (n=17/63)

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

relied on family or friends for transport, indicating accompaniment for a significant share.¹⁵ Among respondents providing cost data over the last three months (n=16), the mean travel spend was £64.80, with a median of £50 and a range of £5 to £300.¹⁵ These findings emphasise that while IVIg remains effective, it requires recurrent hospital visits that may be resource intensive and are logistically challenging, particularly for patients with mobility issues or those living far from infusion centres.¹⁵

The clinician survey findings also highlighted the issue of long-term management. On average, the current CIDP cohort in the UK receives Ig for approximately three years, with 44.4% of patients remaining on treatment indefinitely.¹⁷ While most patients remain on maintenance therapy for extended periods, the continued symptom burden and the lack of clear discontinuation strategies demonstrate a need for treatment optimisation. Clinicians in the survey reported within the proportion of Ig responders (defined as a patient currently receiving maintenance treatment at stable dose with stable symptoms or whose symptoms are improving allowing for a reduction in dose), approximately 30% experience continued symptom burden and side effects, indicating that while IVIg is beneficial for a subset of patients, it is not sufficient for all.¹⁷ The low rate of treatment discontinuation due to refractory status reflects the limited availability of alternative therapies, meaning that some patients may remain on IVIg despite deriving little benefit. This highlights the significant unmet need for additional treatment options that can address non-responders and those who remain functionally limited despite treatment, highlighting the gap between clinical response criteria and meaningful symptom relief.

Although SCIg has the potential to be advantageous for reducing hospital dependency, UK implementation faces significant barriers, including specialist nurse training requirements for administration, limited nursing capacity, patients' reluctance to switch to SCIg because of its frequency and volume of dosing, as well as the administrative and logistical challenges of arranging treatment switches.^{9,83} These practical limitations explain why SCIg remains underutilised in the UK despite theoretical advantages. Novel therapeutic approaches could benefit both patients and caregivers while also easing the strain on hospital infusion services, which are under growing pressure as more targeted biologics require infusion facilities across various therapeutic areas.⁹

Beyond clinical response and practicality, supply resilience is a structural constraint. Ig production depends on plasma pooled from many thousands of donations, and increasing global demand means that supply shortages can and do occur.¹⁰⁸ Global reliance on plasma donations also imposes intrinsic capacity limits, meaning production cannot be scaled rapidly in response to spikes in demand or new indications. NHS procurement has prioritised continuity and resilience, extending the outgoing framework to avoid gaps and to enable controlled product switching.¹⁹

These challenges underscore a multi-dimensional unmet need in CIDP. This spans limited efficacy for refractory and partially responsive patients, practical and logistical burdens for those dependent on Ig therapy, and systemic vulnerability due to constrained immunoglobulin supply. Novel therapeutic approaches that provide more consistent efficacy, improved tolerability, and simplified administration could transform long-term outcomes while reducing strain on NHS capacity and supply resilience. The introduction of alternative, Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

mechanism-based therapies represents a critical opportunity to modernise CIDP care after decades of therapeutic stagnation and address an area of longstanding therapeutic unmet need.^{19,108}

1.3.9.6 Efgartigimod positioning in the current treatment pathway

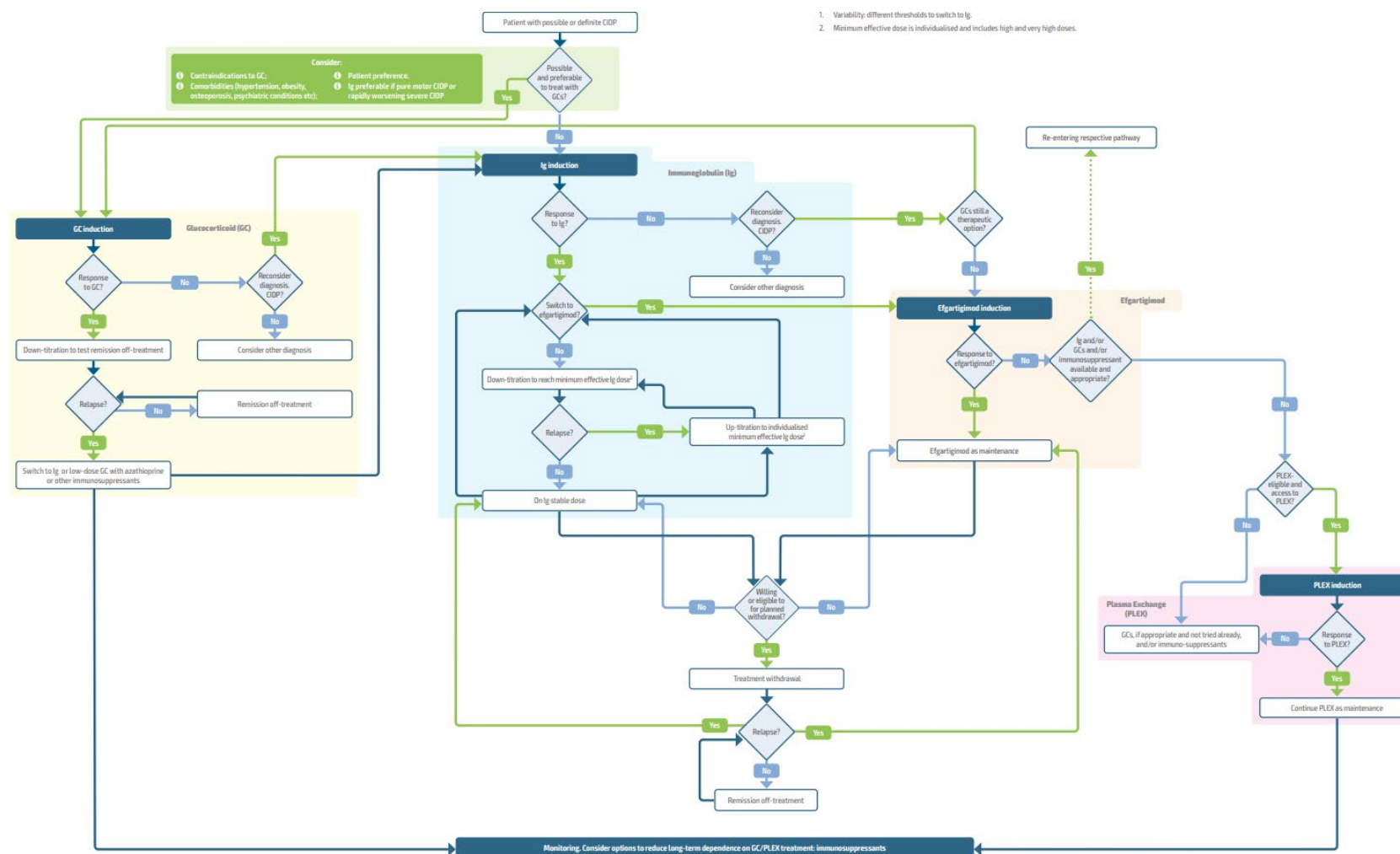
The current UK treatment pathway (with the proposed positioning of efgartigimod) is shown below in **Figure 3**. Efgartigimod should be considered for patients with unsatisfactory treatment with Igs (IVIg or SCIg), which may be defined by at least one of the following criteria:

1. High burden of Ig treatment: patients who have received at least six months of treatment with Igs (IVIg or SCIg for whom ongoing Ig infusions or injections significantly impact daily life, work, or caregiving responsibilities). This category includes patients who remain symptomatic or require high doses or frequency of Ig to maintain benefit and avoid peri-dose fluctuations.
2. Patients who are intolerant or refractory to Ig: patients unable to continue Ig due to AEs, safety concerns (e.g. thromboembolism and heart failure), or relevant comorbidities.

The target population proposed by the Company is based on those who would receive treatment with efgartigimod in clinical practice and reflects an optimised population of the planned UK marketing authorisation. This definition is supported by clinical trial evidence and has been validated by clinical expert opinion, ensuring it is representative of patients who would be treated in NHS practice.¹⁶

In the clinician survey, Igs were highlighted as the mainstay of treatment, with limited use of steroids (8%) and PLEX (5%) in the UK.¹⁷ PLEX remains available as a treatment option within the broader pathway, but clinical experts emphasised that it is rarely used for long-term maintenance due to its invasive nature and associated risks, including infection. Whilst corticosteroids are commonly used as an initiation therapy, they are not typically maintained long-term in patients with refractory or relapsing CIDP due to their side effect profile and limited durability of effect. Clinical experts emphasised the need for an alternative treatment option for patients previously treated with Ig, who experience the greatest treatment-related burden.¹⁷ In addition to addressing the clinical burden associated with Ig treatment, efgartigimod offers practical advantages. The prefilled syringe formulation (5 ml) allows self-administration (20-30 seconds) at home, which will reduce hospital visits and the associated demand on NHS infusion resources.²

Figure 3: Current UK treatment pathway (including efgartigimod)



Abbreviations: CIDP, Chronic inflammatory demyelinating polyneuropathy; CS, Corticosteroids; IVIg, Intravenous immunoglobulin; SCIG, Subcutaneous immunoglobulin; PLEX: Plasma exchange.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

1.4 Equality considerations

No aspects have been identified that could lead to unlawful discrimination or differential access for groups with protected characteristics. While a disproportionate gender distribution is observed in CIDP, this reflects disease epidemiology rather than any discriminatory feature of the proposed scope or technology evaluation process.³⁶ Religion or belief may also be relevant, as some people choose to avoid blood products.¹³⁰ IVIg is made from donated human plasma, so individual patients may decline this option.¹⁰⁸ Efgartigimod is a recombinant, non-plasma-derived medicine and may alleviate such concerns. Care teams should support sensitive discussion and document shared decisions to ensure equitable access to appropriate treatment.

2. Clinical effectiveness

Overview

- The efficacy and safety of efgartigimod in CIDP have been investigated in two key studies: ADHERE (ARGX-113-1802; NCT04281472) and ADHERE+ (ARGX-113-1902; NCT04280718).
- ADHERE was a phase 2, adult-only (≥ 18 years old), multicentre, two treatment stage, randomised-withdrawal, double-blinded, placebo-controlled trial.⁵⁵ ADHERE was event driven, meaning that a clinically meaningful response to efgartigimod was identified in Stage A (open-label), which was followed by Stage B (randomised, placebo controlled), during which the risk of relapse was assessed.⁵⁵
- As the largest CIDP clinical trial to date, ADHERE demonstrates a gold-standard methodology. It incorporated a diagnostic adjudication committee during screening to confirm CIDP diagnosis per European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria, followed by a run-in phase to identify active disease. The two-stage structure—open-label induction followed by randomised withdrawal—enabled robust evaluation of efgartigimod's efficacy and safety in a population with demonstrated treatment responsiveness.
- ADHERE met its primary endpoint of demonstrating a lower risk of relapse in efgartigimod-treated patients compared to placebo. Once-weekly injections of efgartigimod significantly reduced the risk of clinical deterioration (relapse) by 61% at Week 48 compared with placebo, based on time to first adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) score deterioration of ≥ 1 point [hazard ratio (HR) 0.39, 95% CI 0.25 to 0.61, $p < 0.0001$].⁵⁵
- Efgartigimod was effective regardless of CIDP therapy received prior to efgartigimod including treatment with IVIg or SCIg (HR 0.30 [95% CI 0.15 to 0.57] and corticosteroids (HR 0.29 [95% CI 0.11 to 0.81]), and among off-treatment participants (HR 0.72 [95% CI 0.34 to 1.53]).¹³¹
- There are no head-to-head trials comparing maintenance treatment efgartigimod with Igs for patients with CIDP. Therefore, an indirect treatment comparison (ITC) was conducted to compare the efficacy of maintenance treatment with efgartigimod versus Igs in patients with CIDP who were pre-treated with Ig. The ITC results from the MAIC indicate that efgartigimod is associated with a more favourable change in aINCAT than HyQvia during maintenance treatment. The ITC results show that the ADHERE Stage B cohort experiences a mean change in aINCAT from baseline to the end of study visit (EoS) that is [REDACTED] better than the compared Ig cohort.
- In ADHERE, efgartigimod delivered a rapid and meaningful benefit for patients, with evidence of confirmed clinical improvement achieved in 66% patients during the open-label run-in ($n=214/322$; 95% CI 61.0-71.6).⁵⁵ 40% of patients had improved by Week 4, and first improvement was seen as early as nine days after the first dose (median 22.0 days).⁵⁵ These gains were also accompanied by improvements in disability, function and strength across aINCAT, I-RODS, grip strength, MRC sum and TUG scores.⁵⁵ HRQoL, as measured by the EQ-5D-VAS, also improved (+10.7 point increase from baseline) during the open-label run-in phase of the trial.¹³¹

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

- ADHERE+ (NCT04280718) is an open-label, long-term extension study designed to evaluate the safety, tolerability, and efficacy of efgartigimod in adults (≥ 18 years old) with CIDP.^{132,133}
- At an interim data cut-off (16 February 2024), efficacy outcomes demonstrated sustained and further clinically meaningful improvement with long-term efgartigimod treatment.¹³³
- In the ADHERE+ trial patients could become eligible for a substudy where they received one injection every two weeks (q2w schedule).^{134,135} The most recent data (April 2025) from the ADHERE+ substudy showed that [REDACTED] were eligible for the q2w schedule.^{133,134} Of these, [REDACTED] remained on q2w schedule for at least 24 weeks, [REDACTED].¹³⁴
- Overall, efgartigimod was well tolerated in ADHERE, with a safety profile comparable to placebo during the randomised-withdrawal period. No new safety signals were identified; most adverse events (AEs) were mild to moderate, and discontinuations due to AEs were infrequent.
- The safety and tolerability profile of efgartigimod in ADHERE+ remained consistent with that seen in ADHERE, supporting the longer-term use of the treatment in participants with CIDP.¹³³

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify randomised clinical studies for efgartigimod and comparator treatments for the management of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Full details of the methodology and results (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] diagram, included and excluded studies) of the SLR are provided in **Appendix B**.

2.2 List of clinical effectiveness evidence

The key clinical studies supporting efgartigimod for the treatment of CIDP are summarised in Table 5.

Table 5: Clinical effectiveness evidence

Study	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
Study design	Phase 2, multistage, open-label, randomised-withdrawal, double-blind, placebo-controlled trial.	Single-arm, open-label phase 2 extension study with no randomisation.
Population	Adults (≥ 18 years) with definite or probable CIDP (confirmed by expert committee), CDAS score ≥ 2 at screening, and INCAT score ≥ 2 at first run-in visit or stage A baseline. Total enrolled N=322 (Stage A). Patients who demonstrated ECI in Stage A - defined as ≥ 1 point decrease in aINCAT score, ≥ 4 points	Adults (≥ 18 years) with CIDP who either completed Week-48 of Stage B of the ADHERE trial, deteriorated during Stage B, or were offered participation due to early trial termination.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Study	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
	increase in I-RODS, or ≥ 8 kPa increase in grip strength confirmed at two consecutive visits - were eligible to enter Stage B (N=221 randomised).	
Intervention(s)	Subcutaneous administration of efgartigimod (1,000 mg weekly).	Subcutaneous administration of efgartigimod (1,000 mg weekly).
Comparator(s)	Stage A: Single arm (no comparator). Stage B: Placebo (in randomised withdrawal phase).	None
Indicate if study supports application for marketing authorisation	Yes	No
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	Not applicable	Not applicable
Reported outcomes specified in the decision problem	- Physical function change from baseline - Disease progression - Adverse effects of treatment - Health-related quality of life	- Physical function change from baseline - Adverse effects of treatment
All other reported outcomes	- Changes in serum IgG concentrations (total IgG) over time (Stage A and Stage B) - Exploratory endpoints evaluated the following additional patient-reported outcome measures: BPI-SF, TSQM-9, RT-FSS, HADS, and PCIG	Infections by IgG level over time

Source: Allen et al (2024)⁵⁵; Clinical Study Report ARGX-113-1802¹³¹; ADHERE+ PNS publication and clinicaltrials.gov entry^{132,133}

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; BPI-SF: Brief Pain Inventory-Short Form; CDAS: CIDP disease activity status; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ECI: Evidence of clinical improvement; HADS: Hospital Anxiety and Depression Scale; IgG: Immunoglobulin G; I-RODS: Inflammatory Rasch-built Overall Disability Score; INCAT: Inflammatory Neuropathy Cause and Treatment; PCIG: Patient-Centred Impact of GBS Questionnaire; RT-FSS: Rasch-built Fatigue Severity Scale; TSQM-9: Treatment Satisfaction Questionnaire for Medication-9.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

The key methodological characteristics of the included studies are summarised in Table 6.

Table 6: Summary of study methodology

Trial name/number	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
Trial design	Multistage phase 2, open-label, randomised-withdrawal, double-blind, placebo-controlled trial.	Single-arm, open-label phase 2 extension study with no randomisation.
Duration of trial	The total study duration for each participant was up to 80 Weeks, with a maximum cumulative treatment period of 61 Weeks: Participants who were receiving CIDP treatment entered a maximum 12-Week run-in during which intravenous or subcutaneous Ig or corticosteroids were discontinued to identify which participants were likely to have active disease. Participants in the run-in were monitored for clinical change and were required to have ECMD to enter Stage A. Stage A consisted of a treatment period of up to 12 Weeks in which all participants received subcutaneous efgartigimod once weekly until confirmed ECI (an optional additional week for ECI confirmation was allowed in participants who showed ECI only at the last visit in stage A). Stage B (for participants with confirmed ECI) lasted up to 48 Weeks until a total of 88 events (relapses) occurred. Study participation ended when a participant relapsed or completed Week 48 of Stage B.	The ADHERE+ trial commenced September 2020 and runs until April 2027. The trial was structured in repeating 48-Week cycles, with participants monitored throughout each cycle and continuing cycles until study completion. The actual duration for individual participants may vary as it depends on when they enter the study relative to the original ARGX-113-1802 trial completion or early termination.
Settings and locations where data were collected	146 participating clinical sites (academic centres or centres of excellence, hospitals, or smaller private neurology clinics) across 22 countries from different regions in Asia–Pacific, Europe, and North America.	147 sites in 24 countries, including multiple locations in North America, Europe, and Asia. The study distributed sites across major healthcare systems with concentrations in China (18 sites), Japan (16 sites), and several European countries (including 7 UK sites) to ensure broad geographic representation.
	Key inclusion criteria	Key inclusion criteria

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Trial name/number	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
Patient eligibility criteria	Adults (≥18 years) with definite or probable CIDP*, who had: a CDAS score of ≥2 at screening, and an INCAT score of ≥2 (a score of 2 had to be exclusively from leg disability) at the first run-in visit or at Stage. Had never received CIDP treatment or had not received it within 6 months of study entry (“off treatment”) OR receiving CIDP treatment (i.e., corticosteroids, intravenous or subcutaneous immunoglobulin, or both) but willing to discontinue that treatment. Participants who received CIDP treatment within 6 months before study entry or who discontinued treatment were required to have evidence of ECMD[†] in the run-in period, and participants who were off treatment who had documented evidence of recent active disease could directly enter Stage A.	Adults (≥18 years) who completed Week 48 of Stage B in the ARGX-113-1802 trial, deteriorated during Stage B, been offered participation due to early termination, or completed a previous OLE trial cycle.
	Key exclusion criteria The pure sensory CIDP variant Polyneuropathies of other causes A total IgG concentration less than 6 g/L at screening Pregnant, lactating, or planning pregnancy during the trial Significant comorbid disease, recent or planned major surgery, use of prohibited medications/therapies, or any condition that could confound results or pose undue risk	Key exclusion criteria Week-48/end-of-study visit in ADHERE or prior OLE >14 days before OLE start, or >21 days since last IMP dose Pregnant, lactating, or planning pregnancy during the trial Significant comorbid disease, recent or planned major surgery, use of prohibited medications/therapies, or any condition that could confound results or pose undue risk
Trial drugs	Subcutaneously administered. Efgartigimod 1,000 mg once weekly (Stage A and Stage B). Matched placebo containing 2,000 U/ml of PH20 (Stage B only).	Subcutaneously administered. Efgartigimod 1,000 mg once weekly.
Concomitant medication	Efgartigimod is indicated as monotherapy, with no concomitant CIDP therapy permitted during the trial, reflecting its intended use as an alternative to rather than addition to current treatments.	Efgartigimod is approved as a monotherapy and as such no concomitant CIDP therapy was allowed during the trial.
Primary endpoints	Run-in: ECMD to demonstrate active disease before treatment initiation. Stage A: Percentage of participants with confirmed ECI (responders).	Incidence of TEAEs and serious TEAEs by standard of care and PT and incidence of clinically significant laboratory abnormalities.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Trial name/number	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
	ECI was assessed on the same scales on which each participant showed ECMD during run-in: aINCAT, I-RODS, or MGS, so the response measure matched that patient's documented manifestation of disease activity. Stage B: Time to first aINCAT deterioration during Stage B, defined as an increase of ≥ 1 point on the aINCAT score compared with Stage B baseline. Increases of 1 point in aINCAT required confirmation at a second study visit 3-7 days after the original change was documented. Changes of 2 points or more did not require confirmation at a consecutive study visit. Primary endpoints in both Stages A and B were assessed by the site investigator and monitored centrally.	
Other endpoints used in the model/specified in scope	Run-in: No secondary endpoints. Stage A secondary endpoints: Time to initial confirmed ECI during Stage A Time to first improvement (in aINCAT, I-RODS, or grip strength) during Stage A Change from Stage A baseline in aINCAT, I-RODS, MGS, MRC sum and TUG test scores EQ-5D-5L Stage B secondary endpoints: Time to CIDP disease progression in Stage B (from stage B baseline to the first I-RODS score decrease of ≥ 4 points) Proportion of participants with functional improvement compared with Stage B baseline (improvement of ≥ 4 point in I-RODS score) Changes from Stage B baseline in aINCAT, I-RODS, MGS, MRC sum and TUG test scores EQ-5D-5L Safety and tolerability endpoints: Incidence of treatment-emergent adverse events (TEAEs),	Secondary endpoints: Change from baseline over time in aINCAT score, MRC sum score, I-RODS score, MGS, and TUG score Percentage of participants without clinical deterioration over time, defined by aINCAT increase ≥ 1 point compared to baseline Percentage of participants with titres of antidrug antibodies against efgartigimod and the presence of neutralising antibodies against efgartigimod Efgartigimod serum concentrations over time Changes from baseline over time in serum IgG levels (total) Change from baseline over time in EQ-5D-5L, BPI-SF, TSQM-9, RT-FSS, and HADS Percentage of participants with self- or caregiver-administered treatment over time

Trial name/number	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
	discontinuations due to TEAEs, and serious TEAEs in Stages A and B	
Other outcomes of interest	Changes in serum IgG concentrations (total IgG) over time (Stage A and Stage B). Exploratory endpoints evaluated the following additional patient-reported outcome measures: BPI-SF, TSQM-9, RT-FSS, HADS, and PCIG.	Infections by IgG level over time.
Pre-planned subpopulations	Participants were stratified by their aINCAT score during Stage A (i.e., no change in aINCAT score or aINCAT score decrease of ≥ 1 point) and their previous CIDP medication within 6 months before screening (i.e., off treatment, corticosteroid treatment, or intravenous or subcutaneous immunoglobulin treatment).	A pre-planned subpopulation in ADHERE+ was a substudy evaluating less-frequent dosing in stable participants.

Source: Allen et al (2024)⁵⁵, Clinical Study Report ARGX-113-1802¹³¹, ADHERE+ PNS publication and clinicaltrials.gov entry^{132,133}

*A baseline CIDP diagnosis for each participant was confirmed by an independent expert adjudication CIDP confirmation committee of neurologists with extensive clinical and research experience in CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society guidelines (EFNS/PNS) 2010.³⁴

† ECMD was defined as an at least 1-point increase in aINCAT score, at least a 4 point (centile metric) decrease in the I-RODS, or at least an 8 kPa decrease in grip strength.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; BPI-SF: Brief Pain Inventory Short Form; CDAS: CIDP disease activity score; CIDP: Chronic inflammatory demyelinating polyneuropathy; ECI: Evidence of clinical improvement; ECMD: Evidence of clinically meaningful deterioration; EQ-5D-5L: EuroQol 5-Dimension 5-Level Questionnaire; HADS: Hospital Anxiety and Depression Scale; IgG: Immunoglobulin G; INCAT: Inflammatory Neuropathy Cause and Treatment; I-RODS: (24-item) Inflammatory Rasch-built Overall Disability Scale; MGS: Mean grip strength; MRC: Medical Research Council; OLE: Open-label extension; PGIC: Patient Global Impression of Change; PT: Preferred term; RT-FSS: Rasch-transformed Fatigue Severity Scale; TEAE: Treatment-emergent adverse event; TSQM-9: 9-item Treatment Satisfaction Questionnaire for Medication; TUG: Timed Up and Go.

2.3.1. ADHERE

2.3.1.1 Study design

ADHERE was a phase 2, adult-only (≥ 18 years old), multicentre, two treatment stage, randomised-withdrawal, double-blinded, placebo-controlled trial to determine the safety and efficacy of efgartigimod in the management of CIDP.⁵⁵ ADHERE was event driven, meaning that a clinically meaningful response to efgartigimod was identified in Stage A (open-label), which was followed by Stage B (randomised, placebo controlled), during which the risk of relapse was assessed.⁵⁵

The study was designed in consultation with CIDP experts. It used many elements of the PATH study, which was the basis for the approval of IVIg and SCIg (Privigen® and Hizentra®, respectively) for patients with CIDP.¹³¹ These elements include withdrawal of current CIDP treatment and open-label and placebo-controlled withdrawal stages.¹³¹

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

An overview of the study design is presented below in Figure 4.

2.3.1.1.1. Screening and run-in

To strengthen internal validity in a diagnostically challenging condition, screening lasted ≤ 4 Weeks with independent diagnostic adjudication by an external CIDP Confirmation Committee: two neurologists reviewed each anonymised case, with disagreements resolved by the chair.^{55,131} Notably, 28% of screened individuals (179/629) were excluded because their disease was judged not definite or probable CIDP.^{55,131}

A recognised challenge in CIDP is overtreatment, with patients often maintained on therapy while in remission; the protocol therefore included a treatment-free run-in (washout) to verify active disease and avoid exposing stable patients to the study drug.^{55,131} In this design, a placebo-controlled induction phase was not considered feasible because withholding effective therapy in patients with active disease could risk irreversible axonal damage and would likely impair recruitment.^{55,131}

During the run-in of up to 12 Weeks, prior CIDP therapy was stopped; progression to Stage A required objective, clinically meaningful deterioration, defined as adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) score increase ≥ 1 point, I-RODS decrease ≥ 4 points, or grip strength decrease ≥ 8 kPa.^{55,131} Patients off treatment with documented recent active disease could proceed directly to Stage A.^{55,131}

2.3.1.1.2. Stage A design

Following screening and the run-in, eligible participants entered Stage A and received subcutaneous efgartigimod 1,000 mg once weekly for no longer than 12 Weeks.⁵⁵ Participants remained in Stage A until evidence of clinical improvement (ECI) was confirmed after at least four administrations and at two consecutive weekly visits.⁵⁵ If ECI first appeared only at the last scheduled Stage A visit, an optional additional Week 12 visit with an injection was permitted to obtain the second confirmatory assessment. Participants with confirmed ECI were then randomised 1:1 into Stage B.⁵⁵

2.3.1.1.3. How ECI was defined and assessed

ECI was operationalised on a patient-specific basis using the same scales on which ECMD had been documented during run-in:

- For participants who skipped run-in or deteriorated, ECI was ≥ 1 -point aINCAT improvement from the Stage A baseline.⁵⁵
- For participants with no aINCAT change during run-in but deterioration on I-RODS and/or mean grip strength (MGS), ECI was ≥ 4 -point I-RODS increase and/or ≥ 8 kPa mean grip-strength increase, respectively (ECI could also be met by ≥ 1 -point aINCAT improvement).⁵⁵

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

This scale-matching ensured that response was measured in the same domains that evidenced active disease for each individual.⁵⁵

2.3.1.1.4. Stage B design

Participants with confirmed ECI progressed to Stage B, a double blind, randomised withdrawal phase (1:1 weekly subcutaneous efgartigimod 1,000 mg vs placebo) that continued for no more than 48 Weeks or until 88 relapses occurred; participation ended at relapse or Week 48.⁵⁵ Considering Stage A (≤ 12 Weeks), which allowed an optional additional Week 12 visit with an injection to confirm ECI when improvement first appeared only at the last scheduled Stage A visit, and Stage B (≤ 48 Weeks), total on study exposure to investigational product was ≤ 60 Weeks.⁵⁵

Participants in either treatment arm (efgartigimod or placebo) who experienced clinical deterioration (relapse) as defined by aINCAT score increase ≥ 1 point or who completed Week 48 in the randomised stage were withdrawn from the study and could continue to receive efgartigimod treatment in the open-label extension study (ADHERE+); of those eligible to roll over, 99% entered ADHERE+. ^{55,133} Additionally, participants who were still ongoing, in Stage A, B or the run-in phase at the time the eighty-eighth relapse event occurred across all participants in Stage B (the pre-specified threshold for primary endpoint analysis) were eligible to enter the open-label extension.⁵⁵ For those participants who did not continue to the open-label extension study, the follow-up period was 28 days after the final treatment dose.¹³¹

2.3.1.1.5. ADHERE Study design rationale

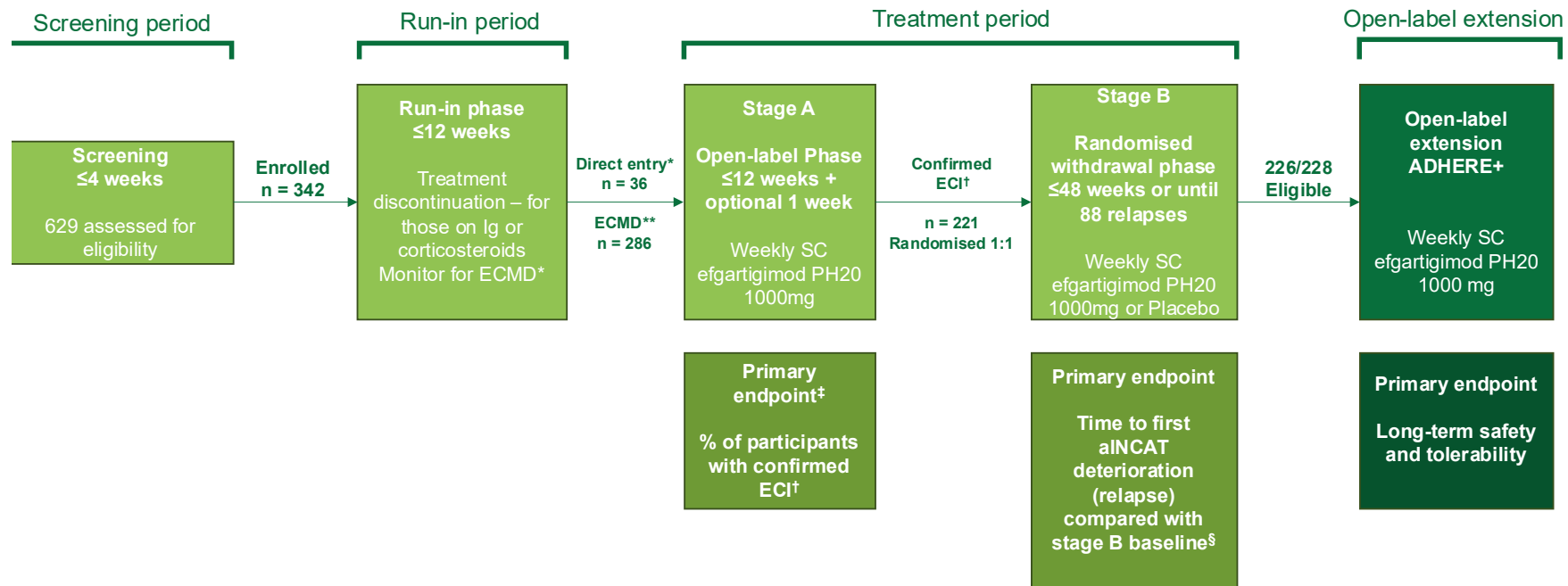
Unlike traditional parallel-group studies, ADHERE utilises an event-driven, placebo-controlled, randomised withdrawal design.⁵⁵ ADHERE is the largest randomised controlled CIDP trial to date.⁵⁵ Participants first demonstrated evidence of clinically meaningful deterioration during withdrawal of standard therapy, then received open-label subcutaneous efgartigimod in Stage A.⁵⁵ Only those with confirmed evidence of clinical improvement, documented on the same scale or scales used for deterioration and confirmed after at least four doses at two consecutive weekly visits, were randomised 1:1 to efgartigimod or placebo in Stage B.⁵⁵ Stage B continued for no more than 48 Weeks or until 88 relapses occurred, and participation ended at relapse or Week 48.⁵⁵ This approach is ethically robust because placebo is not used following the period of active deterioration and efficacy is demonstrated in a population with confirmed responsiveness, in keeping with the trial's conduct under international ethical guidelines.⁵⁵

This design was selected in consultation with regulatory agencies to reflect the fluctuating and heterogeneous nature of CIDP, where periods of relapse and remission make fixed-duration parallel-group studies less sensitive and ethically challenging.⁵⁵ The event-driven, randomised withdrawal approach ensures that efficacy is demonstrated through the prevention of clinically meaningful relapse in patients with confirmed active disease and established treatment responsiveness. Importantly, in UK practice, Ig maintained patients are routinely assessed for disease activity through regular trials of cessation.⁹ In ADHERE,

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

participants were required to demonstrate active disease following Ig withdrawal and subsequent improvement with efgartigimod prior to randomisation, therefore the study population closely reflects the Ig-pretreated patients for whom efgartigimod is intended in this submission.⁵⁵ This provides a rigorous and patient-centred evaluation of durability of effect, which is directly relevant to long-term treatment decisions and aligns with regulator guidance for CIDP trials. A summary of the assessment scales used for ADHERE's endpoints relating to physical function and disease progression is presented in **Appendix J**.

Figure 4: ADHERE and ADHERE+ – study design



Source: Allen et al (2024)⁵⁵

*Off-treatment participants (treatment-naïve or no CIDP treatment within six months) with documented aINCAT worsening in the three months before screening versus a prior score within six months entered Stage A directly.

** ECMD was defined as an aINCAT increase of ≥ 1 points, an I-RODS decrease of ≥ 4 points, or a grip strength decrease of ≥ 8 kPa.

† ECI was defined as a clinical improvement on the parameters that the participant worsened in during run-in (≥ 4 -point increase in I-RODS and/or ≥ 8 -kPa increase in MGS) or clinical improvement (≥ 1 -point decrease) in INCAT. ECI was confirmed after these criteria were met after 4 injections and 2 consecutive visits.

‡ The primary endpoint was assessed once 88 total relapses or events were achieved in Stage B and was based on the HR for the time to first aINCAT deterioration (i.e., relapse).

§ aINCAT deterioration was defined as an increase of ≥ 1 points in aINCAT score compared to Stage B baseline, which was confirmed at a consecutive visit after the first 1-point increase in aINCAT or not confirmed for participants with ≥ 2 -point increase in aINCAT compared with Stage B baseline.

Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; ECI, Evidence of Clinical Improvement; ECMD, Evidence of Clinically Meaningful Deterioration; Ig, Immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-Built Overall Disability Score; MGS, Mean grip strength; SC, Subcutaneous.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

2.3.2 ADHERE+

2.3.2.1 Study design

ADHERE+ (NCT04280718) is an open-label, long-term extension study designed to evaluate the safety, tolerability, and efficacy of efgartigimod in adults (≥ 18 years) with CIDP.^{132,133} Participants were eligible to enrol if they had completed Week 48 of the double-blind Stage B of ADHERE, experienced clinical deterioration during Stage B, or discontinued early once sufficient events for the primary endpoint in ADHERE had been reached and the trial had concluded.⁵⁵ Following a screening period of up to 4 Weeks, participants entered ADHERE+ and received weekly injections of 1,000 mg efgartigimod; of those eligible to roll over from ADHERE, 99% entered ADHERE+.^{55,133} Treatment was continued for up to two years, with all participants receiving active therapy in an open-label setting.^{132,133} The primary objective of ADHERE+ is to assess the long-term safety and tolerability of efgartigimod, while secondary objectives include the evaluation of efficacy outcomes and patient-reported measures over extended exposure.^{132,133}

In ADHERE+, patients who achieve stable disease control with weekly dosing could also enter an optional dosing substudy to evaluate the efficacy of maintenance with bi-weekly (q2w) administration, providing evidence to support potential dosing flexibility in long-term use.¹³⁴ Patients were eligible for the substudy if they had received at least 24 Weeks of the q1w schedule in ADHERE+, and had been stable between the last two scheduled visits (i.e., approximately 12 Weeks).¹³⁴ Transition to bi-weekly dosing is protocol-directed following prespecified stability criteria (no deterioration on aINCAT, I-RODS or grip strength across consecutive assessments), with continued monitoring to confirm maintenance of response.¹³⁴ After starting the q2w schedule, patients were allowed to return to the q1w schedule if they showed signs of clinical deterioration on aINCAT, I-RODS or MGS.¹³⁴

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Statistical methods used in the ADHERE and ADHERE+ trials are summarised in Table 7.

Table 7: ADHERE – Summary of statistical analyses

Trial name/number	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
Hypothesis objective	A formal hypothesis was prespecified to evaluate efficacy: Null hypothesis: the event rate of efgartigimod compared with placebo is 1 (i.e., HR=1) Alternative hypothesis: the event rate of efgartigimod compared with placebo is $\neq 1$ (i.e., HR $\neq 1$).	No formal hypothesis testing will be conducted. If appropriate, 2-sided 95% CIs may be presented.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Trial name/number	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
Statistical analysis	The Stage A primary endpoint was summarised with an exact Clopper–Pearson two-sided test with 95% CI in the safety population. A prespecified sensitivity analysis of the Stage A primary endpoint was performed excluding participants who were ongoing in Stage A at the time of study completion, after the 88th relapse had occurred. The percentage of participants with confirmed ECI by previous CIDP treatment and time to initial confirmed ECI are presented descriptively. The Stage B primary endpoint was analysed via Cox regression modelling in the mITT population. Participants who completed the study at Week 48 without relapse or withdrew early for any other reason (including completion of the trial) were censored at the last aINCAT assessment. The model was stratified for randomisation stratification factors (previous CIDP medication and aINCAT score during Stage A), with a fixed-effect term included as a covariate for randomised treatment. Secondary endpoints in Stage B: The time to CIDP disease progression during Stage B was analysed in the same way as the primary endpoint. The percentage of participants with improved functional level, measured by the I-RODS score during Stage B, was analysed by exact logistic regression, with a fixed effect term for randomised treatment and I-RODS score at the end of Stage A included as a covariate. The odds ratio (OR)	Adverse events will be classified using the latest version of the Medical Dictionary for Regulatory Activities classification system. Adverse events reported from the first dose of efgartigimod until 30 days after the last dose of efgartigimod will be considered as treatment emergent adverse events and will be summarised descriptively. Data from secondary endpoints will be presented using summary statistics.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Trial name/number	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
	was obtained from an exact logistic regression model with treatment as a fixed effect along with the associated 95% CI and two-sided p value; this analysis was done overall and also stratified by previous CIDP therapy and aINCAT score during stage A. Exact Clopper–Pearson two-sided 95% CI limits were calculated for the proportion of participants with disease progression in each arm. Changes from Stage B baseline in aINCAT score, I-RODS score, MGS, and other secondary endpoints in Stage B were analysed descriptively. This study was not powered to detect differences between previous CIDP treatment subpopulations; therefore, no formal statistical analyses were conducted.	
Sample size, power calculation	ADHERE was an event-driven trial, which finished when 88 relapses (events) were reached. Based on a relapse rate of efgartigimod versus placebo for the Stage B primary endpoint of 0.50 (hazard ratio [HR] 0.50), 88 relapses were required to provide 90% power at a one-sided α level of 0.025 with a log-rank test. To obtain a sufficient number of patients randomly assigned into Stage B, up to 360 patients were required to be enrolled into Stage A. Patients continued to be randomly assigned into Stage B until 88 events were observed.	Eligible patients who rolled over from the ADHERE trial will be included.
Interim analyses	A prespecified interim analysis was conducted after the first 30 participants completed Stage A, to inform a go/no-go decision to continue the study.	Not applicable.
Data management, patient withdrawals	eCRF data were captured via data entry by site staff in a database system overseen by the dedicated CRO. Data quality checks were applied using manual and electronic verification	

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Trial name/number	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
	methods. An audit trail was maintained to support data query resolution and any modifications to the data.	

Source: Allen et al (2024)⁵⁵; Clinical Study Report ARGX-113-1802¹³¹, ADHERE+ PNS publication and clinicaltrials.gov entry^{132,133}

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyneuropathy; ECI: Evidence of clinical improvement; I-RODS: (24-item) Inflammatory Rasch-built Overall Disability Scale; MGS: Mean grip strength; mITT: Modified intent-to-treat; OR: Odds ratio.

2.4.1 ADHERE

2.4.1.1 Analysis sets

The main patient data sets analysed in ADHERE are described in Table 8.

Table 8: ADHERE – Analysis sets

Analysis set	Definition	Number of patients
mITT	All randomly assigned participants who received at least one dose or part of a dose of the investigational medicinal product in Stage B.	221 (efgartigimod, 111; Placebo, 110)
PP	Participants from the mITT analysis without major protocol deviations.	184 (efgartigimod, 96; Placebo, 88)
Safety	The safety populations for Stages A and B included all participants who received at least one dose or part of a dose of the investigational medicinal product in the respective stage.	Stage A, 322 Stage B, 221

Source: Allen et al (2024)⁵⁵

Abbreviations: mITT: Modified Intent-to-Treat; PP: Per protocol.

2.4.1.2 Patient disposition

Patient disposition (CONSORT diagram) is included within **Appendix B**.

Between 15 April 2020, and 11 May 2023, 629 participants were screened, of whom 342 met the inclusion criteria. Of the 342 patients enrolled, 306 entered the run-in phase, of whom 20 were withdrawn. Of the 322 participants who entered Stage A (36 directly and 286 after the run-in period), 221 were randomised and treated in Stage B (n=111 with efgartigimod; n=110 with placebo). A total of 226 (99%) of 228 of the eligible participants entered the open-label extension (ADHERE+).⁵⁵

In the run-in, discontinuations were uncommon and were driven mainly by failure to demonstrate evidence of clinically meaningful deterioration (ECMD) after treatment suspension (n=7) or by participants still being on study when the event-driven stop occurred at the 88th relapse (n=7); additional discontinuations reflected administrative or protocol

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

reasons (participant withdrawal, investigator or sponsor decision, or prohibited medication; n=6).⁵⁵ In Stage A, the principal reasons for discontinuation were insufficient efficacy (36 in total: 28 before the end of Stage A and 8 at the end), participants ongoing at the 88th relapse (n=22), AEs (n=20), and participant withdrawal (n=11).⁵⁵ Two deaths occurred in Stage A: one due to cardiac arrest following COVID-19 (not related) and one due to CIDP worsening (unlikely related), and other discontinuations reflected categories such as prohibited medications, loss to follow-up, non-compliance, protocol deviation, or investigator/sponsor decision (n=11).⁵⁵ In Stage B, most discontinuations in both arms reflected the event-driven stop (participants still on study when the 88th relapse was reached); withdrawals and adverse-event discontinuations were infrequent, and one death occurred in the placebo arm due to pneumonia.⁵⁵

2.4.2 ADHERE+

2.4.2.1 Analysis sets

The safety and modified intent-to-treat (mITT) population consists of all participants who rolled over from ADHERE and who received at least one dose of open-label efgartigimod in ADHERE+.

Participants were classified according to the treatment they received during Stage B of ADHERE, i.e. efgartigimod or placebo.

2.4.2.2 Patient disposition

Not applicable as ADHERE+ is ongoing at the time of submission, with an estimated completion date of April 2027.¹³²

2.5. Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment and risk of bias is included in **Appendix B**.

2.6. Clinical effectiveness results of the relevant studies

2.6.1. ADHERE

2.6.1.1. Patient baseline characteristics

Participant demographics and baseline characteristics were similar between Stages A and B, as shown in Table 9 below. Additionally, in Stage B, the numbers of participants randomised to the placebo and efgartigimod treatment groups were comparable. In Stage A, a total of 63 (20%) participants had received previous treatment with corticosteroids, 165 (51%) participants had received previous treatment with intravenous or subcutaneous immunoglobulin, and 94 (29%) were considered to be off treatment. Of the 94 participants who were off treatment prior to entering the study, 34 (36%) had no history of receiving treatment with corticosteroids or intravenous or SCIg for CIDP at any time before starting efgartigimod.⁵⁵

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 9: ADHERE – Baseline characteristics (safety population)

	Stage A: efgartigimod N=322 n (%)	Stage B*	
		efgartigimod n=111 n (%)	Placebo n=110 n (%)
Mean age, years (SD)	54.0 (13.92)	54.5 (13.18)	51.3 (14.47)
Sex, male	208 (65%)	73 (66%)	69 (63%)
Race			
Asian	89 (28%)	33 (30%)	34 (31%)
Black or African American	4 (1%)	1 (1%)	1 (1%)
White	211 (66%)	73 (66%)	71 (65%)
Other	7 (2%)	2 (2%)	1 (1%)
Not reported	11 (3%)	3 (3%)	4 (4%)
Ethnicity			
Hispanic or Latino	23 (7%)	9 (8%)	4 (4%)
Not Hispanic or Latino	288 (89%)	99 (89%)	102 (93%)
Not reported	11 (3%)	3 (3%)	4 (4%)
Time since diagnosis, years			
Mean (SD)	4.9 (6.09)	3.7 (4.40)	3.8 (4.68)
Median (IQR)	2.8 (0.9–6.4)	2.1 (0.6–5.3)	2.2 (0.8–4.8)
Typical CIDP	268 (83%)	97 (87%)	95 (86%)
Atypical CIDP	54 (17%)	14 (13%)	15 (14%)
Asymmetric	29 (9%)	6 (5%)	7 (6%)
Distal	20 (6%)	7 (6%)	7 (6%)
Pure motor	5 (2%)	1 (1%)	1 (1%)
Total INCAT score	4.6 (1.67)	3.1 (1.51)	3.3 (1.57)
I-RODS score	40.1 (14.67)	53.6 (17.91)	51.2 (15.37)
Grip strength, kPa			
Dominant hand	38.5 (24.18)	54.9 (23.64)	58.0 (25.09)
Non-dominant hand	39.0 (24.71)	55.4 (28.29)	56.7 (24.80)
CIDP treatment within the past 6 months†			
Corticosteroids	63 (20%)	24 (22%)	23 (21%)
Immunoglobulins (IV or SC)	165 (51%)	48 (43%)	48 (44%)
Off treatment	94 (29%)	39 (35%)	39 (36%)
CDAS score			
2	6 (2%)	1 (1%)	0
3	96 (30%)	28 (25%)	29 (26%)
4	23 (7%)	8 (7%)	5 (5%)
5	197 (61%)	74 (67%)	76 (69%)

Source: Allen et al (2024)⁵⁵

Data are mean (SD), median (IQR), or n (%). The Stage A and Stage B safety populations included all participants who received at least one dose of the investigational medicinal product in Stage A or part of a dose in Stage B.

* Most baseline characteristics in Stage B refer to Stage A baseline, except for INCAT, I-RODS, and grip strength.

† Stage B baseline values are based on randomised stratification factors.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Abbreviations: CDAS: CIDP disease activity status; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; INCAT: Inflammatory Neuropathy Cause and Treatment; I-RODS: Inflammatory Rasch-built Overall Disability Scale; IV: Intravenous; SC: Subcutaneous.

2.6.1.2. Stage A results (open-label period)

2.6.1.2.1 Stage A primary endpoint efficacy results

In Stage A of the trial, efgartigimod was shown to be clinically effective as 66% (n=214/322, 95% confidence interval [CI]: 61.0-71.6) of participants demonstrated ECI.⁵⁵

The number and percentage of confirmed ECI responders by prior CIDP therapy subpopulation at screening are presented in Table 10.

Table 10: ADHERE Stage A – confirmed ECI responders (primary endpoint) by prior CIDP therapy (Stage A safety analysis set)

	Any prior therapy N=322 n (%)	Corticosteroids n=63 n (%)	IVIg or SCIg n=165 n (%)	Off treatment n=94 n (%)
Number of participants with confirmed ECI	214 (66)	49 (78)	97 (59)	68 (72)
95% CI	61.0-71.6	65.5-87.3	50.9-66.4	62.2-81.1
Number of participants without confirmed ECI	108 (34)	14 (22)	68 (41)	26 (28)
Completed Stage A treatment without confirmed ECI	21 (7)	2 (3)	8 (5)	11 (12)
Discontinued treatment in Stage A	87 (27)	12 (19)	60 (36)	15 (16)
Ongoing in Stage A at 88th relapse event in Stage B	18 (6)	4 (6)	7 (4)	7 (7)
Discontinued early for other reasons	69 (21)	8 (13)	53 (32)	8 (9)

Source: Allen et al (2024)⁵⁵; Clinical Study Report ARGX-113-1802¹³¹

Abbreviations: CI: Confidence interval; ECI: Evidence of clinical improvement; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin.

A pre-specified sensitivity analysis was conducted to validate the primary endpoint results by excluding 18 participants who were ongoing in Stage A at study completion (after the 88th relapse in Stage B).¹³¹ Based on this analysis, a higher percentage (70% (n=214/304) [95% CI: 64.9–75.5) of participants had confirmed ECI.¹³¹ The number and percentage of confirmed ECI responders (sensitivity analysis) by prior CIDP therapy subpopulation at screening are presented in Table 11.

Table 11: ADHERE Stage A – confirmed ECI responders (primary endpoint) by prior CIDP therapy in a sensitivity analysis (Stage A safety analysis set excluding participants ongoing in Stage A at the 88th relapse event in Stage B)

	Any prior therapy n=304 n (%)	Corticosteroids n=59 n (%)	IVIg or SCIg n=158 n (%)	Off treatment n=87 n (%)
Number of participants with confirmed ECI	214 (70)	49 (83)	97 (61)	68 (78)
95% CI	64.9-75.5	71.0-91.6	53.3-69.0	68.0-86.3
Number of participants without confirmed ECI	90 (30)	10 (17)	61 (39)	19 (22)
Completed Stage A treatment without confirmed ECI	21 (7)	2 (3.4)	8 (5)	11 (13)
Discontinued treatment in Stage A	69 (23)	8 (14)	53 (34)	8 (9)
Discontinued early for other reasons	69 (23)	8 (14)	53 (34)	8 (9)

Source: Clinical Study Report ARGX-113-1802¹³¹

Abbreviations: CI: Confidence interval; ECI: Evidence of clinical improvement; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin.

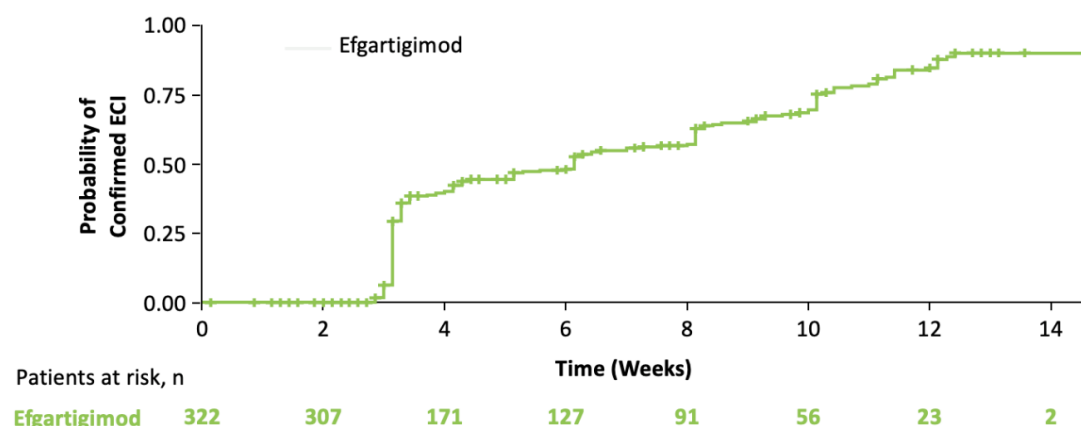
2.6.1.2.2 Stage A secondary endpoint efficacy results

The median time to initial confirmed ECI was 43.0 (95% CI: 31.0 – 51.0) days.¹³¹ By Week 4 (the earliest time point at which the ECI criteria could be met), 40% of participants (n=128/322) treated with efgartigimod had ECI, indicating an early onset of clinical activity.⁵⁵

In Stage A, following efgartigimod treatment (when participants achieved confirmed ECI or reached the maximum 12-Week treatment period), the mean aINCAT score, mean MGS score, and mean I-RODS score all saw improvements from baseline.¹³¹ Mean scores for the EuroQol 5-Dimension 5-Level Visual Analogue Scale (EQ-5D-5L-VAS) also saw improvement from baseline (to confirmed ECI or end of the study period).⁵⁵

A Kaplan–Meier analysis estimated that time to first improvement on any of aINCAT, I-RODS, or grip strength scores in the 25th percentile was 9.0 days (95% CI: 8.0 – 9.0), which can be attributed to the first dose of efgartigimod; the median estimate was 22.0 days (15.0-23.0) (Figure 5).⁵⁵

Figure 5: ADHERE Stage A – Kaplan–Meier plot of the time to initial confirmed ECI in participants treated with open-label efgartigimod (Stage A safety analysis set)



Source: Siddiqi et al (2024)¹³⁶

Abbreviations: ECI: Evidence of clinical improvement.

The change from Stage A baseline to Stage A last assessment in secondary endpoints is summarised in Table 12.

Table 12: ADHERE Stage A – change from Stage A baseline in aINCAT score, I-RODS score, MGS score, MRC sum score, TUG test score and EQ-5D-5L VAS at Stage A last assessment (Stage A safety analysis set)

Secondary endpoint	Efgartigimod (N=322)
aINCAT	
N	██████
Mean (SD)	-0.9 (1.71)
Median (min, max)	██████
I-RODS score	
N	██████
Mean (SD)	7.7 (15.48)
Median (min, max)	██████
MGS (dominant hand), kPa	
N	██████
Mean (SD)	12.3 (18.68)
Median (min, max)	██████
MGS (non-dominant hand), kPa	
N	██████
Mean (SD)	11.2 (21.12)
Median (min, max)	██████
MRC sum score (SD)	██████

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Secondary endpoint	Efgartigimod (N=322)
TUG test score (SD)	██████
EQ-5D-5L VAS	
n	██████
Change from baseline	10.7 (Standard error: 22.3)

Source: Clinical Study Report ARGX-113-1802¹³¹

Note: Data are mean (SD).

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; EQ-5D-5L VAS: 5-Level European Quality of Life 5 Dimensions Visual Analogue Scale; I-RODS: (24-item) Inflammatory Rasch-built Overall Disability Scale; MGS: Mean grip strength; MRC: Medical Research Council; SD: Standard deviation; SE: Standard error; TUG: Timed Up and Go.

The change from Stage A baseline to Stage A last assessment in secondary endpoints, stratified by ECI response is summarised in Table 13.

Table 13: ADHERE Stage A – change from Stage A baseline in aINCAT score, I-RODS score and MGS score at Stage A last assessment (Stage A safety analysis set, post-hoc analysis)

Secondary endpoint	Efgartigimod (N=322)	
	ECI responders	ECI Nonresponders
aINCAT		
n	██████	██████
Mean (SD)	-1.4 (1.54)	0.2 (1.49)
Median (min, max)	██████	██████
I-RODS score		
n	██████	██████
Mean (SD)	12.0 (14.62)	-0.7
Median (min, max)	██████	██████
MGS (dominant hand), kPa		
n	██████	██████
Mean (SD)	17.9 (16.98)	0.8 (16.71)
Median (min, max)	██████	██████
MGS (non-dominant hand), kPa		
n	██████	██████
Mean (SD)	17.2 (19.34)	-1.3 (19.15)
Median (min, max)	██████	██████

Source: Clinical Study Report ARGX-113-1802¹³¹

Note: Data are mean (SD).

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; I-RODS: (24-item) Inflammatory Rasch-built Overall Disability Scale; MGS: Mean grip strength; SD: Standard deviation.

2.6.1.2.3 Stage A exploratory endpoint efficacy results

Pain severity and intensity (Brief Pain Inventory–Short Form [BPI-SF]), fatigue (the Rasch-transformed Fatigue Severity Scale [RT-FSS]), and anxiety and depression (Hospital Anxiety

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

and Depression Scale [HADS]) were reduced with efgartigimod treatment. Global satisfaction with CIDP treatment (9-item Treatment Satisfaction Questionnaire for Medication [TSQM-9]) was also improved, as was the percentage of participants reporting overall improvement (Patient's Global Impression of Change [PGIC]).

The significant positive effect of efgartigimod on HRQoL EuroQol 5-Dimension (EQ-5D) domains of pain, mental health, and fatigue during Stage A was confirmed in a post-hoc analysis. There was a significant reduction in pain severity (-0.7, SD 2.0, $p < 0.0001$) and interference (-1.0, SD 2.6, $p < 0.0001$) following efgartigimod treatment. A reduction in HADS anxiety (-1.3, SD 3.1, $p < 0.0001$) and depression (0.8, SD 3.1, $p < 0.0001$) scores and a reduction in the Rasch-transformed Fatigue Severity Scale (RT-FSS) score (-2.6, SD 5.0, $p < 0.0001$) were also demonstrated following treatment with efgartigimod.¹³⁷

Treatment effects of efgartigimod on the exploratory endpoints are presented in Table 14.

Table 14: ADHERE Stage A – change from Stage A baseline in exploratory endpoints in participants treated with open-label efgartigimod (Stage A safety analysis set)

Exploratory endpoint	Result
BPI-SF	Mean (SE) change from baseline to the last Stage A assessment: Pain interference: -1.0 (0.2) Pain severity: -0.7 (0.1)
TSQM-9	Mean (SE) global satisfaction at baseline vs last Stage A assessment: ██████ vs ██████
RT-FSS	Mean (SE) change from Stage A baseline to the last Stage A assessment: -2.6 (0.3)
HADS	Mean (SE) change from Stage A baseline to the last Stage A assessment: -0.8 (0.2)
PGIC	Percentage of participants reporting improvement at week 1 vs last assessment at Stage A “very much better” ██████ “much better” ██████ “a little better” ██████

Source: Clinical Study Report ARGX-113-1802¹³¹

Abbreviations: BPI-SF: Brief Pain Inventory–Short Form; HADS: Hospital Anxiety and Depression Scale; PGIC: Patient Global Impression of Change; RT-FSS: Rasch-transformed Fatigue Severity Scale; SE: Standard error; TSQM-9: (9-item) Treatment Satisfaction Questionnaire for Medication.

2.6.1.3 Stage B results (double blinded, randomised)

2.6.1.3.1 Stage B primary endpoint efficacy results

ADHERE met its primary endpoint of demonstrating a lower risk of relapse in efgartigimod-treated patients compared to placebo. Once-weekly injections of efgartigimod significantly reduced the risk of clinical deterioration (relapse) by 61% at Week 48 compared with placebo, based on time to first aINCAT score deterioration of ≥ 1 point [hazard ratio (HR) 0.39, 95% CI 0.25 to 0.61, $p < 0.0001$; Figure 6).⁵⁵ Efgartigimod was effective regardless of CIDP therapy received prior to efgartigimod, including treatment with IVIg or SCIg (HR 0.30

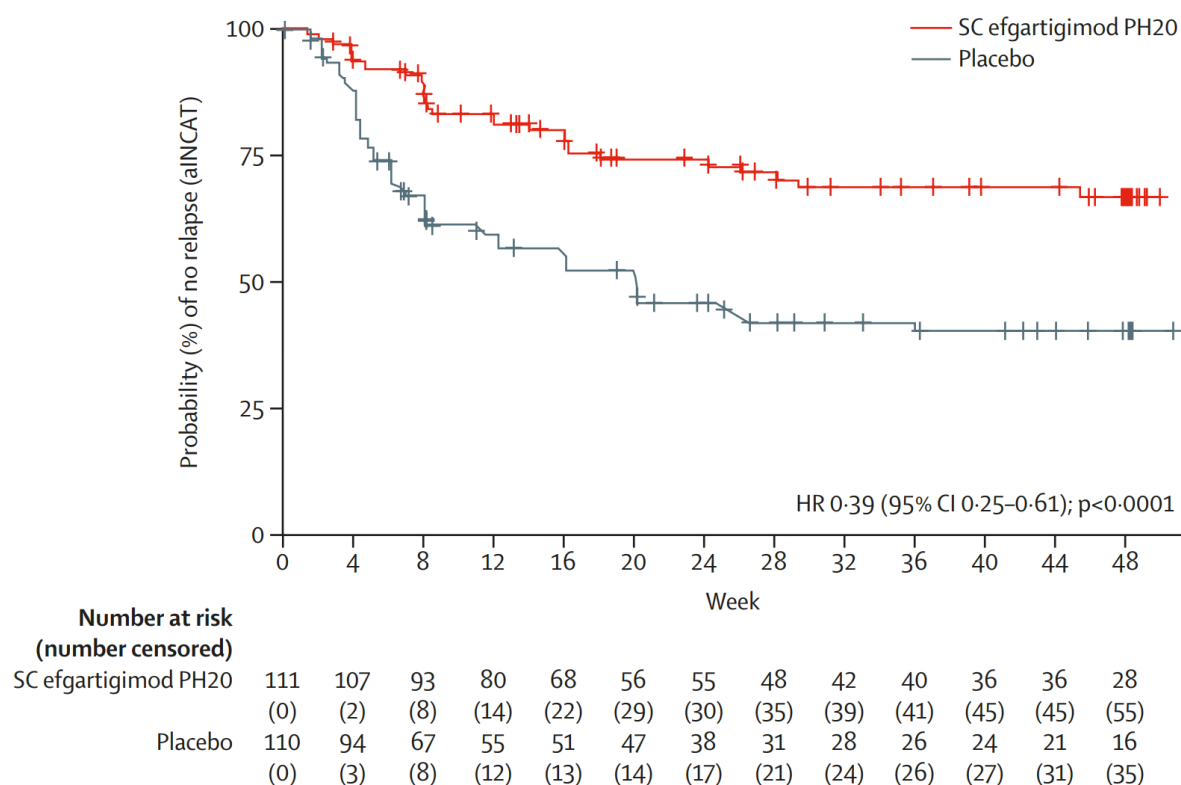
Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

[95% CI 0.15 to 0.57] and corticosteroids (HR 0.29 [95% CI 0.11 to 0.81]), and among off-treatment participants (HR 0.72 [95% CI 0.34 to 1.53]).¹³¹

At the 88th clinical deterioration event, fewer relapses occurred in participants in the efgartigimod arm (27.9%) compared to the placebo arm (53.6%).⁵⁵ Importantly, there was a rapid separation of the Kaplan–Meier curves for the risk of relapse for efgartigimod-treated participants and placebo-treated participants beginning at Week 4, which was sustained through Week 48.⁵⁵

The median (95% CI) time to clinical deterioration could not be calculated for the efgartigimod treatment arm because less than 50% of the participants had clinically deteriorated.⁵⁵ The median (95% CI) for time to deterioration in the placebo arm was 140.0 (75.0 to not calculated [NC]) days.⁵⁵ A lower relapse rate was achieved in participants treated with efgartigimod compared to placebo at Week 48 [REDACTED].¹³¹

Figure 6: ADHERE Stage B – Kaplan–Meier analysis of the relative risk of CIDP relapse based on time to first aINCAT deterioration in participants treated with efgartigimod or placebo (mITT analysis set)



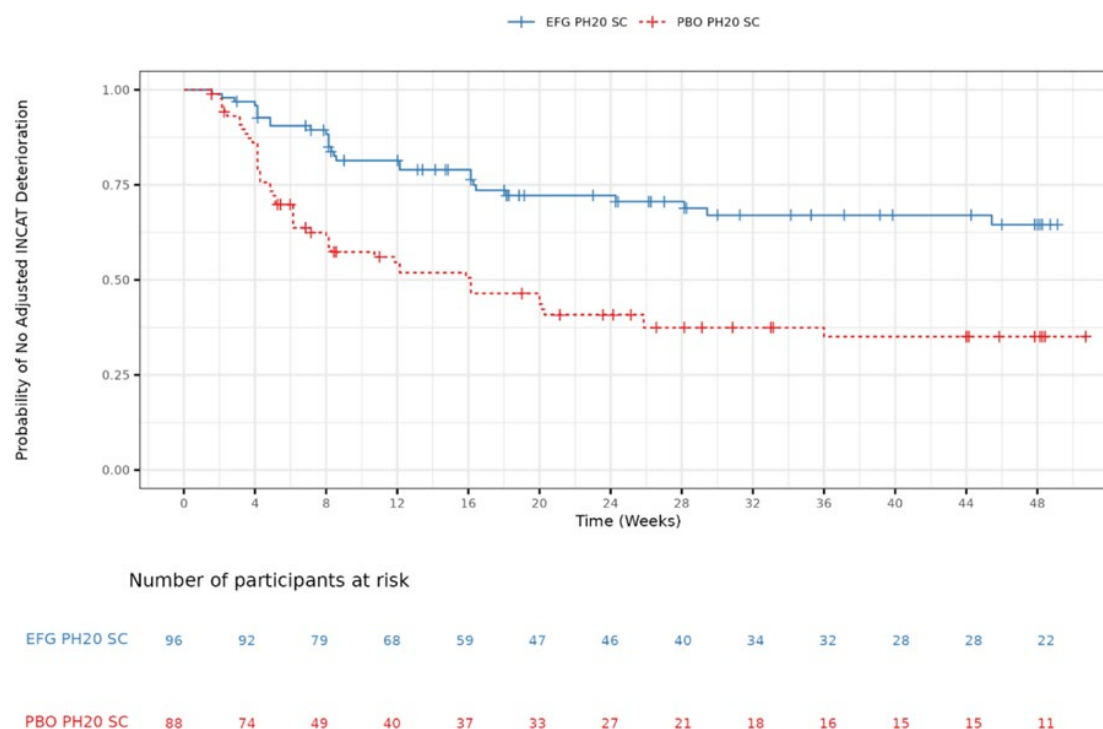
Source: Allen et al (2024)⁵⁵

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; CI: Confidence interval; CIDP: Chronic inflammatory demyelinating neuropathy; HR: Hazard ratio; mITT: Modified intent-to-treat; SC: Subcutaneous.

Using the per protocol analysis set, the HR for the time to clinical deterioration comparing efgartigimod with placebo was estimated. The Kaplan–Meier analysis for the time to clinical deterioration for the per protocol analysis set (Figure 7) was consistent with the primary Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

analysis and demonstrated that the participants in the efgartigimod arm had a lower probability of clinical deterioration than the participants in the placebo arm.

Figure 7: ADHERE Stage B – Kaplan–Meier plot of the time to clinical deterioration, sensitivity analysis (per protocol analysis set)



Source: Clinical Study Report ARGX-113-1802¹³¹

Notes: The time to clinical deterioration is defined as the time in days from the first efgartigimod or placebo administration in Stage B to the first occurrence of either an increase in aINCAT score of ≥ 1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥ 2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first efgartigimod or placebo administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment. Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; SC: Subcutaneous.

2.6.1.3.2 Stage B secondary endpoint efficacy results

The rate of CIDP disease progression, as measured by I-RODS deterioration, was lower in the efgartigimod arm (46% lower risk of I-RODS deterioration) than in the placebo arm (HR 0.54, 95% CI 0.35 to 0.81, nominal $p=0.0034$).⁵⁵ Kaplan–Meier analysis for time to I-RODS deterioration also indicated that participants in the efgartigimod arm had a lower probability of disease progression than participants in the placebo arm.⁵⁵

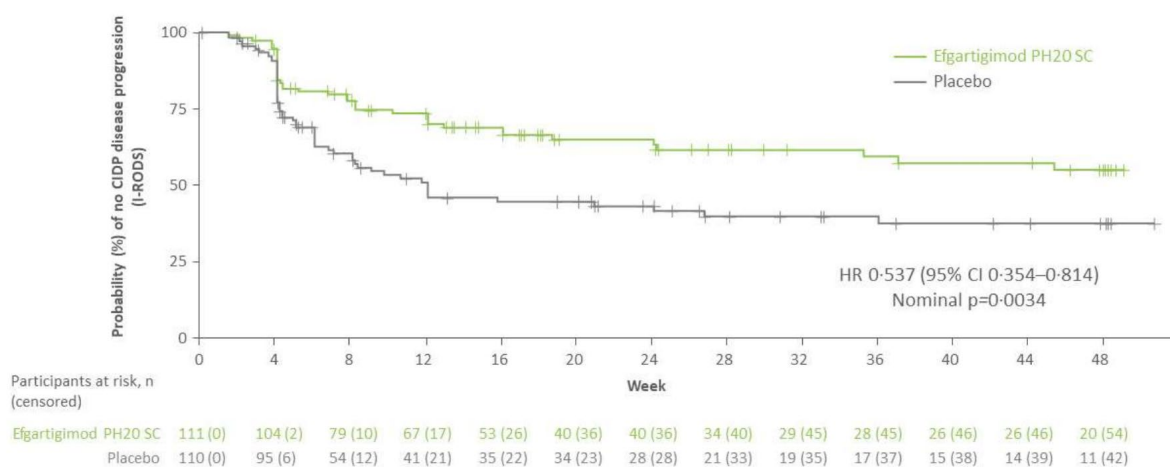
Efgartigimod's benefits extended beyond disease stabilisation. A numerically higher percentage of participants in the efgartigimod arm had improved functional levels, with 45% ($n=50/111$) in the efgartigimod arm achieving meaningful I-RODS improvements (i.e., participants had at least one Stage B I-RODS assessment with an increase of ≥ 4 points) versus 36% in the placebo arm ($n=40/110$).⁵⁵

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Secondary endpoint results consistently showed that while efgartigimod-treated patients maintained or further improved their clinical status across multiple functional measures (including aINCAT, grip strength, MRC sum scores, and TUG test) and quality of life (EuroQol 5-Dimension 5-Level [EQ-5D-5L]), those on placebo experienced deterioration.⁵⁵

The Kaplan–Meier analysis for the time to I-RODS deterioration (Figure 8) indicated that the participants in the efgartigimod arm had a lower probability of I-RODS deterioration than participants in the placebo arm. The median (95% CI) time to I-RODS deterioration could not be calculated (247.0 to not calculated [NC]) for participants in the efgartigimod arm and was 85 (50.0 to 253.0) days in the placebo arm.

Figure 8: ADHERE Stage B – Kaplan–Meier analysis of time to I-RODS deterioration in participants treated with efgartigimod or placebo (mITT analysis set)



Source: Allen et al (2024)⁵⁵

Note: The HR was obtained from a Cox proportional hazard model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and aINCAT during Stage A.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyneuropathy; HR: Hazard ratio; I-RODS: Inflammatory Rasch-built Overall Disability Scale; mITT: Modified intent-to-treat; SC: Subcutaneous.

A summary of the results for the secondary endpoints is presented in Table 15.

Table 15: ADHERE Stage B – summary of secondary endpoint results of participants treated with efgartigimod or placebo

Secondary Endpoint	Measure	Efgartigimod , n (%)	Placebo, n (%)	HR/OR (95% CI)	Nominal p-value
Time to CIDP progression	Time to first I-RODS deterioration ≥4 points	40 (36)	57 (52)	HR 0.54 (0.35-0.81)	0.0034
Improved functional level	I-RODS improvement of ≥4 points from Stage B baseline	50 (45)	40 (36)	OR 1.44 (0.81-2.57)	0.23

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

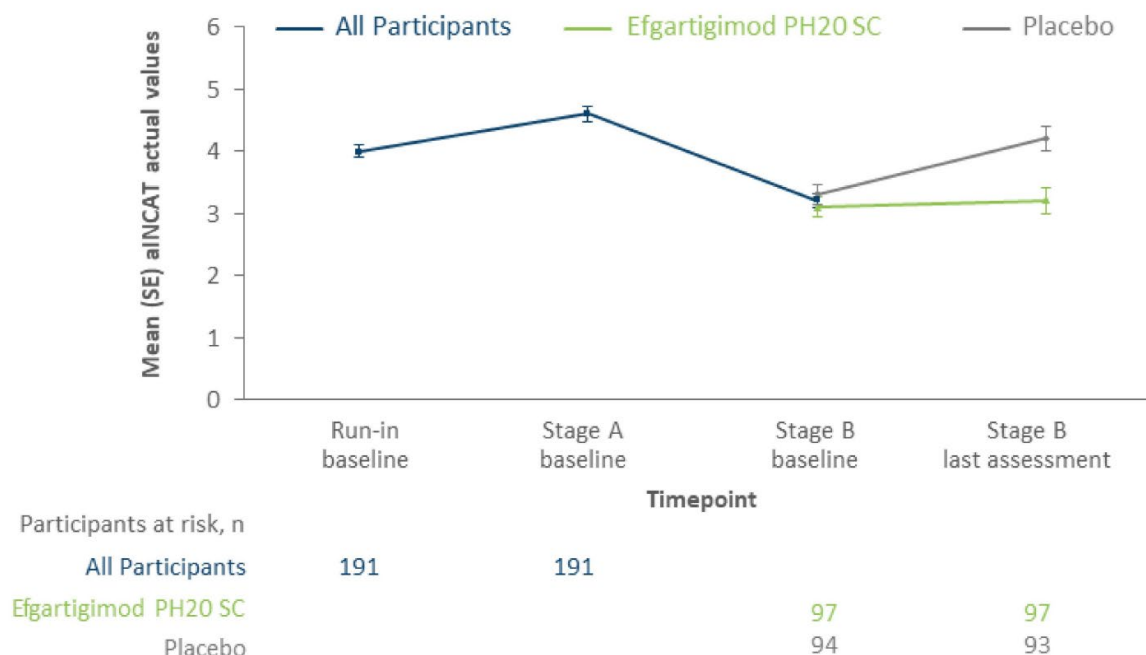
Secondary Endpoint	Measure	Efgartigimod, n (%)	Placebo, n (%)	HR/OR (95% CI)	Nominal p-value
aINCAT score	Mean (SE) change from Stage B baseline to last assessment	0.1 (0.1)	0.9 (0.19)	-	-
I-RODS score	Mean (SE) change from Stage B baseline to last assessment	0.8 (1.17)	-7.0 (1.84)	-	-
MGS (dominant hand), kPa	Mean (SE) change from Stage B baseline to last assessment	2.1 (1.26)	-8.2 (1.98)	-	-
MGS (non-dominant hand), kPa	Mean (SE) change from Stage B baseline to last assessment	2.0 (1.64)	-6.9 (2.04)	-	-
MRC sum score	Mean (SE) change from Stage B baseline to last assessment	-0.3 (0.43)	-3.0 (0.86)	-	-
TUG test, seconds	Mean (SE) change from Stage B baseline to last assessment	0.8 (0.36)	1.9 (0.60)	-	-
EQ-5D-5L VAS	Mean (SD) change from Stage B baseline to last assessment	0.5 (17.4)	-10.2 (23.5)	-	-

Source: Allen et al (2024)⁵⁵

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; CI: Confidence interval; ECI: Evidence of clinical improvement; HR: Hazard ratio; I-RODS: (24-item) Inflammatory Rasch-built Overall Disability Scale; MGS: Mean grip strength; MRC: Medical Research Council; OR: Odds ratio; SD: Standard deviation; SE: Standard error; TUG: Timed Up and Go.

A post-hoc analysis of longitudinal mean aINCAT scores showed improvements from Stage A baseline to Stage B baseline in participants treated with efgartigimod that were maintained up to the last assessment in Stage B; these mean scores deteriorated in participants treated with placebo in Stage B (Figure 9: ADHERE – longitudinal mean aINCAT scores of Stage A responders from run-in baseline to last assessment in Stage B (post-hoc analysis; run-in and mITT analysis sets))

Figure 9: ADHERE – longitudinal mean aINCAT scores of Stage A responders from run-in baseline to last assessment in Stage B (post-hoc analysis; run-in and mITT analysis sets)



Source: Allen et al (2024)⁵⁵

Note: Stages A and B baseline were defined as the last available value before the first administration of the investigational medicinal product in Stages A and B, respectively, and Stage B last assessment as the last, non-missing post-baseline value in Stage B.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; mITT: Modified intent-to-treat; SC: Subcutaneous.

2.6.1.3.3 Stage B exploratory endpoint efficacy results

Results for the exploratory endpoints are provided in Table 16.

Table 16: ADHERE Stage B – summary of exploratory endpoint results in participants treated with efgartigimod or placebo

Exploratory endpoint	Efgartigimod	Placebo
BPI-SF, mean (SE) change from baseline to the last assessment	Pain severity: -0.2 (0.2) Pain interference: -1.0 (0.2)	Pain severity: 0.4 (0.2) Pain interference: 0.6 (0.2)
TSQM-9, mean (SE) global satisfaction	Baseline: ██████ Last assessment: ██████	Baseline: ██████ Last assessment: ██████
RT-FSS, mean (SE) change from baseline to last assessment	0.0 (0.6)	0.5 (0.5)
HADS		
Total anxiety	-0.1 (0.3)	0.6 (0.3)
Total depression	-0.2 (0.3)	0.7 (0.4)
PGIC, at the last assessment	██████████ ██████████ ██████████	██████████ ██████████ ██████████

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Source: Clinical Study Report ARGX-113-1802¹³¹

Abbreviations: BPI-SF: Brief Pain Inventory–Short Form; CIDP: Chronic inflammatory demyelinating polyneuropathy; HADS: Hospital Anxiety and Depression Scale; PGIC: Patient Global Impression of Change; RT-FSS: Rasch-transformed Fatigue Severity Scale; SE: Standard error; TSQM-9: (9-item) Treatment Satisfaction Questionnaire for Medication.

A post-hoc analysis showed that the improvements in pain, mental health and fatigue achieved during Stage A were maintained through Stage B in participants continuing efgartigimod, whereas scores worsened with placebo.¹³⁸ There was a stable reduction in Brief Pain Inventory – Short Form (BPI-SF) scores in efgartigimod-treated participants (severity: -0.2, SD 1.5, $p=0.256$; interference: -0.1, SD 1.7, $p=0.594$), but BPI-SF was significantly worsened in placebo-treated participants (severity: 0.4, SD 1.8, $p=0.023$; interference: 0.6, SD 1.7, $p=0.003$).¹³⁸

There was a continued stabilisation of HADS scores in the efgartigimod group (anxiety: -0.1, SD 2.6, $p=0.612$; depression: -0.2, SD 3.0, $p=0.426$) and HADS scores in the placebo group significantly worsened for anxiety (0.6, SD 3.1, $p=0.003$), and results trended toward a worsening for depression (0.7, SD 3.4, $p=0.064$).¹³⁸

The Rasch-transformed Fatigue Severity Scale (RTFSS) scores remained at a similar level in the efgartigimod group (0.0, SD 5.6, $p=0.971$) and an increase was demonstrated in the placebo group (0.5, SD 5.0, $p=0.299$).¹³⁸

In another post-hoc analysis, all available data from efgartigimod- and placebo-treated participants were pooled to estimate the associations between utility values and each HRQoL domain separately, while adjusting for the INCAT score.¹³⁹

After controlling for INCAT disability, a significant effect of pain severity (slope: -0.035, $p<0.0001$) and pain interference (slope: -0.034, $p<0.0001$) was observed for utility values; a larger pain severity and pain interference were associated with lower utility values.¹³⁹

However, no significant interactions were found between the pain scores and INCAT. Significant interaction effects were found between the HADS score and the INCAT score for depression ($p=0.020$) and anxiety ($p=0.005$), and larger INCAT scores had a larger effect on depression and anxiety on utility values.¹³⁹ A significant interaction effect was also found between RT-FSS fatigue and INCAT ($p=0.033$), and larger INCAT scores corresponded to greater negative effects on utility scores.¹³⁹

The exploratory endpoints demonstrate that efgartigimod's benefits extend beyond preventing relapses to preserving quality of life. While efgartigimod-treated patients maintained stable scores across pain, anxiety, depression, and fatigue measures, placebo patients showed significant worsening in pain and anxiety. Post-hoc analyses revealed that pain consistently impairs quality of life regardless of disability level, while anxiety, depression, and fatigue have progressively greater negative impacts as patients become more disabled. These findings suggest efgartigimod helps preserve the psychological well-being and functional quality of life that deteriorate when CIDP is inadequately controlled.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

2.6.2 ADHERE+

2.6.2.1 Patient baseline characteristics

Baseline characteristics were consistent between ADHERE and ADHERE+, with similar age, sex distribution, disease duration, and functional scores, indicating that the extension population was broadly comparable to the original trial cohort (Table 17).¹³³

Table 17: Baseline characteristics in ADHERE and ADHERE+

Characteristic	ADHERE+ efgartigimod (N=228)
Scores shown were assessed at screening in ADHERE and baseline in ADHERE+	
Age, years, mean (SD)	53.2 (14.1)
Sex, male, n (%)	142 (62.3)
Time since diagnosis, years, mean (SD)	4.9 (5.6)
Typical CIDP diagnosis, n (%)	199 (87.3)
Unstable active disease (CDAS: 5)*, n (%)	151 (66.2)
Prior treatment (within past 6 months) – Corticosteroids	51 (22.4)
Prior treatment (within past 6 months) – Immunoglobulins (IVIg, SCIg)	104 (45.6)
Prior treatment (within past 6 months) – Off treatment	73 (32.0)
Scores shown were assessed at beginning of each stage for ADHERE and at ADHERE Stage A baseline for ADHERE+	
INCAT score, mean (SD) [†]	4.5 (1.6)
I-RODS score, mean (SD) [‡]	41.2 (15.4)
Grip strength (dominant hand), kPa, mean (SD) [‡]	39.0 (23.6)

Source: ADHERE+ PNS publication¹³³

*Unstable active disease was defined as abnormal examination with progressive or relapsing course.

[†]Lower scores represent improvement on INCAT, while higher scores represent improvement for I-RODS.

[‡]Grip strength scores in non-dominant hand were similar.

Abbreviations: CDAS: CIDP disease activity status; CIDP: Chronic inflammatory demyelinating polyneuropathy; INCAT: Inflammatory Neuropathy Cause and Treatment score; I-RODS: Inflammatory Rasch-built Overall Disability Scale; IVIg: Intravenous immunoglobulin; SC: Subcutaneous; SCIg: Subcutaneous immunoglobulin; SD: Standard deviation.

2.6.2.2 Interim efficacy readout (Week 36, February 2024 cut-off)

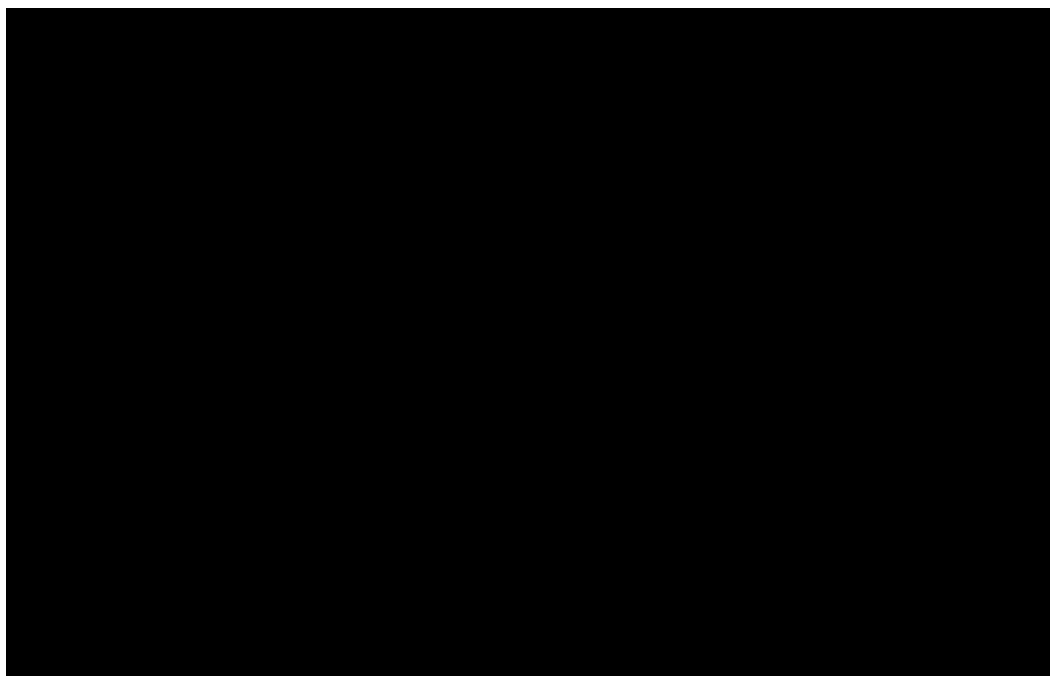
At an interim data cut-off (16 February 2024), efficacy outcomes demonstrated sustained and clinically meaningful improvement with long-term efgartigimod treatment.¹³³ From the ADHERE run-in baseline to Week 36 of ADHERE+, participants showed improvement in functional disability, daily activity, and muscle strength.¹³³ Adjusted INCAT scores declined, reflecting reduced disability, while mean I-RODS scores increased by 8.8 points, indicating better performance in daily activities.¹³³ Objective gains in motor strength were also observed, with MGS in the dominant hand improving by 17.5 kPa.¹³³ These outcomes exceeded established minimal clinically important differences, supporting the durability and clinical relevance of benefit across functional and strength domains in patients with CIDP.¹³³

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

2.6.2.3 Efficacy in patients treated with q2w dosing schedule (ADHERE+ substudy)

As of the latest data cut-off (04 April 2025), [REDACTED] patients in ADHERE+ met the criteria to enter the substudy, of which [REDACTED] enrolled in the substudy and received the q2w dosing schedule.¹³⁴ Participant demographics and baseline characteristics at Stage A baseline were similar for the substudy and overall ADHERE population.¹³⁴ The median time to clinical deterioration (primary endpoint, defined as worsening of adjusted INCAT (≥ 1 point increase) or I-RODS (≥ 4 points decrease) or MGS (≥ 8 kPa decrease) compared to q2w baseline was [REDACTED] ([REDACTED]; Figure 10).¹³⁴ At week 12 and 24, the proportion (95% CI) of patients without clinical deterioration was [REDACTED] and [REDACTED], respectively.¹³⁴ In total, [REDACTED]% of participants who deteriorated on q2w dosing restabilised on weekly dosing. At the first post-q1w baseline visit (week 6) an estimated [REDACTED] of participants had restabilised (Figure 11).¹³⁴

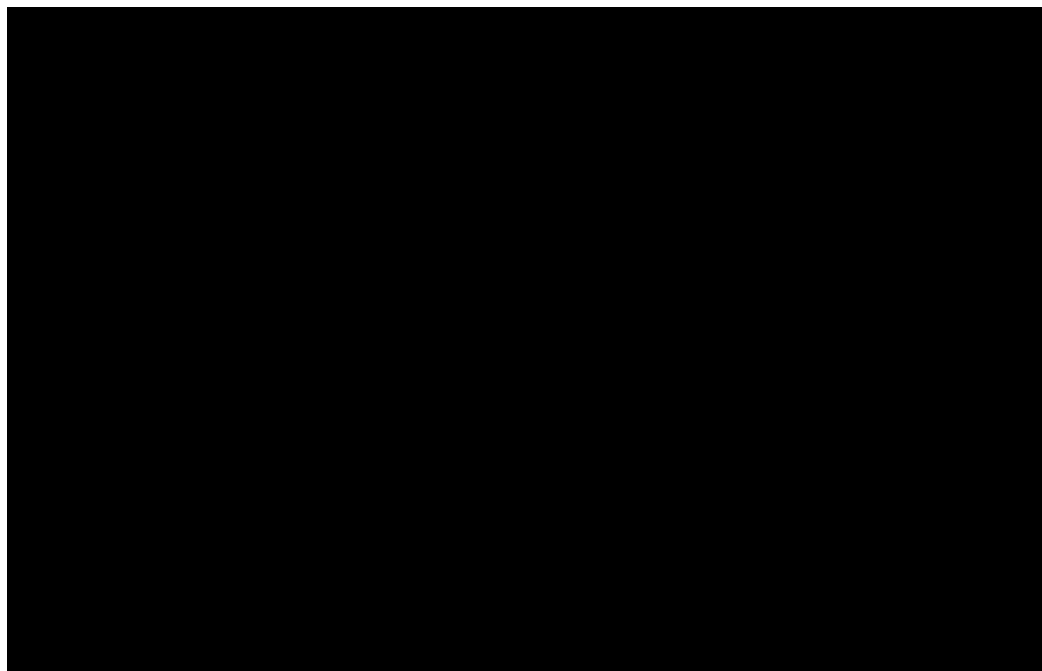
Figure 10: ADHERE+ substudy – Kaplan–Meier analysis of time to clinical deterioration during q2w dosing regimen (efficacy analysis set)



Source: Data on file - ADHERE+ substudy (2025)¹³³

Note: Clinical deterioration (protocol V6) was defined as worsening of adjusted INCAT (≥ 1 point increase) or I-RODS (≥ 4 points decrease) or MGS (≥ 8 kPa decrease) compared to Q2W-1 baseline.

Figure 11: ADHERE+ substudy – Kaplan-Meier time to restabilisation on q1w after clinical deterioration during q2w dosing



Source: Data on file - ADHERE+ substudy (2025)¹³³

Note: Restabilisation (protocol V6) was defined as improvement on at least one of the parameters on which the participant deteriorated in Q2W-1 compared to the Q1W-1 baseline: adjusted INCAT (≥ 1 point decrease), I-RODS (≥ 4 points increase), or MGS (≥ 8 kPa increase).

2.7 Subsequent treatments used in the relevant studies

The collection and analysis of subsequent treatment data is not applicable to this study due to its design. ADHERE was a specific comparison of efgartigimod versus placebo in Stage B, where treatment ended upon either relapse or completion of 48 Weeks in Stage B, at which point participants could enter a separate open-label extension trial (ADHERE+). The study did not involve multiple lines of therapy, combination treatments, or treatment switching strategies that would necessitate subsequent treatment analysis.

2.8 Subpopulation analysis

Following unblinding, post-hoc subpopulation analyses were performed to evaluate ECI response based on baseline disease characteristics, treatment administration duration and prior CIDP therapy.

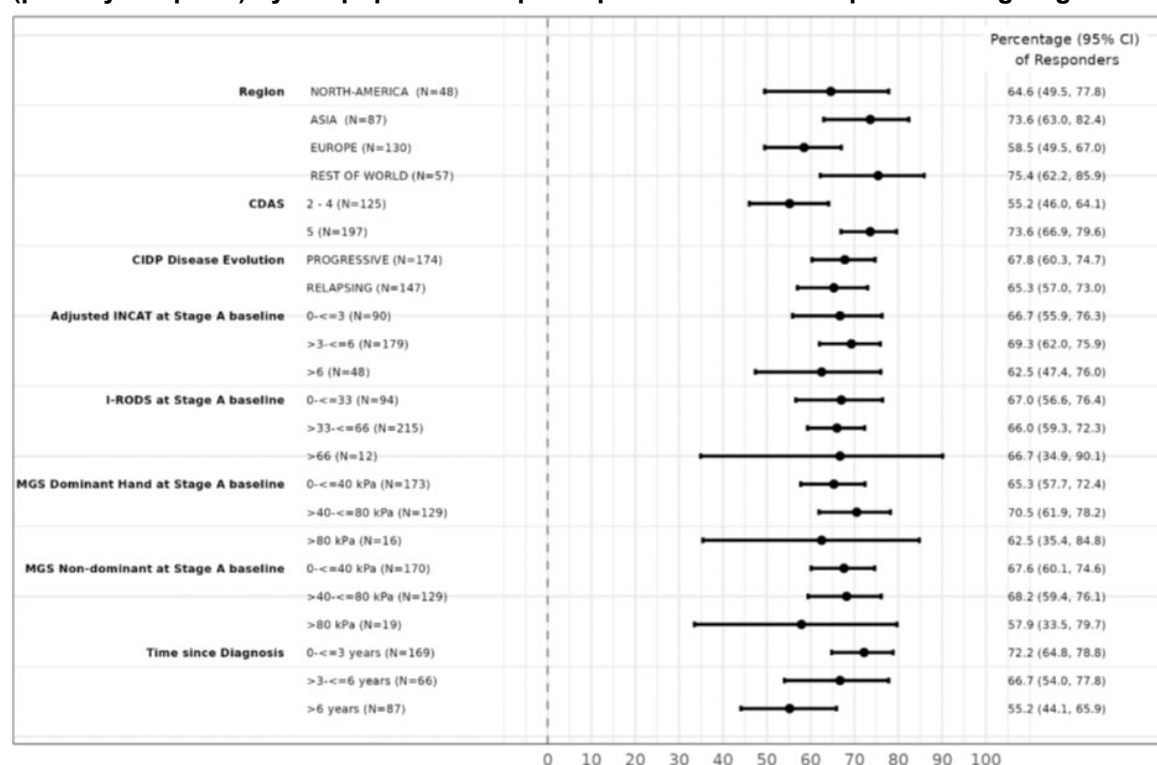
ECI response by prior therapy is detailed in Section 2.6.1.2.

A post-hoc analysis of ECI response by baseline disease characteristics subpopulations is presented in Figure 12. While the effect of efgartigimod was consistent and similar to the overall effect, a higher percentage of ECI responders was observed in participants with unstable disease activity (chronic inflammatory demyelinating polyneuropathy disease activity status [CDAS] score of 5) than those with stable disease activity (CDAS score of 2-4) (73.6% vs 55.2%, respectively). A higher percentage of participants with an ECI response

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

was also observed in participants with more recently diagnosed disease (0 to ≤3 years) compared to those participants that had a longer time (>6 years) since first diagnosis (72.2% vs 55.2%, respectively). Responder rates were comparable between progressive and relapsing disease courses, indicating no meaningful difference by disease course and supporting that these are not distinct subpopulations.

Figure 12: ADHERE Stage A – Forest plot of a post-hoc analysis of confirmed ECI responders (primary endpoint) by subpopulation of participants treated with open-label efgartigimod

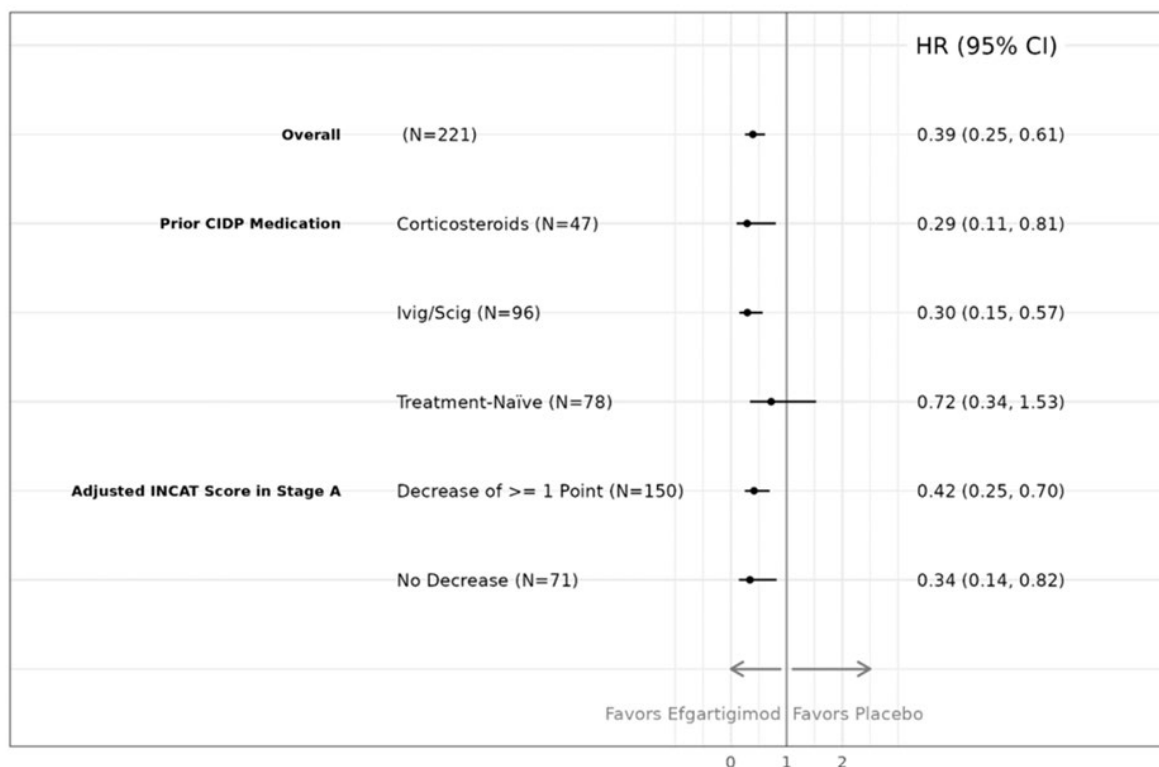


Source: Clinical Study Report ARGX-113-18021

Abbreviations: CDAS: Chronic inflammatory demyelinating polyneuropathy disease activity status; CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyneuropathy; ECI: Evidence of clinical improvement; INCAT: Inflammatory Neuropathy Cause and Treatment score; I-RODS: (24 item) Inflammatory Rasch-built overall disability scale; MGS: Mean grip strength.

For the primary Stage B endpoint, subpopulation analyses were performed by the stratification factors used during randomisation (Figure 13): aINCAT score during Stage A (no change in aINCAT score vs decrease in aINCAT score of ≥1 point) and by prior CIDP therapy (off treatment, corticosteroids within six months before screening, or IVIg/SCIg treatment within six months before screening).

Figure 13: ADHERE Stage B – Forest plot of the time to first occurrence of clinical deterioration, overall and by stratification factors (mITT analysis set)



Source: Clinical Study Report ARGX-113-18021

Note: Treatment-naïve participants were defined as participants with no history of prior CIDP therapy or having discontinued their CIDP therapy (corticosteroids, IVIg, or SCIg therapy) for ≥ 6 months before screening. The HRs were obtained from a Cox proportional hazards model.

Abbreviations: CI: Confidence interval; INCAT: Inflammatory neuropathy cause and treatment; CIDP: Chronic inflammatory demyelinating polyneuropathy; HR: Hazard ratio; IVIg: Intravenous immunoglobulin; mITT: Modified intent-to-treat; SCIg: Subcutaneous immunoglobulin.

A post-hoc analysis evaluated outcomes by prior CIDP treatment during open-label Stage A, double-blind Stage B, and the ADHERE+ extension.¹⁴⁰ The prior Ig-treated patients showed the greatest overall aINCAT improvement by Week 36 of ADHERE+ (mean change -1.4 ; corticosteroids -1.3 ; off treatment -0.9) despite a lower Stage A response rate (ECI 59% vs 78% corticosteroids and 72% off treatment).¹⁴⁰ This pattern can be understood in light of the run-in withdrawal requirement: a higher proportion of prior Ig-treated patients had already worsened by at least one aINCAT point by Stage A baseline, consistent with the relatively rapid wearing-off of Ig, and this group also had higher early discontinuation rates in Stage A (33.3%), with a notable proportion (25.5%) receiving fewer than four efgartigimod injections before discontinuation.¹⁴⁰

2.9 Meta-analysis

Not applicable.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

2.10 Indirect and mixed treatment comparisons

2.10.1 Background and objectives

There are no head-to-head trials comparing maintenance treatment efgartigimod with Igs for patients with CIDP. To support the development of the cost-effectiveness model for efgartigimod, the objective of the indirect treatment comparison (ITC) study was to compare the efficacy of maintenance treatment with efgartigimod versus Igs in patients with CIDP who were pre-treated with Ig. The outcome of interest was the change in aINCAT score.

2.10.2 SLR to inform the ITC

For this purpose, an SLR was conducted to identify clinical evidence evaluating efgartigimod and Igs in CIDP. An SLR was conducted aimed at gathering all relevant efficacy and safety data on efgartigimod and Igs for CIDP. The SLR was designed to identify studies relevant to the ITC. To ensure focus on the planned analysis, it applied a 20-year time restriction and limited eligibility to studies reporting the following interventions: efgartigimod, immunoglobulin, and corticosteroids. For the efgartigimod NICE submission, a broader SLR was also conducted without a time restriction and included a wider range of comparators, such as plasma exchange (PLEX) and neuromodulatory drugs. To ensure that the Company ITC submitted for the NICE assessment was aligned with the broader evidence base and incorporated any newly published relevant studies, both literature reviews were used to inform the ITC.

The pooled results of the two SLRs included a total of 183 publications. While the SLRs collected a substantial amount of data, there were challenges related to inconsistencies in reporting and measurement methods, which were considered further in the ITC feasibility assessment. Full details of the ITC are provided in **Appendix B**; the methodology and results (PRISMA diagram, included and excluded studies) of the Company SLR are also provided in **Appendix B**.

2.10.3 ITC feasibility assessment

The aim of the ITC feasibility assessment was to determine if it was feasible to conduct ITC analyses comparing efgartigimod with European Medicines Agency (EMA)-approved Ig products for CIDP treatment, specifically in terms of the efficacy outcomes reported in the efgartigimod pivotal trial (ADHERE).¹⁴¹ Of the 183 eligible studies identified in the two SLRs and ADHERE, five were considered in the feasibility assessment as they included at least one Ig arm (Table 18), used an RCT or single-arm experimental study design (similar to ADHERE Stage A or B), and reported change in aINCAT. The study designs, patient characteristics, and efficacy endpoints were reviewed.

Of the five studies that were considered for comparison, two (PIMPA¹⁴² and Katzberg 2013¹⁴³) were excluded due to multiple issues and one (PATH⁶⁰) because only the median value of the endpoint was reported. Of the remaining two studies, one study (Epoch 1 of ADVANCE-CIDP 1)¹⁴⁴ was suitable for comparison against data from ADHERE Stage B for

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

change from baseline in aINCAT in patients who were pre-treated with Ig. The ADVANCE-CIDP 1¹⁴⁴ study investigated the safety and efficacy of HyQvia (SCIg) as maintenance treatment in CIDP patients who were on a stable Ig dose. There was heterogeneity in baseline characteristics between the ADHERE and ADVANCE-CIDP 1¹⁴⁴ cohorts. To control for the heterogeneity in baseline characteristics between ADHERE and ADVANCE-CIDP I, an anchored matching-adjusted indirect comparison (MAIC) was the preferred analysis method. Details of the heterogeneity assessment and outcomes of the feasibility assessment are provided in **Appendix B**.

2.10.3.1 Rationale for evidence approach

As CIDP is a rare, chronic, and heterogeneous disease, the evidence base for comparative efficacy is limited. Head-to-head randomised data are not available, and most studies of Ig therapies are single-arm, open-label, or include heterogeneous patient populations and outcome measures. This pattern is consistent with other rare immune-mediated neurological disorders, where ethical and feasibility constraints restrict the use of parallel-group comparator trials. Given these limitations, the Company's approach, using data from the pivotal ADHERE study¹⁴¹ and the most comparable Ig trial (ADVANCE-CIDP I)¹⁴⁴, an anchored MAIC represents the most methodologically robust and feasible strategy to estimate relative treatment effects. This approach aligns with NICE Decision Support Unit guidance for ITCs and with regulatory precedents in rare disease submissions where evidence must be synthesised from limited but high-quality sources.¹⁴⁵

Table 18: Overview of treatments, design and population in studies identified as eligible for inclusion in the ITC feasibility assessment following completion of the study selection process and endpoint heterogeneity assessment

Study	Intervention	Comparator	Design*	Study Length	Population	Countries
ADHERE (ARGX-113-1802) ⁵⁵	Efgartigimod	None	Phase 2 Stage A: Non-randomised, single-arm experimental (pre-RCT) of efgartigimod only	Stage A: Up to 12 Weeks	Adult patients with CIDP.	Global
	Efgartigimod	Placebo	Phase 2 Stage B: RCT of efgartigimod vs placebo	Stage B: Up to 48 Weeks	Adult patients with CIDP Responders from Stage A entered Stage B.	Global
ADVANCE-CIDP 1 (NCT02549170) ¹⁴⁴	HyQvia	Placebo	Phase 3 RCT (Epoch 1)	Epoch 1: Up to 32 Weeks [†]	Adult patients with CIDP previously responded to Ig treatment and receiving a stable dose of IVIg treatment.	Global
PATH (NCT01545076) ⁶⁰	Privigen	None	Non-randomised, single-arm (pre-RCT)	IgG dependency period: Up to 12 Weeks IVIg restabilisation period: Up to 13 Weeks	Adult patients with CIDP previously treated with IVIg (within 8 Weeks before screening). Only patients experiencing CIDP relapse during the Ig dependency test period (up to 12 Weeks) were administered a standardised IVIg regimen during an IVIg restabilisation period.	Global
	Hizentra (low-dose vs high dose)	Placebo	Phase 3 RCT	25 Weeks	Adult patients with CIDP previously treated with IVIg (within 8 Weeks before screening). Only patients that underwent IVIg restabilisation period (pre-randomisation) and improved and maintained aINCAT continued to the SCIg treatment period.	Global

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Study	Intervention	Comparator	Design*	Study Length	Population	Countries
PIMPA ¹⁴²	SCIg (MPT or pump)	N/A	CT	8 months	Definite or probable CIDP, previous sustained response to IVIg therapy with evidence of “wear-off” effect, administration of SCIg through infusion pump for three months prior to enrolment at the same monthly dose as the last IVIg infusion.	Italy
Katzberg 2013 ¹⁴³	Gamunex	N/A	Pilot study	6 months	Patients with CIDP being treated with IVIg.	Canada

Source: Efgartigimod for CIDP: Indirect treatment comparison report¹⁴¹

* Only RCTs or non-randomised experimental studies were eligible (OLEs were excluded). No comparable studies/endpoints were identified for Kiovig or Flebogamma DIF.

† Kaplan-Meier data are reported up to 32 Weeks with no clear information on study length.

Abbreviations: aINCAT: Adjusted inflammatory neuropathy cause and treatment; CIDP: Chronic inflammatory demyelinating polyneuropathy; Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; MPT: Manual push technique; RCT: Randomised controlled trial; SCIg: Subcutaneous immunoglobulin.

2.10.4 ITC Results

The effective sample size (ESS) was 84.0 (87.5% of unweighted sample), and the relative weights distribution did not exhibit any extreme outliers. This suggests that the analysis is based on a sufficiently large sample size and that there are no major outliers potentially driving the results. Finally, the baseline characteristics converged after weighting.

The anchored MAIC results are shown in Table 19 and suggest that the change in aINCAT from baseline was significantly more favourable for efgartigimod than HyQvia. To test the robustness of this finding, a broader unanchored ITC including a wider set of studies was also conducted, yielding a consistent direction of effect (pooled estimate 0.79), further supporting the credibility of the comparative conclusion. These aligned results across two complementary analyses reinforce the overall interpretation that efgartigimod provides a small but meaningful efficacy advantage compared to established Ig maintenance therapy, while offering significant practical and tolerability advantages. Full details of the ITC are provided in **Appendix B**. The impact of the pooled estimate is explored in a scenario analysis (Section 3.11.3).

Table 19: MAIC results for change in aINCAT from baseline for efgartigimod compared with HyQvia at the last assessment up to 32 Weeks^a

N patients		Difference in means (95% CI) [p-value] for efgartigimod vs HyQvia ^c	
ADVANCE-CIDP I	ADHERE ^b	Unweighted	Weighted
132	96	-1.01 (-1.81, -0.21) [0.014]	-0.88 (-1.72, -0.04) [0.040]

^a Follow-up data for ADHERE Stage B were available up to 48 Weeks. Data were analysed up to the same timepoint as that in the comparator study to more closely align the study designs.

^b There were 211 patients in ADHERE Stage B at baseline. Fewer patients were included in the MAIC analyses as the population was restricted before analysis to include only Ig pre-treated patients and to align with the design of ADVANCE-CIDP I

^c Values below 0 favour efgartigimod (i.e., aINCAT improves to a greater extent with efgartigimod) and values above 0 favour Hyqvia.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; CI: Confidence interval; MAIC: Matching-adjusted indirect comparison.

2.10.5 Strengths and limitations

The major strength of this report is that it encompasses high-quality SLR and ITC methods that follow best-practice guidance, thereby allowing for a high level of transparency. The main limitations relate to inconsistencies in reported outcomes between studies and limitations to population adjustments.

2.10.6 ITC conclusions

Overall, the ITC results indicate that efgartigimod is associated with a more favourable change in aINCAT than HyQvia during maintenance treatment. Despite the limitations intrinsic to an ITC approach, the analysis was based on the more robust anchored MAIC methodology and a sufficiently large ESS.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

2.11 Adverse reactions

2.11.1 ADHERE

Overall, efgartigimod was well tolerated in ADHERE, with a safety profile comparable to placebo during the randomised-withdrawal period. No new safety signals were identified; most adverse events (AEs) were mild to moderate and discontinuations due to AEs were infrequent.

2.11.1.1 Stage A

In Stage A, [REDACTED] experienced at least one treatment-emergent adverse event (TEAE) and [REDACTED] had a serious event; the most frequent events were injection-site erythema [REDACTED], CIDP worsening [REDACTED] and headache [REDACTED].⁵⁵ The approximately 30% non-response rate reflects not meeting the trial's confirmed improvement criterion on aINCAT, I-RODS or grip strength across two consecutive weekly assessments after at least four administrations; it does not indicate clinical deterioration, which was separately captured as the 5% CIDP-worsening AE.⁵⁵ Most AEs were mild or moderate in severity ($\leq$ grade 2) with [REDACTED] participants reporting AEs $\geq$ grade 3; [REDACTED] participants had serious adverse events (SAEs) and [REDACTED] participants had AEs grade ≥ 3 considered related to efgartigimod. [REDACTED] participants experienced AEs that led to discontinuation and there were [REDACTED] fatal AEs; both of which were considered to not be related to efgartigimod by the investigator (Table 21).

Table 20: ADHERE Overview of AEs (Stage A)

Type of AE	Efgartigimod (N=322) n (%)
≥ 1 AE	[REDACTED]
≥ 1 SAE	[REDACTED]
≥ 1 Grade 3 or higher AE	[REDACTED]
≥ 1 AESI	[REDACTED]
≥ 1 Injection-related reaction	[REDACTED]
≥ 1 Injection site reaction	[REDACTED]
Fatal AEs	[REDACTED]
≥ 1 TRAE according to PI	[REDACTED]
≥ 1 Treatment- related SAE	[REDACTED]
≥ 1 Procedure-related AE according to PI	[REDACTED]
≥ 1 AE for which efgartigimod was discontinued	[REDACTED]
≥ 1 AE for which efgartigimod was interrupted	[REDACTED]

Source: ARGX-113-1802 CSR Report¹³¹

Abbreviations: AE: Adverse event; AESI: Adverse event of special interest; PI: Principal investigator; SAE: Serious adverse event; TRAE: Treatment-related adverse event.

Table 21: Most common TEAEs in Stage A (reported in ≥5 participants) (secondary analysis; safety population)

Adverse event	Efgartigimod (N=322) n (%)
Any TEAE*	204 (63%)
Injection site erythema	33 (10%)
CIDP worsening	17 (5%)
Headache	16 (5%)
Injection site pain	15 (5%)
Injection site rash	11 (3%)
Rash	11 (3%)
Upper respiratory tract infection	11 (3%)
Arthralgia	9 (3%)
Diarrhoea	8 (3%)
Pain in extremity	8 (3%)
Back pain	7 (2%)
COVID-19	7 (2%)
Alanine aminotransferase increased	6 (2%)
Myalgia	6 (2%)
Fatigue	5 (2%)
Injection site reaction	5 (2%)
Peripheral swelling	5 (2%)
Nasopharyngitis	5 (2%)
Urinary tract infection	5 (2%)
Fall	5 (2%)
Activated partial thromboplastin time prolonged	5 (2%)
Aspartate aminotransferase increased	5 (2%)
Blood triglycerides increased	5 (2%)

*Data are n (%). The Stage A safety population included all participants who received ≥1 doses or part of a dose of efgartigimod in Stage A.

Source: Allen et al. (2024)⁵⁵

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; TEAE: Treatment-related adverse event.

2.11.2.1 Stage B

In Stage B, 64% of (n=74/111) participants in the efgartigimod and 56% of (n=62/110) participants in the placebo group reported a TEAE.⁵⁵ There was no clinically significant difference between the efgartigimod and placebo arms in the occurrence of TEAEs, SAEs, AEs ≥ grade 3, AEs leading to treatment interruption, or adverse event of special interest (AESI).⁵⁵ The most common TEAEs for the efgartigimod were COVID-19 (17% [n=19/111]), injection site bruising (5% [n=6/111]), and injection site erythema (5% [n=6/111]) and for the placebo group were COVID-19 (13% [n=14/110]), upper respiratory tract infections (10% [n=11/110]) (

Table 23).⁵⁵ Most AEs were mild or moderate in severity (≤ grade 2), and only 5% (6) participants reported SAEs and 6% (7) participants reported AEs ≥ grade 3 in both arms.⁵⁵

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

2.7% (n=3/111) of participants in the efgartigimod arm experienced AEs that led to discontinuation whereas 0.9% (n=1/110) in the placebo arm experienced AEs that led to discontinuation; there was one fatal AE, which occurred in the placebo group (Table 22).⁵⁵

Table 22: ADHERE Overview of AEs (Stage B)

Type of AE	Efgartigimod (n=111) n (%)	Placebo (n=110) n (%)
≥1 AE	71 (64.0)	62 (56.4)
≥1 SAE	6 (5.4)	6 (5.5)
≥1 Grade 3 or higher AE	7 (6.3)	7 (6.4)
≥1 AESI	35 (31.5)	37 (33.6)
≥1 Injection-related reaction		
≥1 Injection site reaction	16 (14.4)	7 (6.4)
Fatal AEs	0	1 (0.9)
≥1 TRAE according to PI	27 (24.3)	22 (20.0)
≥1 Treatment-related SAE		
≥1 Procedure-related AE according to PI		
≥1 AE for which efgartigimod was discontinued		
≥1 AE for which the efgartigimod was interrupted		

Source: ARGX-113-1802 CSR Report¹³¹

Abbreviations: AE: Adverse event; AESI: Adverse event of special interest; PI: Principal investigator; SAE: Serious adverse event; TRAE: Treatment-related adverse event.

Table 23: Most common TEAEs in Stage B (reported in ≥3 participants in either arm) (secondary analysis; safety population)

TEAE	Efgartigimod (n=111) n (%)	Placebo (n=110) n (%)
Any TEAE*	71 (64%)	62 (56%)
COVID-19	19 (17%)	14 (13%)
Injection site bruising	6 (5%)	1 (1%)
Injection site erythema	6 (5%)	0
Nasopharyngitis	5 (5%)	3 (3%)
Arthralgia	4 (4%)	5 (5%)
Headache	4 (4%)	2 (2%)
Fatigue	3 (3%)	1 (1%)
Influenza-like illness	3 (3%)	0
Pyrexia	3 (3%)	4 (4%)
Pain in extremity	2 (2%)	4 (4%)
Upper respiratory tract infection	2 (2%)	11 (10%)
Pneumonia	1 (1%)	4 (4%)
Constipation	1 (1%)	3 (3%)
Muscle spasms	0	3 (3%)
Paraesthesia	0	3 (3%)

Source: Allen et al. (2024)⁵⁵

Abbreviations: SC: Subcutaneous; TEAE: Treatment-related adverse event.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

2.11.2 ADHERE+

Overall, efgartigimod was well-tolerated in the ADHERE+ open-label extension trial, and the nature, frequency, and severity of AEs were consistent with the preceding controlled study phases.¹³³ Importantly, there was no evidence of an increase in the rate or severity of TEAEs with longer exposure. Most reported TEAEs were mild or moderate in intensity, and the majority of injection site reactions (ISRs) were transient, mild, and occurred within 24 hours of administration.¹³³

SAEs occurred in 15.4% of participants during ADHERE+, corresponding to a low event rate of 0.25 per participant-year of follow-up (PYFU).¹³³ SAEs were diverse in nature, and discontinuations due to TEAEs remained infrequent, reported in only 7.9% of participants.¹³³ Infections were among the most frequently reported events; however, their incidence was low, not correlated with immunoglobulin G levels, and infections were typically mild to moderate in severity.¹³³ The most common infections included COVID-19, upper respiratory tract infection, nasopharyngitis, and urinary tract infection.¹³³ Two deaths were reported during ADHERE+: one due to CIDP deterioration (considered treatment-related by the investigator but not by the sponsor, with independent data safety monitoring board review concluding no safety concern), and one due to cardiac arrest (not considered related to study treatment).¹³³

The safety and tolerability profile of efgartigimod in ADHERE+ therefore remained consistent with that seen in ADHERE, supporting the longer-term use of the treatment in participants with CIDP¹³³. A detailed summary of safety outcomes, including overall TEAEs, SAEs, discontinuations, deaths, ISRs, and the most frequent TEAEs, is provided in Table 24.

Table 24: Safety and tolerability outcomes in ADHERE and ADHERE+ (safety population)

Safety outcomes	ADHERE Stage A efgartigimod (N=322; PYFU=46.9)	ADHERE Stage B efgartigimod (n=111; PYFU=56.7)	ADHERE Stage B Placebo (n=110; PYFU=42.1)	ADHERE+ efgartigimod (N=228; PYFU=263.0)
Any TEAE, n (%) [event rate]	204 (63.4) [13.43]	71 (64.0) [3.48]	62 (56.4) [5.11]	171 (75.0) [3.10]
Any SAE, n (%) [event rate]	21 (6.5) [0.51]	6 (5.4) [0.14]	6 (5.5) [0.19]	35 (15.4) [0.25]
Any grade ≥3 TEAE, n (%) [event rate]	25 (7.8) [0.62]	7 (6.3) [0.14]	7 (6.4) [0.21]	41 (18.0) [0.31]
Any ISR, n (%) [event rate]	62 (19.3) [2.64]	16 (14.4) [0.39]	7 (6.4) [0.21]	29 (12.7) [0.27]
Discontinued due to TEAEs, n (%) [event rate]	22 (6.8) [0.47]	3 (2.7) [0.05]	1 (0.9) [0.02]	18 (7.9) [0.14]
Deaths, n (%) [event rate]	2 (0.6) [0.04]	0	1 (0.9) [0.02]	2 (0.9) [0.008]
Most common TEAEs (≥5% in ADHERE+)				
Headache	16 (5.0) [0.60]	4 (3.6) [0.11]	2 (1.8) [0.05]	14 (6.1) [0.09]
Upper respiratory tract infection	11 (3.4) [0.26]	2 (1.8) [0.05]	11 (10.0) [0.26]	24 (10.5) [0.15]
COVID-19	7 (2.2) [0.17]	19 (17.1) [0.35]	14 (12.7) [0.33]	37 (16.2) [0.14]
Urinary tract infection	5 (1.6) [0.13]	2 (1.8) [0.04]	2 (1.8) [0.05]	12 (5.3) [0.06]
Nasopharyngitis	5 (1.6) [0.11]	5 (4.5) [0.09]	3 (2.7) [0.07]	16 (7.0) [0.08]

Source: ADHERE+ PNS publication¹³³

Abbreviations: ISR: Injection site reaction; PYFU: Participant-years of follow-up; SAE: Serious adverse event; TEAE: Treatment-emergent adverse event.

2.12 Ongoing studies

Two significant clinical trials are currently underway investigating efgartigimod as a treatment for CIDP, both sponsored by argenx.

To understand the effect of a real-world switching protocol, without the run-in phase used in ADHERE, ARGX-113-2406 (NCT066370726) examines adult CIDP patients transitioning from IVIg treatment to efgartigimod. The trial design employs an open-label, single-group structure with comprehensive outcome measurements. The primary endpoint assesses the proportion of participants who successfully begin treatment with efgartigimod within one week after stopping IVIg therapy and continue receiving it at the end of the 12-Week treatment period. Secondary outcome measures track changes in several assessment tools, including EQ-5D-5L scores, TSQM-9 scores, PGIC scores, and Patient's Global Impression of Severity scores over time, as well as monitoring the incidence of AEs up to 16 Weeks. The trial commenced in December 2024 with an expected completion date Q1 2026.

ADHERE+ (ARGX-113-1902, NCT04280718) is a phase 2 open-label extension trial of the earlier ARGX-113-1802 study and began in September 2020; it has enrolled 229 participants. Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

reduction in the risk of relapse. Participants in the efgartigimod arm maintained a response to treatment longer than participants in the placebo arm. In the placebo arm, the median (95% CI) time to clinical deterioration was 140.0 (75.0 to NC) days, whereas the median (95% CI) time to clinical deterioration could not be calculated for the efgartigimod arm because an insufficient number of participants had clinical deterioration.

Additionally, efgartigimod treatment was favoured in both Stages A and B, as evidenced by the results of the secondary efficacy endpoints:

- During Stage A, clinical improvement was demonstrated across aINCAT, I-RODS, and MGS scores. These improvements were clinically meaningful based on the EAN/PNS criteria 2021, and clinical benefit was maintained with efgartigimod treatment in Stage B, while these scores worsened in the placebo arm.
- During Stage B, efgartigimod substantially reduced the risk of functional deterioration as measured by I-RODS. Of the participants who received efgartigimod, 36.0% deteriorated on I-RODS compared with 51.8% in the placebo arm (HR of 0.537; nominal p-value=0.0034; 95% CI, 0.354-0.814). Additionally, a numerically higher percentage of participants in the efgartigimod arm had improvement in daily functional tasks than in the placebo arm (45.0% and 36.4%, respectively; odds ratio [95% CI] of 1.441 [0.814-2.567]).
- During Stage A, quality of life, as measured by the EQ-5D-5L-VAS scores, improved by the last Stage A assessment. This improvement was maintained with efgartigimod treatment in Stage B, while the score worsened in the placebo arm.

The safety results of Stage A and B demonstrated that once-weekly injections of efgartigimod 1,000 mg for up to 60 weeks were well-tolerated and had a favourable safety profile in participants with CIDP.

An ITC using MAICs pooled individual patient data from ADHERE with aggregate data from EMA-authorized Ig trials to compare efgartigimod with IVIg and SCIg. Against SCIg comparators, anchored MAICs to Stage B achieved adequate balance with effective sample sizes of 46.6-84.0 and showed similar time to aINCAT deterioration but significantly greater improvements with efgartigimod in disability and daily activity and in MGS, while the MRC Sum Score was numerically higher versus SCIg. Unanchored comparisons versus IVIg were not interpretable because of poor baseline overlap and very low effective sample sizes (2.3–4.7). Despite usual cross-trial limitations, the anchored SCIg analyses favour efgartigimod across disability, daily activities and strength, supporting a clinically meaningful benefit relative to current subcutaneous Ig options.

For adults living with CIDP whose treatment with IVIg or SCIg is unsatisfactory, ADHERE provides directly applicable evidence: among participants previously treated with Ig, 59% (n=97/165) achieved confirmed improvement in Stage A and, after randomisation, relapse occurred in 29% (n=14/48) on efgartigimod versus 58% (n=28/48) on placebo in that subpopulation, consistent with the overall reduction in relapse risk versus placebo.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Improvements accrued across function and strength and were maintained with continued efgartigimod in Stage B but were partly lost on placebo. Onset was rapid, with a median 22 days to first improvement in Stage A and the 25th percentile at 9 days. Tolerability was acceptable, with similar SAE rates to placebo in Stage B (5% vs 6%), broadly comparable infection rates (32% vs 34%), and mostly mild to moderate injection-site reactions, supporting use when Ig is poorly tolerated or contraindicated.

Taken together, these data support efgartigimod for patients with inadequate control or high treatment burden on Ig, or who are intolerant or refractory to Ig.

3. Cost-effectiveness

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare disease and imposes a substantial humanistic burden marked by pain, fatigue, functional dependence, and curtailed participation, and these impacts often persist despite maintenance treatment (see Section 1.3.1). The economic analysis presents a robust evaluation of efgartigimod against current clinical practice in England.

As part of the submission, a simple patient access scheme (PAS) has been submitted with a fixed price of (£[REDACTED]). Results for the PAS price have been modelled in the cost-effectiveness analysis.

Overview

Model summary

- A de novo economic model was developed to assess the cost-effectiveness of efgartigimod as a treatment option for patients with CIDP in the UK.
- Health states were defined based on both the level of functional impairment, and on conditions of 'active disease' and 'remission'. The level of functional impairment ranged from very limited to very severe while in 'active disease' and from very limited to moderate while in 'remission'.
- The analysis was consistent with the NICE reference case and took an NHS and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and evaluated over a 45-year time horizon with a cycle length of six months.
- Baseline characteristics and clinical efficacy were sourced from the ADHERE Phase 2 clinical trial for efgartigimod and from the ADHERE open-label extension (ADHERE+). An indirect treatment comparison (ITC) (matching-adjusted indirect comparison [MAIC]) was performed to obtain comparator clinical efficacy.
- EuroQol 5-Dimension 5-Level (EQ-5D-5L) data was collected in the ADHERE clinical trial. This data was used to model the base case for the pathway with efgartigimod arm.
- Long-term treatment assumptions incorporated data from the ADHERE+ open-label extension, including the bi-weekly dosing substudy, which supports potential dosing flexibility in stable responders and informs cost-offset scenarios related to reduced administration frequency.

Base case results

- Efgartigimod is estimated to have a large quality of life benefit for patients versus the pathway without efgartigimod, generating an additional [REDACTED] QALYs. Life years were equal across the treatment arms due to the assumption around equivalent mortality.
- Treatment with efgartigimod is expected to increase the costs of treatment versus the pathway without efgartigimod, with an increase in costs of £[REDACTED].
- Base case results show that efgartigimod was considered cost-effective when compared with the world without efgartigimod at a threshold of £30,000 per quality-adjusted life year (QALY), with an incremental cost-effectiveness ratio (ICER) of £[REDACTED] per QALY gained.

Sensitivity analysis

- Key drivers of the model identified by the deterministic sensitivity analysis (DSA) found that the most influential parameters on the model results are those related to IVIg treatment schedule and dose (including the mean weight in the patient population), and those related to the comparative efficacy of efgartigimod vs immunoglobulin (Ig).
- In probabilistic sensitivity analysis (PSA) it was shown that at a willingness-to-pay threshold (WTP) of £30,000 per QALY, efgartigimod is associated with a [REDACTED] probability of being cost-effective.
- Uncertainty primarily reflects the indirect comparison with Ig trials and extrapolation of relapse prevention data over the long-term horizon, although both are consistent with NICE's accepted approach for rare, chronic neurological conditions.
- The base case analysis incorporates an assumed [REDACTED] discount on the list price of Ig therapies. It is recognised that this is an area of uncertainty in the Company base case. Therefore, scenario analyses exploring a range of intravenous immunoglobulin (IVIg) discount rates ranging from [REDACTED] are provided in Section 3.11.3.
- The scenario analyses demonstrated that the pathway with efgartigimod was cost-effective in the majority of scenarios at a WTP threshold of £30,000 per QALY. The analysis makes conservative assumptions, specifically around the inclusion of induction costs and the uptake of Ig treatments.

Summary

- In summary, the cost-effectiveness analysis (CEA) indicates that a treatment pathway including efgartigimod is cost-effective versus a pathway without efgartigimod at the NICE WTP threshold of £30,000 per QALY.

3.1. Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify economic evidence and published cost-effectiveness studies for efgartigimod and comparator treatments for the management of chronic inflammatory demyelinating polyneuropathy (CIDP). Full details of the methodology and results (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] diagram, included and excluded studies) of the SLR are provided in **Appendix E**. No published studies evaluating the cost-effectiveness of this intervention were identified.

3.2 Economic analysis

The objective of the economic evaluation was to assess the cost-effectiveness of efgartigimod for treating patients with CIDP compared to the treatment pathway without efgartigimod (see Section 1.3.9). The treatment pathway without efgartigimod is aligned to current clinical management in England for patients with CIDP.

A de novo economic model is necessary to evaluate the cost-effectiveness of efgartigimod in CIDP, compared to the treatment pathway without efgartigimod, because no published cost-effectiveness analyses (CEAs) currently exist in this disease area. Existing economic evaluations are limited to budget-impact assessments or simple cost comparisons, most often between intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg) and corticosteroids. These analyses focus on drug acquisition and administration costs and do not incorporate quality-adjusted life years (QALYs), relapse prevention, long-term disability or mortality. As such, they cannot be adapted to support a full cost-utility analysis.

Efgartigimod is a human IgG1 antibody Fc fragment, which is a natural neonatal Fc receptor (FcRn) ligand. Engineered for increased FcRn affinity at both physiological and acidic pH, efgartigimod outcompetes endogenous IgG binding, preventing FcRn-mediated immunoglobulin G (IgG) recycling and increasing IgG degradation.

Efgartigimod's dosing schedule differs fundamentally from the infusion patterns of IVIg and SCIg. Benefits given by the simpler (once weekly, or fortnightly) treatment schedule and the more convenient administration route (5 ml total volume, self-administered in 20-30 seconds) associated with efgartigimod, are not properly captured by existing cost models, which instead assume continuous treatment. In addition, the ADHERE trial reports outcomes which require translation into utilities and QALYs to estimate cost-effectiveness. This in turn requires a model structure that reflects disease progression, intermittent therapy and patient response dynamics, which are not represented in current IVIg-based evaluations.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

The CEA was conducted using an NHS and Personal Social Services (PSS) perspective over a lifetime horizon (45 years). The CEA is based on data from the ADHERE phase 2 clinical trial and the ADHERE open-label extension (ADHERE+) (see Section 2.2).

3.2.1 Patient population

The patient population in the economic model reflects the patient population in the pivotal trial for efgartigimod, ADHERE. The baseline characteristics of the patients in the ADHERE and ADHERE+ trials have been described in Section 2.6.1.1 and Section 2.6.2 respectively.

The clinical data used to inform the cost-effectiveness model (CEM) is based on those that are pre-treated with immunoglobulin (Ig). This is in line with the population defined in the decision problem. There is no evidence to support whether those patients had an 'unsatisfactory treatment' or whether any patients in the clinical trial were previously intolerant or refractory to Ig. This data was not collected in the clinical trial and this is a limitation in the intolerant refractory group because it is assumed that they have the same clinical benefit as Ig-pretreated.

Efgartigimod should be considered for patients with CIDP who have a confirmed diagnosis according to EAN/PNS guidelines¹ but for whom Ig treatment is unsatisfactory, as outlined in the decision problem (Table 1). The eligible population is represented in the economic model divided in three subpopulations, with each population linked to a specific treatment pathway:

- Patients who receive stable Ig maintenance dose. These patients may decide to switch to efgartigimod due to the high treatment-related burden of Ig treatment. Within this group, two further subpopulations can be identified: patients who are Ig-dependent (i.e., they deteriorate whenever they tried to wane off Ig), and those who are Ig-dependent at an ultra-high dose of Ig (i.e., they deteriorate whenever they try to down-titrate from a dose of 2.0 g/kg per treatment cycle).
- Patients who are intolerant to Ig. These patients responded to Ig in the past, but had to discontinue due to safety concerns and hence seek treatment with efgartigimod.
- Patients who are refractory to Ig. These patients failed to show any kind of response to Ig and seek treatment with efgartigimod.

The base case assumes that 95% of the cohort is composed of patients who receive stable Ig maintenance dose, with Ig intolerant and Ig refractory subpopulations each representing 2.5% of the cohort. The proportion of Ig intolerant patients is based on qualitative interviews with UK clinical experts, who confirmed that only a very small minority of patients on Ig maintenance withdraw treatment due to safety concerns or are completely refractory to Ig treatment.¹⁶

Alongside the base case, the model includes three scenarios focusing on the subpopulation of patients who are on Ig maintenance (Subpopulation 1), are Ig dependent (Subpopulation 2), or are Ig-dependent at an ultra-high dose of Ig (Subpopulation 3).

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

The characteristics of the simulated patient cohort at model entry (for both base case and scenarios) are estimated based on the characteristics of the ADHERE cohort (Ig pre-treated patients) at screening (see Table 25). The mean weight in the trial can be seen as a conservative estimate, based on the mean weight of the general English population for 2021.¹⁴⁶

Table 25: Baseline model cohort characteristics

Characteristics	Model Input
Initial age (years), mean	55.1
Weight (kg), mean	80.6
Females (%)	38.8%

3.2.2 Treatment pathways

In both the intervention and the comparator arm, each of the three groups of patients included in the base case population (patients on treatment with Ig, Ig intolerant patients, and Ig refractory patients) is allocated to a different treatment pathway.

3.2.2.1 Treatment pathway in the intervention arm

Although there is no induction protocol for efgartigimod, in the intervention arm, the cohort receives induction with efgartigimod over a three-month period (this is not explicitly modelled, but a one-off cost for this is added at the start of the maintenance phase). After the induction period, the proportion of the cohort that responds to the treatment receives efgartigimod maintenance until death or discontinuation due to unplanned reasons (e.g., adverse events [AEs]).

The proportion of the cohort that does not respond to treatment or that discontinues due to unplanned reasons starts subsequent lines of treatment, which change depending on the patient subpopulation.

3.2.2.1.1 Proportion of cohort on treatment with Ig maintenance before entering the simulation

After efgartigimod discontinuation, the proportion of the cohort that was on treatment with Ig before starting the simulation (95% of the model cohort) can either restart Ig maintenance or is distributed across a basket of other treatments (plasma exchange [PLEX], corticosteroids, or immunosuppressants). The distribution of patients across the basket of other treatments was informed by UK clinical experts, with the distribution detailed in Table 26.

Table 26: Distribution across treatments after efgartigimod discontinuation

Treatment	Cohort distribution after efgartigimod discontinuation
Ig	31.0%
PLEX	14.5%
Corticosteroids	49.9%
Immunosuppressants	4.6%

Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Over time, the proportion that restarted Ig maintenance can discontinue Ig due to unplanned reasons and is also distributed across the basket of other treatments (Table 27 and Figure 14). The distribution of patients across the basket of other treatments was informed by UK clinical experts.¹⁶

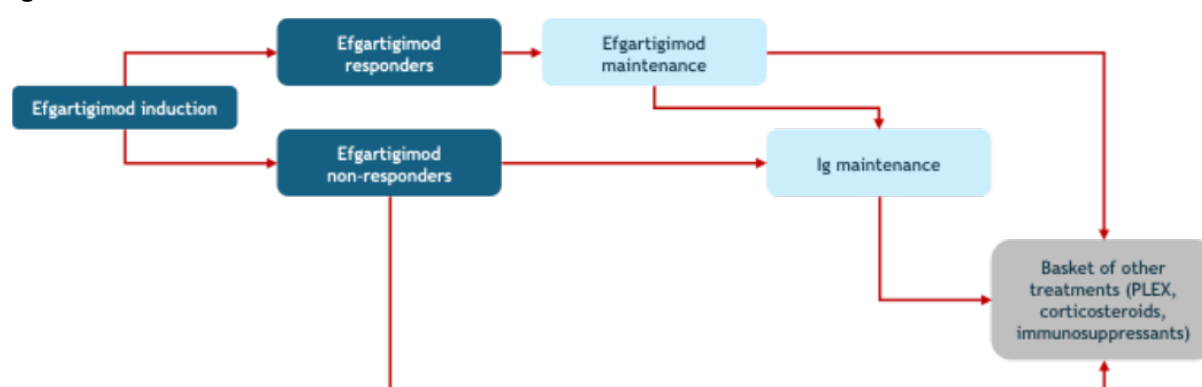
Table 27: Distribution across treatments after Ig discontinuation

Treatment	Cohort distribution after Ig discontinuation
PLEX	22.9%
Corticosteroids	77.0%
Immunosuppressants	0.1%

Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange.

No further unplanned discontinuations are assumed for the proportion of the cohort that is treated with the basket of other treatments.

Figure 14: Treatment pathway in the intervention arm, proportion of cohort on treatment with Ig before simulation start

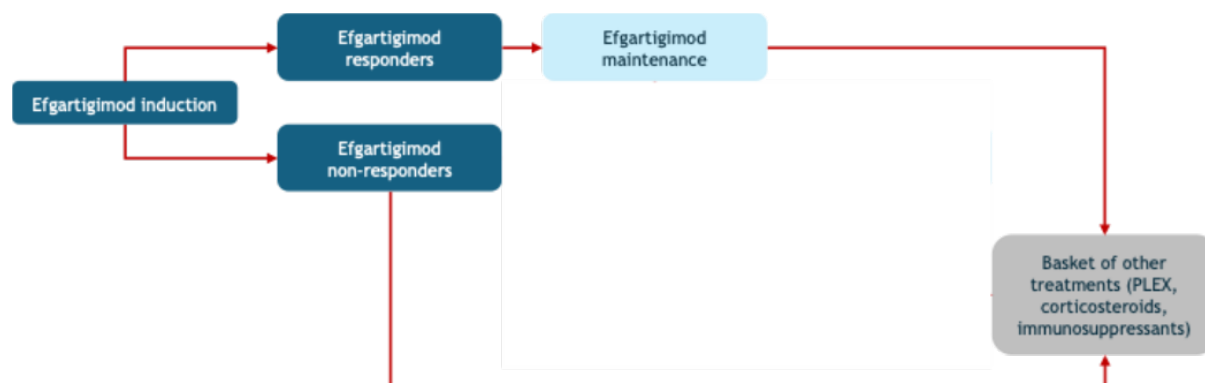


Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange.

3.2.2.1.2 Proportion of Ig-intolerant and Ig-refractory cohort

After efgartigimod discontinuation, the proportion of the cohort that was either Ig intolerant (2.5%) or Ig refractory (2.5%) before starting the simulation is fully allocated to a basket of other treatments (PLEX, corticosteroids, or immunosuppressants), with no part of the cohort starting treatment with Ig (Figure 15 and Table 27).¹⁶

Figure 15: Treatment pathway in the intervention arm, proportion of Ig intolerant and Ig refractory cohort



Abbreviations: PLEX: Plasma exchange.

3.2.2.2 Treatment pathway in the comparator arm

As for the intervention arm, the treatment pathway in the comparator arm depends on the specific patient subpopulation.

3.2.2.2.1 Proportion of cohort on treatment with Ig maintenance before entering the simulation

The proportion of the cohort that is treated with Ig maintenance continues receiving it after starting the simulation but can discontinue over time due to unplanned reasons. A one-off cost covering three months of maintenance treatment is included in the first model cycle to align with the costs of three months of induction therapy added one-off to the efgartigimod arm.

The proportion of the cohort that discontinues Ig maintenance is distributed across the same basket of treatments used in the pathway for the intervention arm (PLEX, corticosteroids, immunosuppressants) (Figure 16 and Table 27).

Figure 16: Treatment pathway in the comparator arm, proportion of cohort on treatment with Ig maintenance before simulation start



Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange.

3.2.2.2.2 Proportion of Ig-intolerant and Ig-refractory cohort

In the comparator arm, the proportion of the cohort that is Ig-intolerant or Ig-refractory starts the simulation already allocated to the basket of other treatments (PLEX, corticosteroids, immunosuppressants). The distribution across treatments is assumed to be the same as after Ig discontinuation and is detailed in Table 27. This assumption is consistent with the approach adopted, for which, unless there is a clear clinical rationale to model differences between two treatments, they have been treated as the same.

3.2.2.2.3 Ig products included in the CEM

The CEM includes the following Ig products:

- Privigen (IVIg)
- Gamunex (IVIg)
- Hizentra (SCIg)
- Flebogamma DIF (IVIg)

All Ig products are assumed to be associated with the same efficacy (see section 3.3.3.3). However, the drug acquisition costs are informed separately for each Ig product, as detailed in Section 3.5. Similarly, the incidence of AEs is informed separately for each Ig product (see Section 3.3.3.2). The administration schedule is informed separately for IVIg and SCIg products, with all products in each category assumed to be administered based on the same schedule (see Section 3.5.1.3).

The weighting applied to the Ig products is described in Table 28. This data was informed by data from a UK chart review study²³.

Table 28: Cohort distribution across Ig products

Ig products	Cohort distribution
Privigen	51.28%
Gamunex	38.46%
Flebogamma DIF	5.13%
Hizentra	5.13%

Abbreviations: Ig: immunoglobulin

The comparators modelled are representative of the Ig products currently in use across UK neurology centres. Under the new national immunoglobulin framework, product availability may change, and certain brands may no longer be routinely supplied.¹⁹ Transitions to alternative products are expected to occur progressively, with some patients remaining on legacy therapies. To maintain simplicity and comparability, the analysis applies a uniform discount to Ig list prices (■■■■), and any future brand substitution is unlikely to materially affect overall cost estimates given the small inter-product price differentials. The non-drug costs of Ig treatment can be found in (Section 3.5.2).

3.2.3 Model health states

The health states are defined based on both the disease severity level and whether patients have active disease or are in remission.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

A two-pronged procedure was used to identify relevant health states:

- In the first step, a quantitative analysis of the ADHERE data was used to cluster the observations in health states representing different levels of disease severity.
 - The quantitative analysis clustered the ADHERE observations based on the total adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) score to obtain health states that were differentiated in terms of disease severity. A machine learning algorithm was developed to cluster the observations according to the following criteria:
 - Observations from the same level of the aINCAT total score could not be assigned to different health states.
 - To limit the possible combinations, only observations belonging to adjacent levels of the aINCAT total score could be clustered in the same health state.
 - Finally, the observations were clustered so that the disease severity was as differentiated as possible across different health states but as similar as possible within each health state. The EuroQol 5-Dimensions (EQ-5D) data based on UK preference weights was used as a measure of disease severity.
 - Starting from 11 health states corresponding to each level of the total aINCAT score, each iteration of the algorithm tested possible aggregations of the existing health states and selected the aggregation associated with the lowest increase in within-cluster dissimilarity across the sample. Dissimilarity was assessed using the sum of squares residuals, and the optimal number of health states was selected using the Gap statistic.¹⁴⁷
 - The algorithm was run on 1,000 bootstrap data samples from ADHERE to assess which set of health states were most frequently selected as optimal. The four most commonly selected sets were advanced to the second step of the analysis. ANOVA was used to test whether the health states in each of these four sets were significantly different in terms of health-related quality of life (HRQoL).
- In the second step, the health states determined with the quantitative analyses were refined by considering the definition of functional impairment associated with each level of the aINCAT disability score⁵⁶.
 - Table 29 provides an overview of the functional impairment definitions associated with each level of the aINCAT score for the two separate components.

Table 29: Functional impairment associated with each level of the aINCAT disability score⁵⁶

aINCAT disability score	Arm component	Leg component
Level 0	No upper limb problems	Walking not affected
Level 1	Symptoms, in one or both arms, not affecting the ability to perform ADLs ¹	Walking affected, but walks independently outdoors
Level 2	Symptoms, in one arm or both arms, affecting but not preventing any ADLs ¹	Usually uses unilateral support to walk outdoors
Level 3	Symptoms, in one arm or both arms, preventing one or two ADLs ¹	Usually uses bilateral support to walk outdoors
Level 4	Symptoms, in one arm or both arms, preventing three or all ADLs ¹	Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps with help
Level 5	Inability to use either arm for any purposeful movement	Restricted to wheelchair, unable to stand and walk a few steps with help
1. Doing all zips and buttons; washing or brushing hair; using a knife and fork together; handling small coins		

Abbreviations: ADL: Activity of daily living; aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score.

The aINCAT disability score is preferred over other measures of functional impairment available from ADHERE such as the Inflammatory Rasch-built Overall Disability Scale (I-RODS) score, Medical Research Council (MRC) sum score, Timed Up and Go (TUG) and MGS, for the following reasons:

- It is used to define the primary endpoints in the ADHERE trial.⁵⁵
- It is commonly reported in the literature as a measure of functional impairment.
- Compared to other measures of functional impairment, aINCAT was considered more suitable for measuring disease severity since it is not based on patient-reported outcomes and captures sensory impairments.
 - Although the two separate components of aINCAT may allow capturing the health state of patients who are impaired only in the arms or legs in more detail, the total aINCAT score represents an appropriate choice for most CIDP patients.
 - Moreover, using the total aINCAT score as a base to define the CEM health states avoids an overly complex model structure.

Four clinical experts validated the health states defined through the two-pronged approach. The clinicians used were not the same as the clinicians that provided input into other aspects of the submission, displaying the consistency in feedback that exists across multiple experts. The validation process consists of two rounds of interviews.¹⁴⁸ In Round 1, individual interviews were conducted with the single experts.¹⁴⁸ In Round 2, a consensus meeting was conducted with all clinical experts.¹⁴⁸

The analysis results in five levels of disease severity (Very limited impairment, Mild impairment, Moderate impairment, Severe impairment, and Very severe impairment) which are presented in Table 30. The five health states are well-differentiated in terms of mean HRQoL (Table 31 and Figure 17).

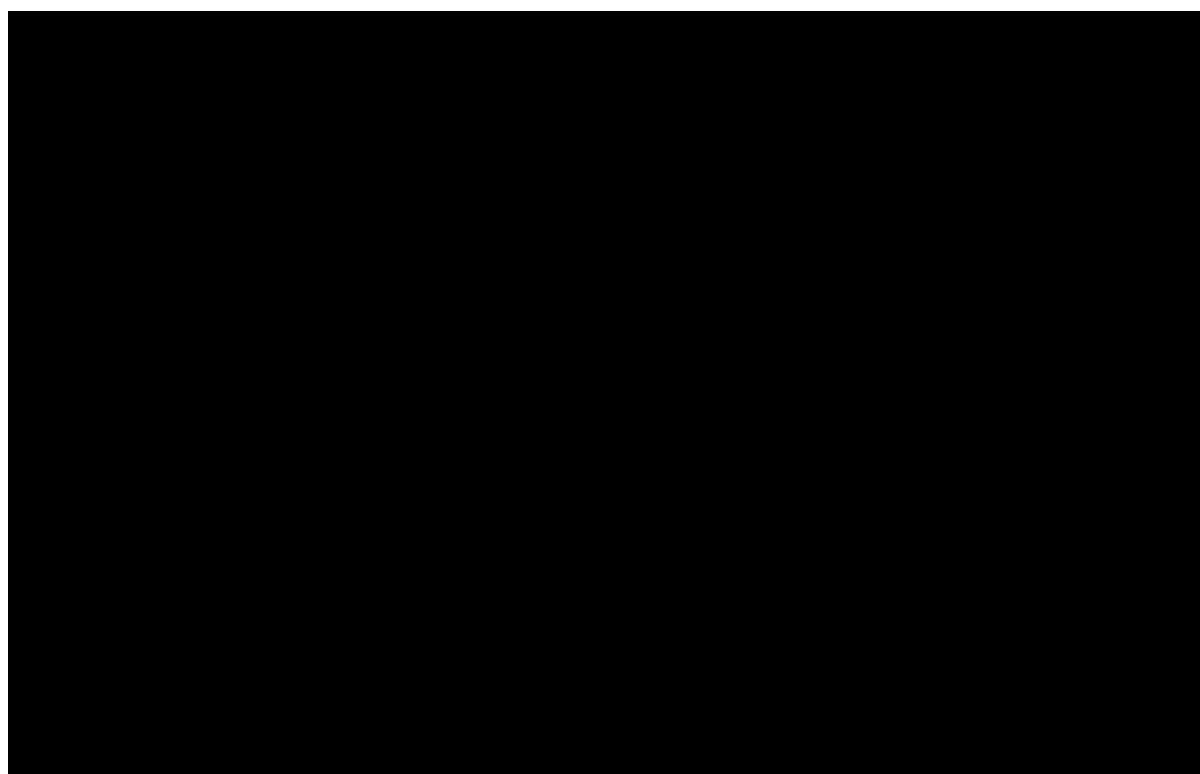
Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 30: Definitions of model health states

Health State	aINCAT score ⁵⁶
Very limited impairment, active disease	0-1
Very limited impairment, remission	
Mild impairment, active disease	2-3
Mild impairment, remission	
Moderate impairment, active disease	4-6
Moderate impairment, remission	
Severe impairment, active disease	7-8
Very severe impairment, active disease	9-10
Death	N/A

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment.

Figure 17: Health state EQ-5D values



Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; CI: Confidence interval.

Importantly, the utility drops progressively through each level of severity with larger drops in aINCAT scores where a wheelchair is often required, reflecting the continuous nature of the disease and particularly high burden at more advanced stages.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 31: Utility associated with each health state

Health state	N	Mean (SD)	Median (IQR)	Min-max
Very limited impairment				
Mild impairment				
Moderate impairment				
Severe impairment				
Very severe impairment				

Abbreviations: IQR: Inter-quartile range; SD : Standard deviation.

For the three lower levels of disease severity (Very limited, Mild, and Moderate impairment), there are distinct health states for active disease versus remission. This is based on literature data showing that CIDP patients on maintenance treatment undergo regular cessation trials to assess whether they are in remission and no longer require treatment^{117,118}. This was further confirmed by UK clinical experts.¹⁴⁸ In UK clinical practice, this process is applied selectively, with only a proportion of patients considered eligible for formal cessation trials as part of ongoing Ig review and optimisation programmes.¹⁴⁸

3.2.4 Model structure

A de-novo Markov model was developed in Microsoft Excel. The cohort can transition between different health states at each Markov cycle based on transition probabilities (TPs). For the cohort on treatment with efgartigimod maintenance, the TPs are estimated based on the ADHERE data. For the proportion of the cohort treated with Ig maintenance, the TPs are estimated by applying the results of an indirect treatment comparison (ITC) analysis to the ADHERE data.

At the start of the simulation, the cohorts in both arms are distributed across active disease health states as follows:

- The proportion of the cohort that is on Ig-maintenance before entering the simulation (95% in the base case) and the proportion that is Ig-intolerant (2.5% in the base case) are distributed based on the disease severity observed at ADHERE run-in baseline (before patients interrupted any prior treatment).
- The proportion of Ig-refractory cohort (2.5% in the base case) is distributed based on the disease severity observed at ADHERE Stage A baseline (when patients had deteriorated following treatment withdrawal).

After one cycle in the simulation, the proportion of the cohort that responds to efgartigimod is assumed to switch to the disease severity observed at Stage B baseline in ADHERE.

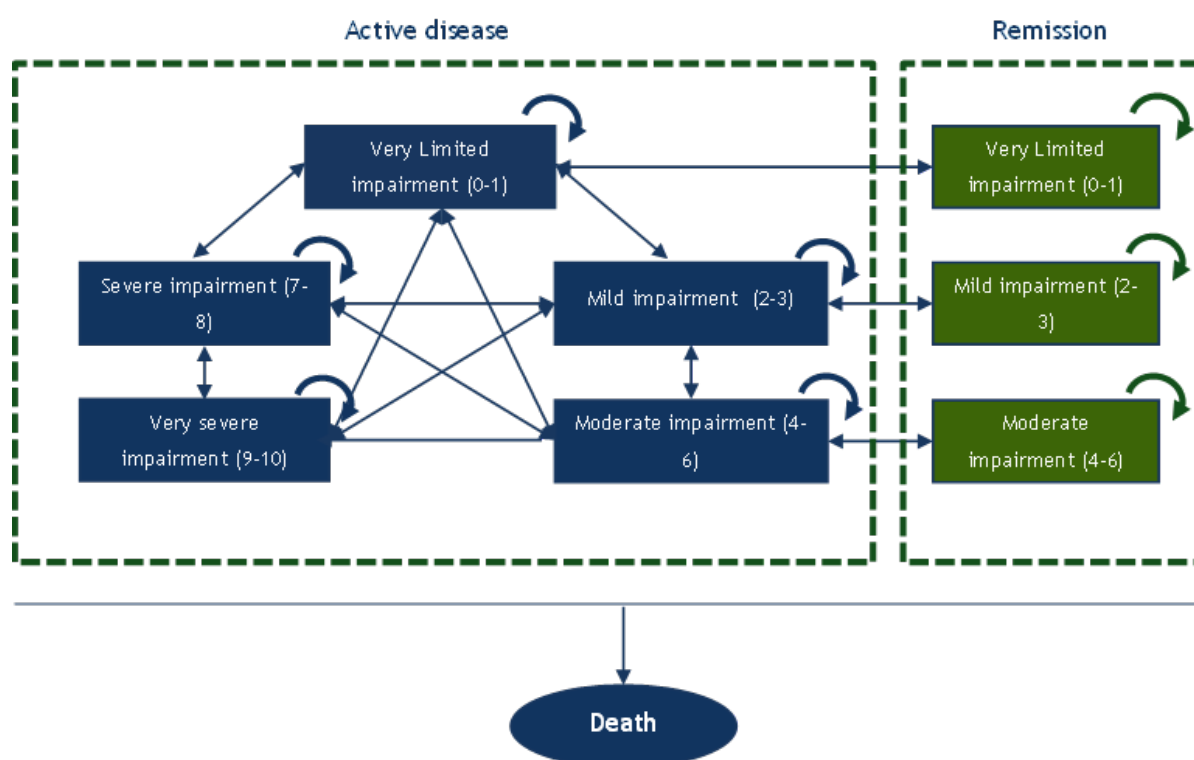
Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

At each cycle, the cohort in the three lower levels of disease severity (Very limited, Mild, and Moderate impairment) can enter remission. While in remission, no change in disease severity is assumed (i.e., there is no transition across health states), and the cohort does not incur any treatment cost. In the base case, the cohort treated with efgartigimod can enter remission only starting from the third model cycle as patients are assumed to remain on treatment for at least 12 months before attempting a dependency test. The cohort treated with Ig maintenance can enter remission from simulation start. Alternative scenarios allow remission in both arms at simulation start, at three months, or disable it entirely. At each cycle, the cohort in remission can return to active disease, with the cycle probability of returning to active disease being [REDACTED] (Table 36).

In both arms, the cohort that discontinued Ig maintenance and is treated with the basket of other treatments is assumed to always remain in a state of active disease.

In the base case, the cohort can move between the health states and death as given in Figure 18.

Figure 18: Model structure



3.2.4.1 Distribution at baseline

The baseline disease severity for both arms is as per Table 32. The distribution of the cohort in the Ig-refractory population is provided in Table 33. Both cohorts are assumed to start the simulation in active disease.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

The cohort that responds to efgartigimod induction moves to the distribution shown in Table 34 at the second cycle of the simulation.

Table 32: Distribution of the cohort at baseline (intervention and comparator arms)

CIDP state	Health State	Proportion
Active disease	Very limited impairment	0.0%
	Mild impairment	42.1%
	Moderate impairment	51.8%
	Severe impairment	5.5%
	Very severe impairment	0.6%
Remission	Very limited impairment	0.0%
	Mild impairment	0.0%
	Moderate impairment	0.0%

Source: ADHERE data; screening baseline

Abbreviations: CIDP: chronic inflammatory demyelinating polyneuropathy.

Table 33: Distribution of the cohort at baseline (Ig-refractory)

CIDP state	Health state	Proportion
Active disease	Very limited impairment	0.0%
	Mild impairment	27.4%
	Moderate impairment	58.5%
	Severe impairment	9.8%
	Very severe impairment	4.3%
Remission	Very limited impairment	0.0%
	Mild impairment	0.0%
	Moderate impairment	0.0%

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy.

Table 34: Distribution of the cohort after response to efgartigimod

CIDP state	Health State	Proportion
Active disease	Very limited impairment	19.8%
	Mild impairment	54.2%
	Moderate impairment	24.0%
	Severe impairment	2.1%
	Very severe impairment	0.0%
Remission	Very limited impairment	0.0%
	Mild impairment	0.0%
	Moderate impairment	0.0%

Source: ADHERE data; stage B baseline

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy.

3.2.5 Features of the economic analysis

An overview of the features of the economic analysis is provided in Table 35, which outlines model parameters and sources that were considered when performing the analysis for efgartigimod.

Due to the chronic nature of the disease, the time horizon of the simulation corresponds to a patient's lifetime. The simulation is conducted in six-month cycles, with the first cycle incorporating the three-month induction phase for efgartigimod, and runs for a total of 45 years (90 cycles). This is in line with the NICE recommendation that the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared¹⁴⁹ the time horizon was estimated as 100 – mean age at baseline (100 – 55 = 45 years).

A six-month cycle duration aligns well with standard intervals for assessing dose adjustments of Ig, while remaining short enough to detect the changes in the aINCAT disability score from ADHERE, which are used to estimate the transition probabilities in the model (see Section 3.3.3).

In line with the NICE reference case, benefits and costs were accrued in each cycle and were discounted annually at a rate of 3.5% for both benefits and costs.

Table 35: Features of economic analysis

Factor	NICE Reference case	Current evaluation, chosen values	Current evaluation, justification
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	Lifetime horizon	Due to the chronic nature of the disease, the time horizon of the simulation corresponds to a patient's lifetime (up until an average age of 100-years). The simulation runs for a total of 800 cycles.
Cycle length	The cycle length should be sufficiently short enough to capture clinical changes, but long enough to maintain computational efficiency.	6-months	The duration aligns with standard intervals for assessing dose adjustments of Ig, while remaining short enough to detect the changes in the aINCAT disability score from ADHERE.
Source of utilities	EQ-5D measured directly from patients, valued using UK population preferences.	The quality of life was stratified by health state. No treatment-specific utility values are used.	A mixed model is fitted on the ADHERE data to estimate the utility (measured using UK Tariffs) associated with each health state. All observations in both Stage A and Stage B (including the placebo arm) were used. The mixed model includes a random effect

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Factor	NICE Reference case	Current evaluation, chosen values	Current evaluation, justification
			that accounts for repeated observations from the same patient.
Source of costs	NHS and PSS perspective, using prices relevant to NHS and PSS.	The costs are presented in 2024 British Pounds (£). Costs were sourced from the following: • PSSRU 2023 • PSSRU 2015 • NHS National Cost Collection 2023/24 • 25/26 NHSPS Annex A	In line with NICE reference case. ¹⁵⁰

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; EQ-5D: EuroQol 5-Dimension Quality of Life Measure; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; NHSPS: NHS Payment Scheme; UK: United Kingdom.

3.2.6 Intervention technology and comparators

The economic model allows the cost and efficacy of efgartigimod to be compared with established clinical management without efgartigimod, including but not limited to:

- Corticosteroids
- Igs (IVIg and SCIg)
- PLEX
- Immunosuppressive therapies

The base case model population reflects patients with CIDP who have been previously treated with immunoglobulin, consistent with the ADHERE trial population and current UK clinical practice, where the mainstay of maintenance therapy is IVIg or SCIg (Table 28). This alignment ensures that the economic evaluation captures the most clinically relevant and appropriate subpopulation for whom efgartigimod would be considered an alternative treatment option.

3.3 Clinical parameters and variables

The clinical parameters that inform the CEM include the response rate to efgartigimod, the TPs between the health states, and the risk of hospitalisation.

3.3.1 Response rate

The response rate associated with efgartigimod is informed based on the response rate observed during ADHERE Stage A. For the Ig pre-treated population, the response rate is 58.8% (95%CI: 50.9%, 66.4%).

3.3.2 Probability to enter remission and relapse

In the comparator arm, the probability of going into remission while on Ig maintenance was calculated based on the following:

- The proportion of patients on a stable Ig dose at each cycle, as estimated based on Koay et al¹⁵¹, who report that 76 out of 125 patients (60.8%) on Ig maintenance had been on a stable dose for the previous 12 months. In the CEM, this was interpreted as a cross-sectional estimate—i.e., at any given time, 60.8% of patients on Ig maintenance are assumed to be on a stable dose.
- Among patients on stable Ig dose, the proportion of patients eligible and willing to undergo a dependency test at each cycle. This was multiplied by the probability of remaining clinically stable for at least six months after a successful dependency test. These values were informed through a Structured Expert Elicitation (SEE) process with five clinical experts in the UK. This led to a probability of 8.52% to go into remission at each cycle (see Table 36 below).

In the intervention arm, the probability of entering remission while on efgartigimod maintenance was informed using the same inputs. This was validated by UK clinical experts who indicated that remission rates are driven by the nature of the disease rather than the treatment itself. Additionally, experts explicitly confirmed that applying the same remission rate to both arms in the CEM is appropriate.

The probability of returning to active disease from remission was also informed through the SEE process.¹⁶ Clinical experts were asked to estimate the proportion of patients, among those in remission at six months, who remain in remission for one additional year.¹⁶ The complement of this value, adjusted for a six-month duration, was used to inform the cycle probability of returning to active disease, leading to a probability of 10.3% (see Table 36 below).

In the base case, there is no deterioration upon return to active disease, as patients are regularly monitored and expected to restart treatment before any clinically meaningful worsening occurs.

The probabilities of transitioning between active disease and remission were incorporated into the health state TPs by adjusting the latter to reflect the combined likelihood of both health state progression and remission status changes within each cycle.

Table 36: Inputs to inform cycle probability of entering remission and returning to active disease

Parameter	Value	Source
Proportion of patients on a stable dose of Ig at each cycle	60.8%	Koay et al, 2025 ¹⁵¹
Proportion of patients on Ig stable dose willing and eligible to undergo a dependency test	45.2%	SEE with UK clinical experts ¹⁶
Proportion of patients who successfully discontinue Ig after the dependency test and remain clinically stable for the following 6 months	31.0%	SEE with UK clinical experts ¹⁶
Cycle probability of remission (both treatment arms)	8.52%	Product of the three parameters above
Proportion of patients, among those in remission at 6 months, who remain in remission for an additional 12 months	79.38%	SEE with UK clinical experts ¹⁶
Cycle probability of returning to active disease (both treatment arms)	10.31%	Complement of the value above, divided by two

Abbreviations: Ig: Immunoglobulin; SEE: Structured Expert Elicitation.

3.3.3 Transition probabilities

The TPs between different health states reflect the efficacy of efgartigimod and Ig. Therefore, they are estimated based on the aINCAT score values reported in the literature and observed in ADHERE. The efficacy of the basket of other treatments is assumed to be the same as for Ig, based on the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guidelines¹.

Time dependent TPs are used to inform the probability for the cohort to shift between different health states:

- As mentioned in Section 3.2.2, the induction phase is not being modelled explicitly. All patients start the simulation on maintenance treatment (however, one-off induction costs are included).
- To model the transitions during treatment maintenance, four sets of TPs are applied in sequence, each set applied to each of the first four cycles. The four sets are different for efgartigimod and Ig, to reflect the difference in treatment efficacy. For both treatments, transitions beyond cycle 4 (two years) are extrapolated assuming no further change in disease severity (no transition between health states), but the cohort can still transition between remission and active disease (if not being treated with PLEX, corticosteroids, or immunosuppressants).
- In the efgartigimod arm, the cohort that does not respond to induction or that discontinue maintenance due to unplanned reasons is assumed to start a subsequent line with either Ig or a basket of other treatments (see Section 3.2.2). Upon discontinuation, the same TPs as in the comparator arm are applied.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Sections 3.3.3.1 and 3.3.3.3 below detail how the TPs for the Intervention and the Comparator arm were informed.

3.3.3.1 Intervention arm

3.3.3.1.1 Maintenance with efgartigimod

To inform the TPs in the proportion of the cohort that receives efgartigimod maintenance, data from ADHERE Stage B and ADHERE open-label extension (ADHERE+) are pooled and analysed. To do the pooling, datasets from ADHERE and ADHERE+ were combined, and visit numbers in ADHERE+ were shifted so that numbering continued sequentially from baseline Stage B in ADHERE. The data cover a time horizon of ~36 months (144 Weeks), although data after ~24 months are based on a very limited number of patients (<10) and are, therefore, excluded from the analysis. The analysis includes only patients that are randomised to efgartigimod during ADHERE Stage B.

Starting from the baseline of Stage B, the number of patients shifting from each health state to the others over four distinct periods of 24 Weeks (for a total of 96 Weeks, ~24 months) is recorded. This provides four sets of TPs: from baseline to Week 24, from Week 24 to Week 48, from Week 48 to Week 72, and from Week 72 to Week 96. The four sets are applied, respectively, to the first four cycles of the simulation. In the base case, from the fifth cycle onwards, the identity matrix is applied, with the cohort only allowed to shift from active disease to remission and vice versa. Note that a scenario analysis is conducted in which the TP matrix used in cycle 4 is recycled over the entire time horizon (Section 3.11.3).

For patients in ADHERE who have a recorded visit at the beginning of each period but no recorded visit at the target date at the end of the period, the last available observation within the correspondent period is used. For example, if a patient has no recorded visit at Week 24 but a record at Week 22, the latter is used in the analysis.

Table 37 to Table 41 reports the TPs used in the cohort that is on-treatment with efgartigimod.

Table 37: Efgartigimod maintenance, cycle 1

		Active disease					Remission		
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited								
	Mild								
	Moderate								
	Severe								
	Very Severe								
Remission	Very Limited								
	Mild								
	Moderate								

Table 38: Efgartigimod maintenance, cycle 2

		Active disease					Remission		
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited								
	Mild								
	Moderate								
	Severe								
	Very Severe								
Remission	Very Limited								
	Mild								
	Moderate								

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 39: Efgartigimod maintenance, cycle 3

		Active disease					Remission		
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited								
	Mild								
	Moderate								
	Severe								
	Very Severe								
Remission	Very Limited								
	Mild								
	Moderate								

Table 40: Efgartigimod maintenance, cycle 4

		Active disease					Remission		
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited								
	Mild								
	Moderate								
	Severe								
	Very Severe								
Remission	Very Limited								
	Mild								
	Moderate								

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 41: Efgartigimod maintenance, cycle 5 onwards

		Active disease					Remission		
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited								
	Mild								
	Moderate								
	Severe								
	Very Severe								
Remission	Very Limited								
	Mild								
	Moderate								

3.3.3.2 Efgartigimod non-responders

The proportion of the cohort in the Intervention arm that does not respond to efgartigimod either restarts Ig maintenance or is distributed across a basket of other treatments (see Section 3.2.2.1). The same TPs as for the Comparator arm are applied, with no difference between Ig maintenance and maintenance with the basket of other treatments (see Section 3.3.3.3).

3.3.3.2.1 Post-discontinuation of efgartigimod maintenance

Upon discontinuation of efgartigimod maintenance due to unplanned reason (e.g. AEs), the cohort can either restart Ig maintenance or is distributed across a basket of other treatments (see Section 3.3.3.3).

The same TPs are applied for both maintenance with Ig and with the basket of other treatments. In both cases, upon efgartigimod discontinuation, a first TP set distributes the cohort across the health states to match the distribution observed at cycle 4 in the Comparator arm (Table 42 and Table 43 below), i.e., within one cycle the cohort is assumed to shift to the long term disease severity level associated with the comparator treatments. This allows to account for the different efficacy between efgartigimod and its comparators, while avoiding excessive computational complexity. In the base case, the cohort is distributed across health states in active disease only.

After the first cycle post-efgartigimod discontinuation, the same long-term TPs (cycle 5 onwards) used in the Comparator arm is applied (see Section 3.3.3.3). For the cohort's proportion that starts Ig maintenance after efgartigimod and further progresses to maintenance with the basket of other treatments, no additional deterioration is assumed (the same TPs continue to apply).

Table 42: Cohort distribution at cycle 4 in the Comparator arm (active disease only)

Health state	Distribution of the cohort (considering only active disease, excluding the proportion in the dead state)
Very Limited Impairment	■
Mild Impairment	■
Moderate Impairment	■
Severe Impairment	■
Very Severe Impairment	■

Table 43: Intervention arm, first cycle after efgartigimod discontinuation

		Active disease					Remission		
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited	■	■	■	■	■	■	■	■
	Mild	■	■	■	■	■	■	■	■
	Moderate	■	■	■	■	■	■	■	■
	Severe	■	■	■	■	■	■	■	■
	Very Severe	■	■	■	■	■	■	■	■
Remission	Very Limited	■	■	■	■	■	■	■	■
	Mild	■	■	■	■	■	■	■	■
	Moderate	■	■	■	■	■	■	■	■

3.3.3.3 Comparator arm: Ig maintenance

3.3.3.3.1 Comparative treatment efficacy

To reflect the comparative efficacy efgartigimod vs Ig maintenance, the results of an ITC were used to derive specific TPs that were applied to the cohort treated with the comparator treatments. The ITC results show that the ADHERE Stage B cohort experiences a mean change in aINCAT from baseline to the end of study visit (EoS) that is [REDACTED] better than the compared Ig cohort. A detailed description of the ITC methods is provided in Section 2.10 and **Appendix B**. This result is consistent with the unweighted analysis, which estimated the hazard ratio (HR) to be [REDACTED]. To translate this difference in TPs, the following approach is used:

- Starting from the shift counts used in the efgartigimod cohort, new sets of shift counts are estimated by assuming a difference of +1 point on the aINCAT scale from the efgartigimod cohort. For example, if a certain number of patients in the efgartigimod cohort transitions from aINCAT 1 to aINCAT 3 (a change in aINCAT of +2 points), the new set of shift counts assumes that they transition from aINCAT 1 to aINCAT 4 (a change in aINCAT of +3 points).
- The point estimates of the TP are obtained from the new sets of shift counts following the same approach used for the efgartigimod cohort (see Section 3.3.3.1.1).
- To reflect the difference between the cohort of [REDACTED], the final sets of TPs are obtained using a weighted average of the efgartigimod TPs and the new TPs obtained following the steps above, with [REDACTED]% of the weight given to the new TPs.

In the base case, it is assumed that efgartigimod treatment effect vs Ig applies for the first four cycles (two years) and does not persist beyond that time point. This assumption, based on the results of the MAIC analysis between ADHERE and ADVANCE-CIDP I (Section 2.10), is considered reasonable and consistent with the available clinical evidence and expert consensus regarding the relative efficacy of efgartigimod and Ig maintenance therapy in Ig-pretreated patients. The MAIC results for the pooled Ig treatment options (low-dose Hizentra, high-dose Hizentra, Hyqvia, Gamunex) resulted in a statistically significant difference between efgartigimod and Ig, further supporting the findings. The value from this output is used in the scenario analysis.

3.3.3.3.2 Transition probabilities

The TP matrices during maintenance with Ig mirror those used for efgartigimod (see Section 3.3.3.1.1 above), with the difference that the probability estimates are adjusted to reflect the comparative efficacy vs efgartigimod. The adjustment is done following the procedure detailed in Section 3.3.3.3 above. In the base case, similarly to what is done for efgartigimod maintenance, the identity matrix is applied beyond cycle 4, with the cohort only shifting between remission and active disease. Table 44 to Table 48 report the TP matrices used in the Ig cohort for maintenance with Ig.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

3.3.3.3.3 Post-discontinuation of Ig

Based on the EAN/PNS guidelines¹, the same efficacy is assumed for all comparators. Thus, the same TPs as for Ig maintenance (see Section 3.3.3.3) are used to inform the transitions after Ig discontinuation, the only difference being that patients are assumed to always remain on active disease.

3.3.3.4 Permanent treatment discontinuations

3.3.3.4.1 Permanent discontinuations of efgartigimod

The probability of unplanned treatment discontinuations is estimated based on the time on treatment observed in the pooled ADHERE Stage B and ADHERE+ data. To do the pooling, datasets from ADHERE and ADHERE+ were combined, and visit numbers in ADHERE+ were shifted so that numbering continued sequentially from baseline Stage B in ADHERE. A time-to-event analysis is conducted on the 49 patients who received efgartigimod in ADHERE Stage B. These patients are followed from baseline of ADHERE Stage B until their last observation in the pooled ADHERE and ADHERE+ dataset. Patients who do not roll-over to ADHERE Stage B are considered to have discontinued the treatment. Only discontinuations due to AEs or safety concerns (n=6) are considered for the analysis. Patients who discontinued treatment due to lack of efficacy, sponsor's decision, withdrawal from the trial, or use of prohibited medications are censored (n=4), since treatment with efgartigimod is unlikely to be discontinued for these reasons in a real-world setting.

There is uncertainty around long-term extrapolations of time on treatment with efgartigimod, and the values predicted by the parametric curves may lack face validity. Therefore, the base case only applies the Exponential curve (best fitting) for 18 months (three model cycles) and assume no further unplanned discontinuation from efgartigimod maintenance over the remaining time horizon. This aligns with the assumptions used to inform the time on treatment with Ig maintenance (see Section 3.3.3.4.2).

Parametric curves are fitted on the data (Table 49 and Figure 19).

Table 44: Ig maintenance, cycle 1

		Active disease						Remission	
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited								
	Mild								
	Moderate								
	Severe								
	Very Severe								
Remission	Very Limited								
	Mild								
	Moderate								

Abbreviations: Ig: Immunoglobulin.

Table 45: Ig maintenance, cycle 2

		Active disease						Remission	
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited								
	Mild								
	Moderate								
	Severe								
	Very Severe								
Remission	Very Limited								
	Mild								
	Moderate								

Abbreviations: Ig: Immunoglobulin.

Table 46: Ig maintenance, cycle 3

		Active disease					Remission		
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited	■	■	■	■	■	■	■	■
	Mild	■	■	■	■	■	■	■	■
	Moderate	■	■	■	■	■	■	■	■
	Severe	■	■	■	■	■	■	■	■
	Very Severe	■	■	■	■	■	■	■	■
Remission	Very Limited	■	■	■	■	■	■	■	■
	Mild	■	■	■	■	■	■	■	■
	Moderate	■	■	■	■	■	■	■	■

Abbreviations: Ig: Immunoglobulin.

Table 47: Ig maintenance, cycle 4

		Active disease					Remission		
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited	■	■	■	■	■	■	■	■
	Mild	■	■	■	■	■	■	■	■
	Moderate	■	■	■	■	■	■	■	■
	Severe	■	■	■	■	■	■	■	■
	Very Severe	■	■	■	■	■	■	■	■
Remission	Very Limited	■	■	■	■	■	■	■	■
	Mild	■	■	■	■	■	■	■	■
	Moderate	■	■	■	■	■	■	■	■

Abbreviations: Ig: Immunoglobulin.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 48: Ig maintenance, cycle 5 onwards

		Active disease					Remission		
		Very Limited	Mild	Moderate	Severe	Very severe	Very Limited	Mild	Moderate
Active disease	Very Limited	■	■	■	■	■	■	■	■
	Mild	■	■	■	■	■	■	■	■
	Moderate	■	■	■	■	■	■	■	■
	Severe	■	■	■	■	■	■	■	■
	Very Severe	■	■	■	■	■	■	■	■
Remission	Very Limited	■	■	■	■	■	■	■	■
	Mild	■	■	■	■	■	■	■	■
	Moderate	■	■	■	■	■	■	■	■

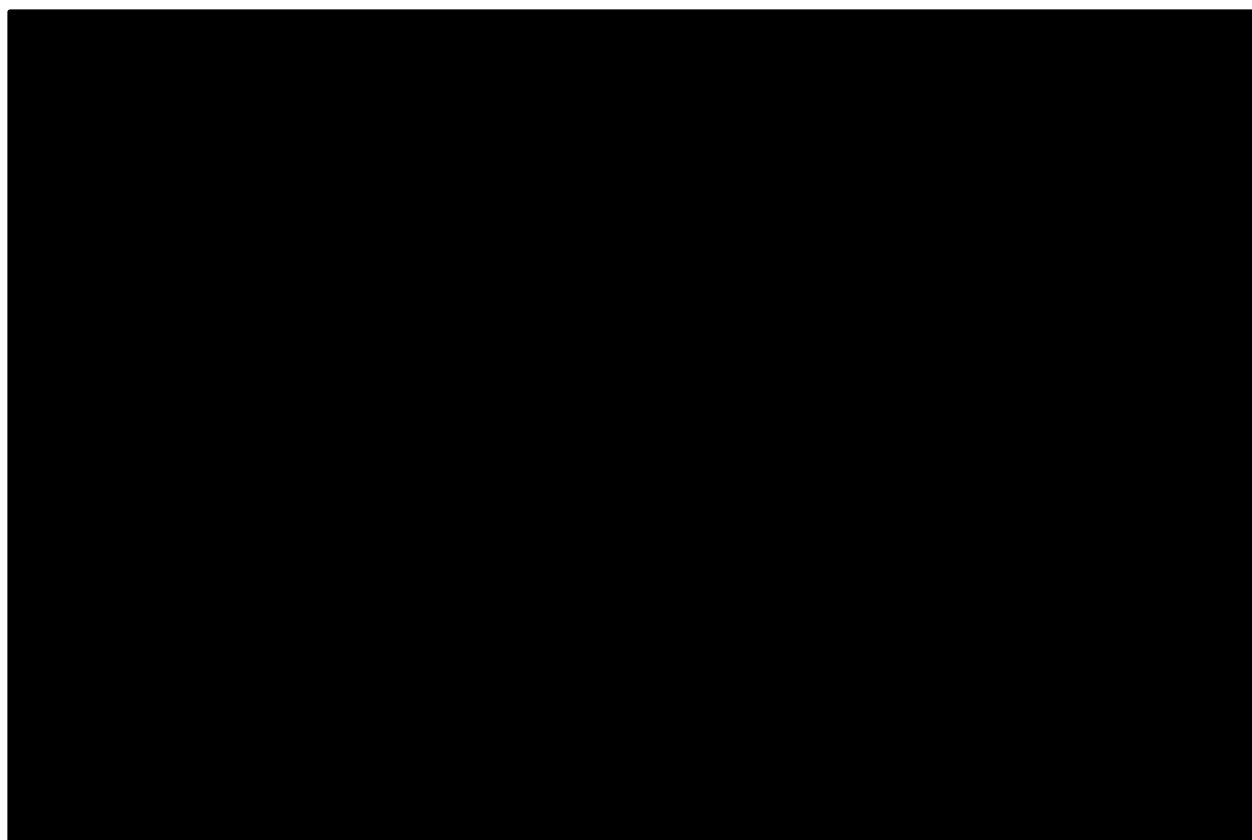
Abbreviations: Ig: Immunoglobulin.

Table 49: Fitting of the parametric curves on the Time on Treatment data from pooled ADHERE and ADHERE+

Statistics	Exponential	Weibull	Lognormal	Loglogistic	Gompertz	Gamma
AIC+ BIC						
AIC						
BIC						

Abbreviations: AIC: Aikake information criterion; BIC: Bayesian information criterion.

Figure 19: Time on Treatment on efgartigimod maintenance



Abbreviations: KM: Kaplan-Meier. *Please note that the y-axis begins at 50% in Figure 19. This is to display the granularity of the differences between the curves. There is no detail omitted from the graph by restricting the view to beginning at 50%.

3.3.3.4.2 Permanent treatment discontinuations in the Ig arm

The risk of discontinuing Ig maintenance is assumed to decline over time, as intolerant patients tend to stop early, leaving a more tolerant cohort that is less likely to discontinue. This was confirmed by clinical experts in the UK, who noted that Ig discontinuations due to AEs or other unplanned reasons are uncommon beyond 12–18 months of treatment.¹⁵²

To account for this, two different inputs are used in the model, representing, respectively, the risk of discontinuation in the first cycle (zero to six months), and in the second and third cycles (six to 18 months). Beyond 18 months, the risk of discontinuing Ig maintenance is set to zero.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

The inputs are informed based on aggregate data from the literature, considering the pivotal studies for Gamunex (ICE study)⁵⁷ and Hizentra (PATH study and PATH study open-label extension)^{60,153}. The trial's time horizon, the number of exposed patients, and the number of discontinuations due to unplanned reasons were used to estimate the discontinuation rate, which was then transformed in the corresponding six-month probability. Estimates from the ICE study⁵⁷, and the PATH study⁶⁰ were averaged and used to inform the discontinuation probability during the first cycle, as all these studies have a six-month time horizon. Data from the PATH study open-label extension (extending the time horizon for one additional year beyond the PATH study)¹⁵³ were used to inform the probability during the second and third cycles. For each study, the relevant unplanned reasons considered for the analysis include AEs and physician decision.

Table 50 shows the inputs used to inform the probability of unplanned discontinuations of Ig maintenance.

Table 50: Unplanned discontinuation of Ig maintenance

Cycle	Probability of Ig unplanned discontinuation	Source
Cycle 1 (0 to 6 months)	7.49%	Pooled estimates from ICE study ⁵⁷ and PATH study ⁶⁰
Cycle 2 and Cycle 3 (6 to 18 months)	3.36%	PATH open-label extension ¹⁵³
Cycle 4 onwards	0.00%	Assumption based on input from clinical experts in the UK

Abbreviations: Ig: Immunoglobulin.

3.3.3.5 Hospitalisations

The model includes hospitalisation events due to CIDP worsening. The risk of hospitalisation events was informed based on the results of the Adelphi study, a patient and physician cross-sectional survey conducted in France, Germany, Italy, Spain, the UK, Japan, and the US between September 2022 and April 2023.⁷⁷

The study reports the number and duration of hospitalisations in the 12 months prior to the survey, stratified by disease severity. The survey further distinguished between hospitalisations with and without ICU admission (Table 51 and Table 52). The six-month probability was derived from the annual probability by using standard statistical formulas. The risk of hospitalisation events is only applied to the proportion of the cohort in active disease states.

Table 51: Risk of hospitalisation without ICU admission

Disease severity level	6-month probability
Very limited impairment	3.36%
Mild impairment	4.97%
Moderate impairment	4.71%
Severe impairment	6.12%
Very severe impairment	6.12%

Abbreviations: ICU: Intensive care unit.

Table 52: Risk of hospitalisation with ICU admission

Disease severity level	6-month probability
Very limited impairment	0.00%
Mild impairment	0.00%
Moderate impairment	3.20%
Severe impairment	25.03%
Very severe impairment	25.03%

Abbreviations: ICU: Intensive care unit.

3.3.3.6 Mortality

The model cohort is assumed to have the same mortality as the general population. This is in line with the literature on CIDP, which found that CIDP patients have a similar life expectancy as the general population.⁹¹ Age- and sex-specific all-cause mortality rates for the general UK population are applied to the cohort at each cycle¹⁵⁴. The mortality rate is the same across health states.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

HRQoL data used in the model was sourced from the ADHERE clinical trial. A mixed model was fitted to the ADHERE clinical trial data to estimate the utility values for each health state.

An SLR used to identify HRQoL studies for efgartigimod and comparator treatments was conducted and is described below.

3.4.2 Mapping

EQ-5D-5L data from Trial A were converted into health utility values using the mapping algorithm developed by Hernández-Alava et al.¹⁵⁵

3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify HRQoL studies for efgartigimod and comparator treatments for the management of CIDP. Full details of the methodology and results

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

(PRISMA diagram, included and excluded studies) of the SLR are provided in **Appendix E and F**.

3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

3.4.4.1 Health state utilities

The quality of life was stratified by health state. No treatment-specific utility values are used. A mixed model is fitted on the ADHERE data to estimate the utility (measured using UK Tariffs) associated with each health state. All observations in both Stage A and Stage B (including the placebo arm) were used. The mixed model includes a random effect that accounts for repeated observations from the same patient.

The negative utility value for the very severe impairment state (−0.216) reflects the substantial loss of function and independence observed in this subpopulation, consistent with health states that patients perceive as worse than death. This cohort represents a small proportion of the overall model population but illustrates the profound impact of end-stage CIDP on quality of life. The negative utility value is consistent with the findings in the Adelphi publication (n=1,056), which reports a lower bound EQ-5D value of -0.225⁷⁷. The Adelphi study also conducted an analysis on the UK data set¹⁵⁶ which showed that those with an INCAT of 9-10 had a mean utility of -0.11. However, it should be noted that this is based on a sample size of two and therefore should be interpreted with caution. There is precedent for negative health state utilities in other technology appraisals e.g. advanced multiple sclerosis. In the ponesimod NICE appraisal (TA767) the committee papers note the health states for EDSS 8 and 9 used negative utilities.

Table 53: Utility by health state

Health state	Mean (SE) utility
Very limited impairment	0.851 (0.024)
Mild impairment	0.630 (0.013)
Moderate impairment	0.426 (0.012)
Severe impairment	0.084 (0.025)
Very severe impairment	-0.216 (0.046)

Source: ADHERE data.

Abbreviations: SE: Standard error.

3.4.4.2 General population utility values

The sex- and age-specific utility of the general population is used to adjust the utility values of the cohort for aging of the cohort. The utility in the general population by age and sex is based on the data reported in the study by Hernández Alava et al. (2018)¹⁵⁷

3.4.5 Adverse events

3.4.5.1 Efgartigimod maintenance

The incidence of AEs associated with efgartigimod in the model is based on data from the ADHERE trial. The analysis includes treatment-emergent AEs observed in Stage B, affecting at least 5% of patients treated with efgartigimod. The model includes the AE incidence after adjusting for the monthly cycle length (Table 54).

Table 54: Incidence of AEs per cycle for efgartigimod arm (affecting at least 5% of patients in the full safety population)

Type of AE	Incidence	Source
Infusion/injection site reaction	██████	ARGX-113-1802 CSR, Table 37
Upper respiratory tract infection	██████	ARGX-113-1802 CSR, Table 37

Abbreviations: AE: Adverse event.

3.4.5.2 Ig maintenance

The incidence of AEs associated with Ig is based on data reported in the literature, adjusted for the monthly cycle length^{57,144,153,158}.

The probability of AEs for the cohort treated with IVIg (Privigen and Gamunex) is adjusted to account for differences in dosing regimens. Both the PATH pre-randomisation phase¹⁵⁸ and the ICE study⁵⁷ use a maintenance schedule of 1 g/kg, which is considered the reference dose, i.e., the rates estimated from the trial data are considered as baseline rates (for a dose of 0.5–0.99 g/kg). HRs for doses of <0.5 g/kg, 1.0–2.0 g/kg, and 2.0 g/kg are sourced from Waheed et al¹⁵⁹ and applied to the baseline rate to derive the rate of AEs at different maintenance doses. Finally, to obtain a unique value for the AEs associated with Gamunex and Privigen, rates are transformed in six-month probabilities and averaged, weighting for distribution of the cohort across maintenance doses.

The CEM uses the average AE frequency in Privigen, Flebogamma, Gamunex, and Hizentra, weighted according to the cohort's distribution across the three treatments during the maintenance phase.

Table 55 and Table 56 below shows the HR reported by Waheed et al¹⁵⁹ and the per-cycle probability of AEs used in the CEM, respectively.

Table 55: HR for AEs at different IVIg doses

Dose in the model	HR	Source
<0.50 g/kg	1.10	Predicted odds of AE per infusion, dose: <0.50 g/kg per course ¹⁵⁹
0.50–0.99 g/kg	1.00	Predicted odds of AE per infusion, dose: 0.50–0.99 g/kg per course ¹⁵⁹
1.00–1.75 g/kg	2.50	Predicted odds of AE per infusion, dose: 1.00–1.75 g/kg per course ¹⁵⁹
>1.75 g/kg	4.58	Predicted odds of AE per infusion, dose: >1.75 g/kg per course ¹⁵⁹

Abbreviations: AE: Adverse event; HR: Hazard ratio; IVIg: Intravenous immunoglobulin.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 56: Per-cycle probability of AE in Ig maintenance

Type of AE	Per cycle probability
Arthralgia and pain in the extremities	4.9%
Asthenia	4.5%
Back pain	11.3%
Dizziness	1.5%
Fatigue	13.1%
Headache	52.4%
Haemolysis	9.0%
Hypertension	17.1%
Influenza	2.8%
Infusion/injection site reaction	19.9%
Nasopharyngitis	14.3%
Nausea	18.1%
Pyrexia	10.3%

Abbreviations: AE: Adverse event; Ig: Immunoglobulin.

3.4.5.3 Basket of other treatments

The probability of AEs for the cohort treated with PLEX is informed based on the values reported by Dorst et al, who investigated safety and tolerability of PLEX in neuroinflammatory diseases (including CIDP).¹⁶⁰ The authors reported incidence of different AEs over five exchanges; this was transformed in incidence per exchange and then in incidence per model-cycle (based on total of 24 exchange per cycle, as described in Section 3.5.1.6).

Table 57: Per-cycle probability of AE in PLEX maintenance

Type of AE	Reported incidence per 5 exchanges	Incidence per exchange	Per cycle probability
Infections	5.60%	1.15%	24.17%
Infusion/injection site reaction	5.60%	1.15%	24.17%
Fatigues	5.60%	1.15%	24.17%

Abbreviations: AE: Adverse event; PLEX: Plasma exchange.

The probability of AEs for the cohort treated with corticosteroids is informed based on values reported by Nobile-Orazio et al, who reported the incidence of AEs associated with a six-month cycle of intravenous methylprednisolone in 21 CIDP patients.¹²⁶ The reported incidence is applied directly in the model to inform the probability of AEs during one model cycle.

Table 58: Per-cycle probability of AE with corticosteroids

Type of AE	Per cycle probability
Arthralgia and pain in the extremities	4.76%
Hypertension	14.29%
Infections	4.76%
Psychiatric disorders	23.81%
Abdominal pain	14.29%
Endocrine disorders	9.52%
Peripheral oedema	9.52%

Abbreviations: AE: Adverse event.

The probability of AEs in the cohort treated with immunosuppressants is informed based on the rate of AEs reported by Narayanaswami et al, who reported incidence of AEs in patients suffering from myasthenia gravis (an autoimmune disorder of the neuromuscular junction) treated with mycophenolate mofetil for a median follow-up time of 25 months.¹⁶¹

Table 59: Per-cycle probability of AE with immunosuppressants

Type of AE	Per cycle probability
Anaemia	0.51%
Gastrointestinal disturbances	3.51%
Peripheral oedema	0.51%

Abbreviations: AE: Adverse event.

3.4.5.4 Complications related to intravenous administration route

In addition to the side effects associated with the active treatment, the intravenous administration carries the risk of complications such as phlebitis, infiltration, extravasation, and infections.^{162,163} To reflect this, in the CEM, the cohort receiving maintenance with IVIg or PLEX is subjected to an additional risk of developing complication related with the intravenous access.

The type and the incidence of complications was informed based on the parameter inputs used in a previously published budget impact model in CIDP and are reported in Table 60 below.¹⁶⁴

Table 60: Complications related to intravenous access

Type of complication	Per cycle probability
Permanent PICC, surgically implanted CVC, infusion port	10.0%
Catheter-related infections	0.5%
Catheter-related blood infections	0.8%
Thrombophlebitis	1.1%
Infiltration and extravasation	0.3%
Thromboembolic events	0.2%

Abbreviations: CVC: Central venous catheter; PICC: Peripherally inserted central catheter.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

3.4.6 Adverse event utility decrements

AE disutilities are included in the model. A targeted literature review (TLR) was conducted to identify the disutility associated with specific AEs (as detailed in **Appendix F**). Moreover, the duration of each AE is obtained from TA706, a NICE submission for a product targeting multiple sclerosis.¹⁶⁵ When the duration of a certain AE could not be retrieved, the average duration of other AEs is applied.

Two sources are used to calculate the utility decrements: Sullivan et al and TA706.^{165,166} If a disutility for a specific AE is reported in both sources, the average of the two values is used. For AEs where no disutility values are available, the average disutility of the other AEs is used.

Table 61: Duration of AEs

AE	Duration (day)
Arthralgia and pain in the extremities	11.47
Asthenia	Not available, the average duration of 21.56 days is used
Back Pain	11.47
Dizziness	Not available, the average duration of 21.56 days is used
Fatigue	Not available, the average duration of 21.56 days is used
Headache	11.45
Haemolysis	Not available, the average duration of 21.56 days is used
Hypertension	Not available, the average duration of 21.56 days is used
Influenza	1.00
Infusion/injection site reaction	13.00
Nasopharyngitis	Not available, the average duration of 21.56 days is used
Nausea	Not available, the average duration of 21.56 days is used
Pyrexia	Not available, the average duration of 21.56 days is used
Upper respiratory tract infection	7.48
Infections	Not available, the average duration of 21.56 days is used
Sleep disorders	21.56
Psychiatric disorders	95.03
Abdominal pain	Not available, the average duration of 21.56 days is used
Endocrine disorders	Not available, the average duration of 21.56 days is used
Anaemia	Not available, the average duration of 21.56 days is used
Gastrointestinal disturbances	Not available, the average duration of 21.56 days is used
Renal dysfunction	Not available, the average duration of 21.56 days is used
Peripheral oedema	Not available, the average duration of 21.56 days is used

Abbreviations: AE: Adverse event.

Table 62: AE disutilities

AE	Decrement	Source
Arthralgia and pain in the extremities	-0.160	NICE TA706, ¹⁶⁵ Sullivan et al (2011) ¹⁶⁶
Asthenia	-0.102	Not available in the literature. The average disutility value was used.
Back pain	-0.180	NICE TA706, ¹⁶⁵ Sullivan et al (2011) ¹⁶⁶
Dizziness	-0.102	Not available in the literature. The average disutility value was used.
Fatigue	-0.102	Not available in the literature. The average disutility value was used.
Headache	-0.102	NICE TA706, ¹⁶⁵ Sullivan et al (2011) ¹⁶⁶
Haemolysis	-0.060	Sullivan et al (2011) ¹⁶⁶
Hypertension	-0.050	Sullivan et al (2011) ¹⁶⁶
Influenza	-0.080	NICE TA706 ¹⁶⁵
Infusion/injection site reaction	-0.010	NICE TA706 ¹⁶⁵
Nasopharyngitis	-0.020	NICE TA706 ¹⁶⁵ Sullivan et al (2011) ¹⁶⁶
Nausea	-0.070	Sullivan et al (2011) ¹⁶⁶
Pyrexia	-0.102	Not available in the literature. The average disutility value was used.
Upper respiratory tract infection	-0.120	NICE TA706 ¹⁶⁵ Sullivan et al (2011) ¹⁶⁶
Infections	-0.102	Not available in the literature. The average disutility value was used.
Sleep disorders	-0.095	Sullivan et al (2011) ¹⁶⁶
Psychiatric disorders	-0.143	Sullivan et al (2011) ¹⁶⁶
Abdominal pain	-0.044	Sullivan et al (2011) ¹⁶⁶
Endocrine disorders	-0.030	Sullivan et al (2011) ¹⁶⁶
Anaemia	-0.022	Sullivan et al (2011) ¹⁶⁶
Gastrointestinal disturbances	-0.044	Sullivan et al (2011) ¹⁶⁶
Renal dysfunction	-0.101	Sullivan et al (2011) ¹⁶⁶
Peripheral oedema	-0.040	Sullivan et al (2011) ¹⁶⁶

Abbreviations: AE: Adverse event.

3.4.7 Disutilities associated with complications related to intravenous access

For the proportion of cohort treated with IVIg and PLEX, the CEM includes disutilities caused by complications related to intravenous access. These were informed based on values reported by Sullivan et al and by a previous NICE technology appraisal (NICE TA804).^{166,167}

Table 63: Disutilities related to intravenous access

Complication	Decrement	Duration (days)	Source
Permanent PICC, surgically implanted CVC, infusion port	-0.250	7	Average values
Catheter-related infections	-0.520	7	TA804 ¹⁶⁷
Catheter-related blood infections	-0.520	7	TA804 ¹⁶⁷
Thrombophlebitis	-0.083	7	Sullivan 2011 ¹⁶⁶
Infiltration and extravasation	-0.065	7	Sullivan 2011 ¹⁶⁶
Thromboembolic events	-0.063	7	Sullivan 2011 ¹⁶⁶

Abbreviations: CVC: Central venous catheter; PICC: Peripherally inserted central catheter.

3.4.8 Disutilities associated with drug administration

No administration disutility is attached to any subcutaneous product. For IVIg products (Privigen, Gamunex, and Flebogamma DIF), an additional disutility per cycle was implemented based on the following:

- The intravenous administration route is less convenient than the subcutaneous administration route
- The in-hospital setting is less convenient than the at-home setting
- The frequency of the infusions
- The duration of the infusions

Three TLRs were conducted to inform how the elements above impact the HRQoL (as detailed in **Appendix F**). Jørgensen et al. reported the HRQoL associated with different administration routes, with different administration settings, and for different frequencies of administration.¹⁶⁸ By fitting a linear regression model on the reported values, it is possible to derive the incremental disutility associated with intravenous administrations, in-hospital administrations, and the number of administrations per cycle.

The paper by Matza et al¹⁶⁹, which reports the disutility associated with intravenous infusions of different duration, is used to derive the disutility associated with a longer administration time. The duration of infusion for Privigen and Gamunex is taken by the correspondent product information^{170,171} and amounts to 3.9 and 3.3 hours, respectively.

Table 64: Per-cycle disutilities associated with IVIg administration

Administration	Decrement	Source
Disutility associated with IV administration route	-0.022	Derived from the values reported by Jørgensen et al ¹⁶⁸
Disutility associated with in-hospital setting	-0.011	
Disutility associated with the number of administrations per cycle (the decrement represents the marginal disutility associated with each additional administration)	-0.006	
Disutility associated with increasing length of infusion (decrement per hour of infusion)	-0.009	Matza et al ¹⁶⁹

Abbreviations: IV: Intravenous; IVIg: Intravenous immunoglobulin.

3.4.9 Caregiver disutilities

CIDP imposes substantial burden on patients as well as caregivers due to impaired physical function, and challenges associated with diagnosis, access, and management often contribute to increased healthcare resource utilisation (HCRU)¹³. Subsequently, it is important to capture the burden on caregivers when conducting economic evaluation for this disease.

The disutility depends on the health state since worse health states are assumed to require a higher level of assistance. A TLR was conducted to estimate the caregiver disutility associated with different levels of disease severity in CIDP (detailed in **Appendix F**). As the literature does not report specific disutility values for caregivers of CIDP patients, the caregiver disutility associated with multiple sclerosis (MS) is used as a proxy. Both CIDP and MS impact the patient's ability to walk autonomously and perform activities of daily living, therefore requiring similar levels of assistance.

The use of MS as a proxy for CIDP caregiver disutility has precedent in prior NICE evaluations, where MS caregiver utility decrements have been accepted as the most appropriate analogue for neurological conditions involving progressive or relapsing loss of motor function. This approach is therefore considered reasonable and methodologically consistent with NICE's reference case in the absence of condition-specific data.

Disutilities associated with caregiving are included as detailed in Table 65. The values are obtained from NICE submission HST9¹⁷², which, in turn, used values from Gani et al.¹⁷³

Table 65: Caregiver disutility per cycle

Health State	Disutility	Number of carers
Very limited impairment	0.000	1
Mild impairment	-0.003	1
Moderate impairment	-0.028	1
Severe impairment	-0.250	2
Very severe impairment	-0.250	2

3.5 Cost and healthcare resource use identification, measurement and valuation

The identification of cost and healthcare resource use data to inform the economic analysis is described in detail in **Appendix G**.

3.5.1. Intervention and comparators' costs and resource use

3.5.1.1 Efgartigimod induction

A one-off induction cost of £183,690 (£■■■■■ with PAS) is applied in the first cycle of the Markov Trace to account for the drug acquisition costs of three months of induction. Note Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

that this is conservative since it implies that all patients receive 3 months of induction therapy before achieving response, while the average time to achieve response observed in ADHERE was shorter (median time of 43 days).¹³¹

The one-off drug acquisition cost is calculated by multiplying the cost per pack of efgartigimod by the number of administrations during the induction phase (once per week for a total of 12 administrations), as detailed in Table 66 below.

Table 66: Efgartigimod drug acquisition cost during induction

Parameter for efgartigimod	Value
Cost per unit	£15,307.47 [REDACTED] with PAS)
Number of administrations during induction phase	12
One-off cost for induction	£183,690.00 [REDACTED] with PAS)

Abbreviations: PAS: Patient Access Scheme.

3.5.1.2 Efgartigimod administration costs

For efgartigimod, 100% of the administrations in the induction phase are assumed to be performed in an in-hospital setting. For the maintenance phase, only 8% of the administrations are assumed to be performed in the hospital, while the remaining are performed independently by the patients at home. This is based on the ADHERE+ protocol, which allows for home administration during efgartigimod maintenance. The administration costs generated during the induction phase are applied one-off at the beginning of the simulation.¹³⁵

The unit costs associated with one hospital administration of efgartigimod is £126.64, no cost is attached to home administration (Table 67).

Table 67: Inputs used to inform the drug administration costs for efgartigimod

HCRU	Unit cost (£)	Source
Hospital administration, efgartigimod	£126.64	National Schedule of NHS Costs - Year 2023/24 - NHS trusts and NHS foundation trusts. Dept code NCL; Service Code 303; Reference: WF02A; Procedure: Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up. ¹⁷⁴

Abbreviations: HCRU: Health care resource utilisation.

3.5.1.3 Efgartigimod maintenance

In the ADHERE trial, patients received weekly administration of efgartigimod maintenance (q1w schedule). However, in ADHERE+, patients could become eligible for a substudy where they received one injection every two Weeks (q2w schedule). To become eligible, they needed to remain on treatment on the q1w schedule for at least 24 Weeks, of which the last 12 with a stable disease severity as measured on the aINCAT scale. After starting the q2w schedule, patients were allowed to return to the q1w schedule if they showed signs of clinical deterioration on aINCAT, I-RODS or MGS.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

The most recent data (April 2025) from the ADHERE+ substudy showed that [REDACTED] out of [REDACTED] patients [REDACTED] were eligible for the q2w schedule.¹³⁴ Of those, [REDACTED] enrolled in the substudy and received the q2w dosing schedule; [REDACTED] remained on q2w schedule for at least 24 Weeks, with [REDACTED]¹³⁴

In the CEM, these data are used to inform the proportion of patients on q2w efgartigimod maintenance. To reflect eligibility criteria for q2w schedule, the full efgartigimod cohort is assumed to be on q1w schedule during the first model cycle. From the second cycle onwards, the proportion on q2w schedule is calculated by multiplying the eligible proportion [REDACTED] by [REDACTED] (Table 68).

Table 68: Proportion of cohort eligible for q2w efgartigimod maintenance

Parameter	Value	Source
Proportion of efgartigimod cohort eligible for q2w schedule after the first model cycle	[REDACTED]	ADHERE+ substudy ¹³⁴
Among eligible cohort, proportion remaining on q2w schedule for ≥24 Weeks	[REDACTED]	ADHERE+ substudy ¹³⁴
Fixed proportion on efgartigimod q2w schedule used in the CEM from model cycle 2 onwards	[REDACTED]	Product of the two values above

Abbreviations: CEM: Cost-effectiveness model.

It is assumed that the treatment schedule does not change over time, i.e. the same number of administrations per cycle is applied over the entire time on efgartigimod maintenance.

Table 69: Costs per cycle for efgartigimod maintenance

	Cost per unit	Unit/admin	Admins/cycle (adjusting for 90% adherence rate)	Cost/cycle
Efgartigimod, maintenance q1w	£15,307.47 [REDACTED] with PAS)	1	26.09	[REDACTED]
Efgartigimod, maintenance q2w			13.04	[REDACTED]

Abbreviations: PAS: Patient Access Scheme.

Admin/cycle is rounded to 2 decimal places.

3.5.1.4 Ig maintenance costs

In the CEM, the cohort on IVIg maintenance is distributed across four different IVIg doses per cycle: <0.50 g/kg, 0.50-0.99 g/kg, 1.00–1.99 g/kg, and 2.00 g/kg. For each dose, the average time interval between treatment cycles is informed separately and translated into the average number of IVIg treatment cycles per six-month period. Inputs from five UK clinical expert, collected through a SEE process, inform these parameters.

For the cohort receiving SCIg maintenance (Hizentra), only two doses (0.50-0.99 g/kg, 1.00–1.99 g/kg) are included in the model, with the proportion of the SCIg-treated cohort receiving 1.00–1.99 g/kg set equal to the proportion of the IVIg-treated cohort receiving ≥1.00 g/kg. The SCIg dose is broke down into weekly doses (i.e., divided by four) and the average time

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

interval between treatment cycles is set to one week, as per Hizentra summary of product characteristics (SmPC).¹⁷⁵

Table 70 and Table 71 below summarise the inputs used to inform the treatment schedule for Ig maintenance.

Table 70: Distribution of the cohort across different Ig maintenance doses

Product	Dose	Proportion	Source
IVIg	<0.50 g/kg	0.17%	SEE with 5 UK clinical experts
	0.50 – 0.99 g/kg	15.51%	
	1.00 – 1.99 g/kg	60.30%	
	2.00 g/kg	24.03%	
SCIg (Hizentra)	0.50 – 0.99 g/kg	15.67%	Proportion on 1.00 -1.99 g/kg set equal to the proportion of IVIg-treated cohort receiving ≥1.00 g/kg
	1.00 – 1.99 g/kg	84.33%	

Abbreviations: Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin; SEE: Structured Expert Elicitation; SmPC: Summary of product characteristics.

Table 71: Average time between IVIg treatment cycles

Product	Dose	Average time between treatment cycles (weeks)	Average n. of Ig cycles per 6-month period	Source
IVIg	<0.50 g/kg	3.63	7.19	SEE with 5 UK clinical experts
	0.50 – 0.99 g/kg	3.79	6.88	
	1.00 – 1.99 g/kg	4.08	6.39	
	2.00 g/kg	4.11	6.35	
SCIg (Hizentra)	0.50 – 0.99 g/kg	1.0	26.09	Hizentra SmPC
	1.00 – 1.99 g/kg	1.0*	26.09	

Abbreviations: Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin; SEE: Structured Expert Elicitation; SmPC: Summary of product characteristics. *Please note that, in the model, the dose is administered weekly by dividing the monthly dose into weekly doses.

To calculate the average amount of mg/kg administered during each treatment cycle, the doses presented in Table 70 above are pooled, weighting for the corresponded proportion of the cohort. The midpoint between each dose's upper and lower bounds is used for the calculation.

The resulting value is then multiplied by the mean weight of the cohort, to get to the total amount of Ig administered during each treatment cycle. Based on this, the number of packs per treatment cycle is calculated, assuming no vial sharing (Table 72 below).

Finally, the total cost per Ig treatment cycle is calculated by multiplying the cost per pack (including an estimated [REDACTED] discount on the list price) by the number of packs used, and the Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

total cost per six-month period (i.e., per model cycle) is calculated by multiplying the cost per treatment cycle by the number of treatment cycles reported in Table 71 above.

The base case analysis applies a mean [REDACTED] discount to the list price of Ig therapies, consistent with the indicative NHS procurement discount range provided by NICE in the efgartigimod appraisal (TA1069). This assumption aims to ensure the base case reflects the prices paid in the NHS. Given recent changes to the NHS Ig framework and the confidential nature of current discounts for comparator technologies, this parameter remains an area of uncertainty in the Company's base case. Therefore, scenario analyses exploring Ig discount rates from [REDACTED] discounts are presented in Section 3.11.3. to assess the sensitivity of the ICER to Ig pricing assumptions.

Table 72: Drug acquisition costs

Ig product	mg/pack	Pack/Ig treatment cycle	Cost per pack (£) – list price	Cost per pack (£) – including a [REDACTED] discount on listed price	Cost per Ig treatment cycle (£)	Cost per 6month period (£)
IVIg-Privigen	2,500	2.0	£172.50	[REDACTED]	[REDACTED]	[REDACTED]
IVIg-Privigen	5,000	1.0	£345.00	[REDACTED]		
IVIg-Privigen	10,000	1.0	£690.00	[REDACTED]		
IVIg-Privigen	20,000	3.0	£1,380.00	[REDACTED]		
IVIg-Gamunex	5,000	2.0	£332.50	[REDACTED]	[REDACTED]	[REDACTED]
IVIg-Gamunex	10,000	1.0	£665.00	[REDACTED]		
IVIg-Gamunex	20,000	3.0	£1,330.00	[REDACTED]		
IVIg-Flebogamma DIF	2,500	2.0	£175.00	[REDACTED]	[REDACTED]	[REDACTED]
IVIg-Flebogamma DIF	5,000	1.0	£350.00	[REDACTED]		
IVIg-Flebogamma DIF	10,000	1.0	£700.00	[REDACTED]		
IVIg-Flebogamma DIF	20,000	5.0	£1,400.00	[REDACTED]		
SCIg - Hizentra	2,000	2.0	£138.00	[REDACTED]	[REDACTED]	[REDACTED]
SCIg - Hizentra	4,000	7.0	£276.00	[REDACTED]		

Abbreviations: Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin.
Source: Ig product list prices are sourced from the British National Formulary.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

To obtain a single input to use in the CEM, the drug acquisition costs associated with each Ig product are averaged, weighted for the distribution of the cohort across different Ig products. In the base case, these are informed based on data from a UK chart review study²³.

The resulting drug acquisition cost per cycle for Ig amounts to [REDACTED], which includes a [REDACTED] discount on each product's list price.

3.5.1.5 Ig administration costs

All IVIg products are assumed to be administered in hospital. For SCIg products (Hizentra), 8% are assumed to receive treatment in hospital, in line with the parameter inputs used for efgartigimod. Each Ig treatment cycle is assumed to be administered over an average number of 3.2 days, based on the results from the UK chart review study²³. Furthermore, the cohort that receives Ig in hospital can either receive it in an outpatient setting (in which case only the cost per day of the infusion chair is considered), or be admitted for the night (in which case a higher cost per day is applied, to reflect the higher cost attached to an inpatient admission).

Table 73 below summarises the inputs used to inform the cost of administration for efgartigimod and Ig.

Table 73: Inputs used to inform the drug administration costs for Ig

HCRU	Unit cost (£)	Source
Daily cost for IV infusion chair, outpatient setting	£284.40	National Schedule of NHS Costs - Year 2023/24 - NHS trusts and NHS foundation trusts, Dept code Daycase, Reference: SA45A - Injection of Rh Immune Globulin or Other Blood Transfusion, 19 years and over. ¹⁷⁴
Daily cost for IV infusion, inpatient setting	£857	PSSRU, Unit Costs of Health and Social Care 2024 Document. NHS reference costs for hospital services (National average); non elective inpatient stays (short stays) ¹⁷⁶
Proportion of cohort receiving IVIg in hospital	100.0%	During the structured expert elicitation process, UK clinical experts confirmed that only a negligible minority of IVIg-treated patients receive treatment at home ¹⁶
Proportion of cohort receiving SCIg (Hizentra) in hospital	8.0%	Set equal to the parameter input for efgartigimod
Among the cohort receiving Ig in hospital, proportion that is admitted for the night (applied for both IVIg and SCIg)	3.1%	Informed through the structured expert elicitation process with five UK clinical experts ¹⁶
Average n. of days required for each Ig treatment cycle	3.2	Informed through chart review study ²³

Abbreviations: Ig: Immunoglobulin; IV: intravenous; IVIg: Intravenous immunoglobulin; PSSRU: Personal Social Services Research Unit; SCIg: Subcutaneous immunoglobulin.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

The total drug administration costs per six-month period are obtained by multiplying the administration costs per Ig treatment cycle by the number of treatment cycles for each product. For Ig, the administration costs associated with each product are averaged, weighting for the proportion of the cohort allocated to each product.

No drug administration costs are attached to immunosuppressants and corticosteroids.

Table 74: Drug administration costs per-cycle

Treatment	Cost per cycle (£)
Efgartigimod	
One off cost for Induction (corresponding to 12 in-hospital administrations)	
Maintenance phase, q1w	
Maintenance phase, q2w	
Ig	
Privigen	
Gamunex	
Flebogamma DIF	
Hizentra	
Ig administration cost per 6-month period	
Basket of other treatments	
PLEX	
Corticosteroids	
Immunosuppressants	

Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange.

3.5.1.6 Basket of other treatments

3.5.1.6.1 PLEX costs

The cost per PLEX administration is obtained from NHS Reference costs 2024/2025 and amounts to £273.00.¹⁷⁴ The number of PLEX administrations per six-month period is based on the recommendations from the EFNS/PNS guidelines and is set to 24.¹ This results in a total cost per cycle of £6,552.00.

3.5.1.6.2 Corticosteroids costs

The proportion of the cohort treated with corticosteroid is assumed to receive methylprednisolone for one model cycle and to remain off treatment afterwards. The dose of methylprednisolone is informed based on the schedule used by Nobile-Orazio et al and amounts to four 0.5-gram administrations per month.¹⁷⁷ The median length of treatment is set to 3.5 months, based on the value elicited through the structured elicitation process with five UK clinical experts.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

The cost of one 40mg unit of methylprednisolone is sourced from the British National Formulary (BNF) database and amounts to £1.58, corresponding to a cost per administration of £19.75 and a total cost of £257.54 for the entire 3.5-month treatment.

3.5.1.6.3 Immunosuppressants

The proportion of the cohort treated with immunosuppressants is assumed to receive 2.0 g/day of mycophenolate mofetil, based on the mean dose reported by Bedi et al.¹⁷⁸ The cost of fifty 500mg tablets of mycophenolate mofetil is sourced from the BNF database and amounts to £5.81, leading to a total cost per model cycle of £84.88.

3.5.2 Health-state unit costs and resource use

3.5.2.1 Healthcare professionals

Based on the information reported by Mahdi Rogers et al¹²., it is assumed that disease monitoring covers 4 services: visits to the general practitioner (GP), neurology outpatient visits, physiotherapist visits and occupational therapist visits.¹² The number of visits per model cycle is reported in Table 75 below and is assumed to be the same for all health states. The unit cost per visit is obtained from the latest National Schedule of Reference costs and Personal Social Services Research Unit and is reported in Table 76.^{174,179} The total cost associated with disease monitoring amounts to £1,989.60 per model cycle.

Data from the Adelphi study show that patients with Moderate, Severe, and Very Severe Impairment require increasing support from professional caregivers.⁷⁷ The proportion of patients requiring professional caregivers and the average hours per patients used in the CEM are reported in Table 75. The hourly cost of professional caregivers is set to £27 based on the 2024 NHS Unit Costs of Health and Social Care.¹⁷⁶ The cost per model cycle for professional caregiving was calculated as the product of the hourly wage, the average number of caregiving hours, and the proportion of patients requiring care.

Table 75: Disease monitoring - healthcare resource use per model cycle

HCRU	n. of visits per month	n. of visits per model cycle	Source
General practitioner visit	0.36	2.16	Mahdi-Rogers et al ¹⁸⁰
Specialist visit, neurology out-patient	0.40	2.40	
Physiotherapist	0.27	1.62	
Occupational therapist	0.38	2.28	

Abbreviations: HCRU: Healthcare resource utilisation.

Table 76: Disease monitoring - unit cost per healthcare professional

Service	Unit cost	Reference
General practitioner visit	£251.00	PSSRU, Unit Costs of Health and Social Care 2023. Cost per hour - GP Unit cost including direct care ¹⁷⁹
Specialist visit, neurology out-patient	£223.00	2022/2023 National Schedule for Reference costs. ¹⁷⁴
Physiotherapist	£78.00	PSSRU, Unit Costs of Health and Social Care 2023 Document. Section 6.1 (Table 6.1.1.) Cost per hour community services (one to one). Physiotherapy ¹⁷⁹
Occupational therapist	£106.00	PSSRU, Unit Costs of Health and Social Care 2023 Document. Section 6.1 (Table 6.1.1.) Cost per hour community services (one to one). Occupational therapy ¹⁷⁹

Abbreviations: GP: General practitioner; PSSRU: Personal Social Services Research Unit.

Table 77: Professional caregiving - consumption and cost

Health State	Proportion of patients requiring professional caregiving	Hours of professional caregiving per week	Total cost per model cycle for professional caregiving
Very limited impairment	0.0%	0.0	£0.0
Mild impairment	0.0%	0.0	£0.0
Moderate impairment	9.0%	21.3	£1,449.2
Severe impairment	80.0%	45.0	£27,215.0
Very severe impairment	80.0%	45.0	£27,215.0

3.5.2.2 Mobility aids

The Adelphi study showed that an increasing proportion of patients in Moderate, Severe, and Very severe health states require manual or motorized wheelchair (Table 78).⁷⁷ These data are used to inform the CEM, with costs of £774 and £1,627 for manual and motorised wheelchairs respectively sourced from NHS 2023/2024 National Cost Collection. These values are inflated to £830.66 and £1,746.10 respectively.

Table 78: Mobility aids

Health State	Proportion of patients requiring manual wheelchair	Proportion of patients requiring motorized wheelchair
Very limited impairment	████	████
Mild impairment	████	████
Moderate impairment	████	████
Severe impairment	████	████
Very severe impairment	████	████

3.5.2.3 Hospitalisation costs

The average length of hospitalisation stratified by health state and by ICU admission is sourced from the Adelphi study and is shown in Table 79 below. The cost of each hospitalisation event is obtained by multiplying the mean duration by the cost for a standard bed or for ICU, as reported, respectively, in the 2025/2026 NHS payment scheme and in the 2023/2024 NHS National Cost Collection data.

Table 79: Length of hospitalisation event

Health State	Average length of hospitalisation event– no ICU admission	Average length of hospitalisation event – ICU admission
Very limited impairment	4.00	0.00
Mild impairment	3.80	0.00
Moderate impairment	6.20	4.00
Severe impairment	8.30	2.70
Very severe impairment	8.30	2.70

Abbreviations: ICU: Intensive care unit.

Table 80: Cost per day of hospitalisation event

Service	Unit cost	Reference
Cost per day of ICU	£2,276.00	NHS 2023/2024 National Cost Collection Data, Critical Care, Adults, Service code: CCU01 to CCU91 ¹⁷⁴
Cost per day of standard bed	£354.00	2025/26 NHS payment scheme; Average of per-day long-stay payment across all non-elective admitted HRG ¹⁸¹

Abbreviations: HRG: Healthcare resource group; ICU: Intensive care unit.

3.5.3 Adverse reaction unit costs and resource use

The AEs are associated with a cost per event that reflects the healthcare resources used to treat them. The costs are retrieved from the NHS Prices Workbook, and the aggregate cost of each AE-related treatment is obtained by averaging the codes associated with it.¹⁸²

The costs of each AE-related treatment are adjusted in the model for the correspondent incidence per cycle. Table 81 and Table 82 report, respectively, the costs associated with AEs and the complications related to the intravenous access, together with the NHS codes used as a source.

Table 81: Costs associated with AEs

Adverse event	Base Case (£)	HRG Code
Arthralgia and pain in the extremities	£1,105.00	WH08A, WH08B
Asthenia	£2,152.00	WH12A
Back Pain	£1,172.50	HC32G, HC32H, HC32J, HC32K
Dizziness	£2,152.00	WH12A
Fatigue	£2,152.00	WH12A
Headache	£910.00	AA31D
Haemolysis	£535.50	SA03G, SA03H
Hypertension	£470.00	EB04Z
Influenza	£1,762.80	DZ19H, DZ19J, DZ19K, DZ19L, DZ19M, DZ19N
Infusion/injection site reaction	£4,200.30	WH07A, WH07B, WH07C, WH07D, WH07E, WH07F, WH07G
Nasopharyngitis	£1,762.80	DZ19H, DZ19J, DZ19K, DZ19L, DZ19M, DZ19N
Nausea	£4,076.30	FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10G, FD10H, FD10J, FD10K, FD10L, FD10M
Pyrexia	£3,442.30	WJ07A, WJ07B, WJ07C, WJ07D
Upper respiratory tract infection	£1,762.80	DZ19H, DZ19J, DZ19K, DZ19L, DZ19M, DZ19N
Infections	£5,731.00	WH07
Sleep disorders	£575.00	AA43
Psychiatric disorders	£584.00	10MHPS, 11MHPS, 12MHPS, 35MHPS, 36MHPS, 37MHPS, 38MHPS, 40MHPS
Abdominal pain	£1,666.00	FD05A, FD05B
Endocrine disorders	£544.00	KA80
Anaemia	£2,933.00	SA01 SA03
Gastrointestinal disturbances	£1,666.00	FD05A, FD05B
Renal dysfunction	£1,721.00	LA09M, LA09N, LA09P, LA09Q
Peripheral oedema	£716.00	WH10A, WH10B

Abbreviations: AEs: Adverse events; HRG: Healthcare resource group.

Table 82: Costs of complications related to intravenous access

Complication	Base Case (£)	HRG Code
Permanent PICC, surgically implanted CVC, infusion port	£1,673.00	YR40, YR41, YR42 (average of HRG codes)
Catheter-related infections	£5731.00	WH07 (average of HRG codes)
Catheter-related blood infections	£7682.00	WJ06 (average of HRG codes)
Thrombophlebitis	£4389.00	YQ50 (average of HRG codes)
Infiltration and extravasation	£4389.00	YQ50 (average of HRG codes)
Thromboembolic events	£3202.00	YQ51 (average of HRG codes)

Abbreviations: CVC: Central venous catheter; HRG: Healthcare resource group; PICC: Peripherally inserted central catheter.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

3.5.4 Miscellaneous unit costs and resource use

Not applicable.

3.6 Severity

The severity modifier was deemed not to be applicable for this submission.

3.7 Uncertainty

Uncertainty in the model is explored in Section 3.11. Uncertainty relating to the model parameters is assessed through probabilistic sensitivity analysis (PSA) in Section 3.11.1 and deterministic sensitivity analysis (DSA) in Section 3.11.2. Scenario analyses are also used to analyse the impact of uncertainty on model input and assumptions are discussed in Section 3.11.3.

3.8 Managed access proposal

The ADHERE+ study is ongoing, however based on results from ADHERE and interim data from ADHERE+, efgartigimod has demonstrated a sustained treatment effect that is maintained over time.

As outlined in Section 2.3, ADHERE+ is an open-label, phase 2 extension study designed to collect long-term safety and efficacy data in patients previously treated with efgartigimod. As of the latest data cut-off, the trial remains on-going with study completion anticipated in April 2027.

While the ADHERE+ study will provide additional information on long-term outcomes, duration of response and safety, it will not generate comparative data, as it is open-label and single arm in design. As such, the evidence collected will not address the uncertainties regarding comparative effectiveness versus existing IVIg therapies, and any subsequent cost-effectiveness modelling would continue to rely on indirect treatment comparisons to estimate relative benefit and duration of treatment effect versus IVIg.

Given that further data collection from ADHERE+ will not provide new comparative evidence, efgartigimod is therefore not currently considered an appropriate candidate for a Managed Access Agreement. Nevertheless, the Company remains open to further discussion with NICE and NHS England on how emerging outcomes data may be used to inform future access considerations.

3.9 Summary of base case analysis inputs and assumptions

3.9.1 Summary of base case analysis inputs

The base case inputs used in the analysis are provided in **Appendix M** (Table 48).

3.9.2 Assumptions

The main assumptions of the economic model, alongside supporting justification and scenario analyses, are presented in Table 83.

Table 83: Assumptions

Model input and cross reference	Source/assumption	Rationale
Time horizon	Life-time horizon	Preference specified in NICE reference case ¹⁵⁰
Discounting	3.5% for outcomes and for costs	Preference specified in NICE reference case ¹⁵⁰
Intervention arm, initial treatment	Induction with efgartigimod, followed by: For responders: efgartigimod maintenance For non-responders: Ig maintenance	Treatment pathway from ADHERE and ADHERE+
Intervention arm, subsequent treatments for efgartigimod responders	Proportion of cohort pre-treated with Ig (95%): Upon discontinuation of efgartigimod maintenance, 31.0% of the cohort re-starts Ig maintenance, 69.0% start treatment with a basket of other treatments (14.5% PLEX, 49.9% corticosteroids, 4.6% immunosuppressants) The proportion that re-starts Ig maintenance can further discontinue Ig and start treatment with the basket of other treatments (22.9% PLEX, 77.0% corticosteroids, 0.1% immunosuppressants) Proportion of cohort that is Ig intolerant (2.5%) or Ig refractory (2.5%):	Assumed distributions based on UK clinical expert opinion (SEE process) ¹⁶

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

	Upon discontinuation of efgartigimod maintenance, 100% of the cohort starts treatment with the basket of other treatments (22.9% PLEX, 77.0% corticosteroids, 0.1% immunosuppressants)	
Intervention arm, subsequent treatments for efgartigimod non-responders	Proportion of the cohort pre-treated with Ig (95%): At the beginning of the simulation, the cohort is distributed across Ig (31.0%) and the basket of other treatments (14.5% PLEX, 49.9% corticosteroids, 4.6% immunosuppressants) The proportion allocated to Ig maintenance can further discontinue due to unplanned reasons. Upon discontinuation, it starts treatment with the basket of other treatments (22.9% PLEX, 77.0% corticosteroids, 0.1% immunosuppressants) Proportion of the cohort that is Ig intolerant (2.5%) or Ig refractory (2.5%): At the beginning of the simulation, 100% of the cohort starts treatment with the basket of other treatments (22.9% PLEX, 77.0% corticosteroids, 0.1% immunosuppressants)	Assumed distributions based on UK clinical expert opinion (SEE process) ¹⁶
Comparator arm, initial treatment	The cohort starts the simulation on Ig maintenance	As per the treatment pathway and ADHERE and ADHERE+ trial protocols
Transitions on efgartigimod maintenance	Efgartigimod arm of ADHERE stage B followed by ADHERE+: Stage B baseline to 6 months, applied to cycle 1; 6 to 12 months, applied to cycle 2; 12 to 18 months, applied to cycle 3; 18 to 24 months, applied to cycle 4; Extrapolation: identity matrix applied beyond cycle 4, with transitions only allowed from active disease to remission, and vice versa.	Model transitions were directly informed by data from the ADHERE and ADHERE+ clinical trials.
Transitions on Ig maintenance	Efgartigimod matrices with difference between Ig and efgartigimod (as estimated by the ITC) in aINCAT change applied from cycle 1 to 4; Extrapolation: identity matrix applied beyond cycle 4, with transitions only allowed from active disease to remission, and vice versa.	

Transitions post-efgartigimod discontinuation	First cycle post-discontinuation: worsening to the distribution in cycle 4 (two years) in Comparator arm (only active disease states), applied as one-off Second cycle post-discontinuation onwards: For the cohort re-starting Ig maintenance: identity matrix, with transitions only allowed from active disease to remission, and vice versa; For the cohort in the basket of other treatments (PLEX, corticosteroids, immunosuppressants): identity matrix, active disease only	
Transitions post-Ig discontinuation	The same transition probabilities as during Ig maintenance are applied without solution of continuity, based on the assumption of equivalent efficacy between Ig and the basket of other treatments. However, after Ig discontinuation, the cohort always remain on active disease.	Assumption of equivalence between Ig and the basket of treatments is made in the absence of alternative data sources, and to minimise uncertainty. Based on the EAN/PNS guidelines ¹ .
Transition probability from active disease to remission	Per cycle remission rate: 8.52%, based on the following: Proportion of cohort on stable (≥ 12 months) Ig dose at each cycle: 60.8%, based on Koay et al; Proportion of cohort on stable (≥ 12 months) Ig dose eligible and willing to undergo dependency test: 45.2%, based on SEE process with UK clinical experts; Proportion of cohort that remains clinically stable for 6 months after successfully discontinuing Ig: 31.0%, based on SEE process with UK clinical experts Transitions from active disease to remission and vice versa are equal between treatment arms, as they are assumed not to depend on the intervention.	Transition probabilities estimated based on aINCAT score values reported in the literature and in ADHERE. The efficacy of the basket of other treatments is assumed to be the same as for Ig, based on the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guidelines ¹ .
Transition probability from remission to active disease	Per cycle risk of returning to active disease: 10.31%, based on the following: Proportion of cohort that successfully discontinues Ig and remain clinically stable for one additional year after the first 6 months (18 months in total): 79.38%, based on SEE process with UK clinical experts.	Assumption based on UK clinical expert opinion (SEE process).

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

	Transitions from active disease to remission and vice versa are equal between treatment arms, as they are assumed not to depend on the intervention.	
Mortality	Equal to the general population in all health states	This is in line with the literature on CIDP, which found that CIDP patients have a similar life expectancy as the general population. ^{77,91}
Disease monitoring and management costs	Number of visits with healthcare professionals based on Mahdi-Rogers et al, assumed to be the same for all health states Proportion of patients requiring professional caregiving and average number of caregiving hours per week based on data from Adelphi study Proportion of patients using manual and motorised wheelchair informed based on data from Adelphi study	Assumption based on the Adelphi study, providing data on the proportion of patients expected to require a mobility aid.
Administration costs	Efgartigimod: 100.0% in hospital in induction phase 8.0% in hospital; 92.0% at home in maintenance phase IVIg : 100% administered in hospital SCIg: 8.0% administered in hospital (assumed equal to efgartigimod) Proportion of cohort receiving Ig in hospital that is admitted overnight: 3.10% (based on SEE process with UK clinical experts). Average duration of a single Ig treatment cycle: 3.2 days (based on data from the UK chart review study).	Assumptions based on clinical expert opinion (SEE process) and assumptions based on the method of administration of efgartigimod and IVIg/SCIg.
Health state utilities	Based on ADHERE regression analysis – mixed model	The analysis defined five health states (Very limited impairment [aINCAT 0-1], Mild impairment [aINCAT 2-3], Moderate impairment [aINCAT 4-6], Severe impairment [aINCAT 7-8], and very severe impairment [aINCAT 9-10]) that are well-differentiated in terms of HRQoL. Clinical experts validated the health states and deemed them appropriate to model different levels of CIDP severity. ¹⁶ The utility values were estimated using a mixed model to align to the health states.

Caregiver utilities	Based on algorithm from Gani et al, as used in NICE HST9	CIDP imposes substantial burden on patients as well as caregivers due to impaired physical function, and challenges associated with diagnosis, access, and management often contribute to increased healthcare resource utilization (HCRU). The literature does not report specific disutility values for caregivers of CIDP patients, the caregiver disutility associated with multiple sclerosis is used as a proxy
Disutility associated with administration	Applied only to IV products. Based on the formula reported by Jorgensen et al, the disutility accounts for: The fact that products are administered intravenously The fact that all IV administrations are given in a hospital setting The number of administrations per cycle specific for each IV product. Moreover, based on the formula reported by Matza 2013, ¹⁶⁹ the disutility accounts for the length of administration specific for each IV product.	Values sourced from the available literature.
Disutilities associated with AEs and with complications due to intravenous access	Included based on Sullivan et al. and NICE TA706 (Ozanimod in MS) ^{165,166}	Values sourced from the available literature and NICE TA precedence.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; Ig: Immunoglobulin; ITC: Indirect treatment comparison; IV: Intravenous; IVIg: Intravenous immunoglobulin; PLEX: Plasma exchange; SEE: Structured Expert Elicitation; SCIg: Subcutaneous immunoglobulin.

3.10 Base case results

3.10.1 Base case incremental cost-effectiveness analysis results

The base case results are presented in Table 84 and Table 85. Clinical outcomes and the disaggregated results are presented in **Appendix H**.

All the results presented in Sections 3.10 to 3.11.3 use the PAS fixed price for efgartigimod. List prices with an assumed [REDACTED] discount are used for all other treatment (Privigen, Gamunex, Flebogamma DIF, Hizentra). The base case results show that the pathway with efgartigimod is associated with an increase of [REDACTED] QALYs versus the pathway without efgartigimod. The pathway with efgartigimod is associated with an increase in costs of [REDACTED] versus the pathway without efgartigimod, based on the PAS fixed price for efgartigimod. This results in an ICER of [REDACTED] compared to the pathway without efgartigimod.

The base case net health benefit at £20,000 and £30,000 WTP thresholds are shown in Table 85. The base case net health benefit shows a net health benefit (NHB) of [REDACTED] at the £20,000 WTP threshold, and an NHB of [REDACTED] at the £30,000 WTP threshold, based on the PAS fixed price for efgartigimod (Table 84).

Table 84: Base-case results at PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Intervention - pathway with efgartigimod	[REDACTED]	17.17	6.26	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Comparator - pathway without efgartigimod	[REDACTED]	17.17	1.71	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years.

Table 85: Net health benefit at PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Intervention - pathway with efgartigimod	[REDACTED]	6.26	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Comparator - pathway without efgartigimod	[REDACTED]	1.71	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; NHB: Net health benefit; QALYs: Quality-adjusted life years.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

PSA was performed by varying all parameters in the model simultaneously by sampling from probability distributions. The ranges and the distributions assumed are shown in **Appendix M**. Population characteristics are not included in the PSA since they represent first order uncertainty.

The results of the pairwise PSA are shown in Table 86. These results were generated based on 1,000 simulations (convergence of the ICER was achieved by approximately the 67th simulation). The PSA results show the pathway with efgartigimod to be cost-effective at the £20,000 WTP threshold. The ICER is [REDACTED] in the probabilistic analysis, and [REDACTED] in the deterministic analysis when compared to the pathway without efgartigimod.

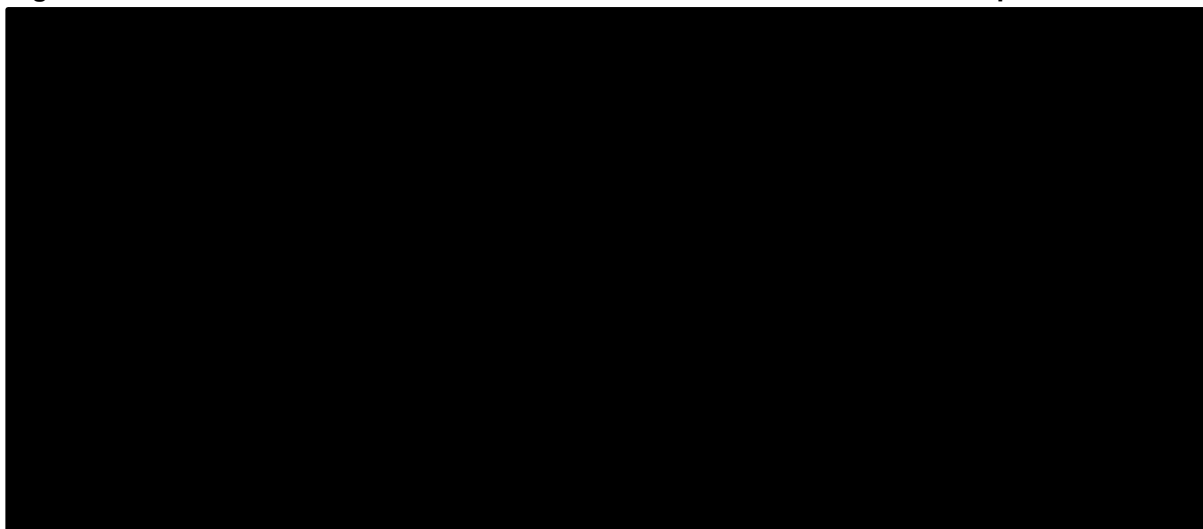
The results were plotted in a cost-effectiveness acceptability curve (CEAC) which shows the probability of either treatment being the most cost-effective across a range of WTP thresholds (Figure 21). At a willingness to pay threshold of £30,000, the pathway with efgartigimod is associated with a [REDACTED] probability of being cost-effective.

Table 86: Base case probabilistic incremental cost-effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Intervention - pathway with efgartigimod	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Comparator - pathway without efgartigimod	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

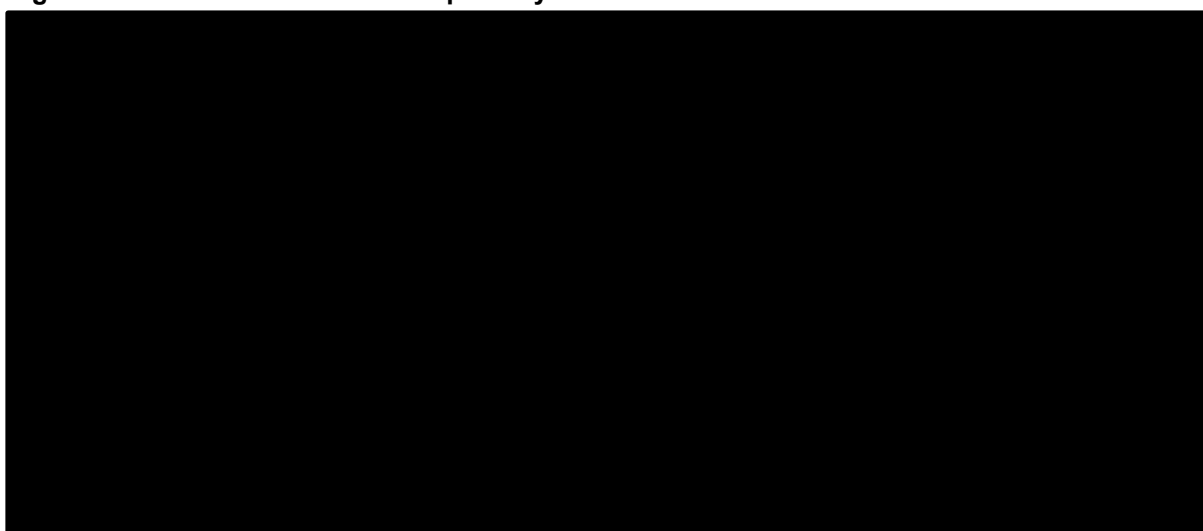
Abbreviations: ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years.

Figure 20: Distribution of results of PSA simulations in the cost-effectiveness plane



Abbreviations: CE: Cost-effectiveness; GBP: Great British Pounds; PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life year.

Figure 21: Cost-effectiveness acceptability curve



Abbreviations: GBP: Great British Pounds; QALY: Quality-adjusted life year; WTP: Willingness-to-pay.

3.11.2 Deterministic sensitivity analysis

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses (OWSAs) are performed in which key model parameters are varied one at a time around their base-case values. The 95% confidence limits are used as the high and low values when reported in the data reference. If not reported, the 95% CI is approximated by setting high and low values at the base-case value $\pm 1.96 \times \text{SE}$. When the SE is not reported, 10% of the base-case value is used as a proxy. High and low values used in the OWSA are presented in **Appendix M**. The results show that the most influential parameters on the model results are those that are related to the time between IVIg cycles,

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

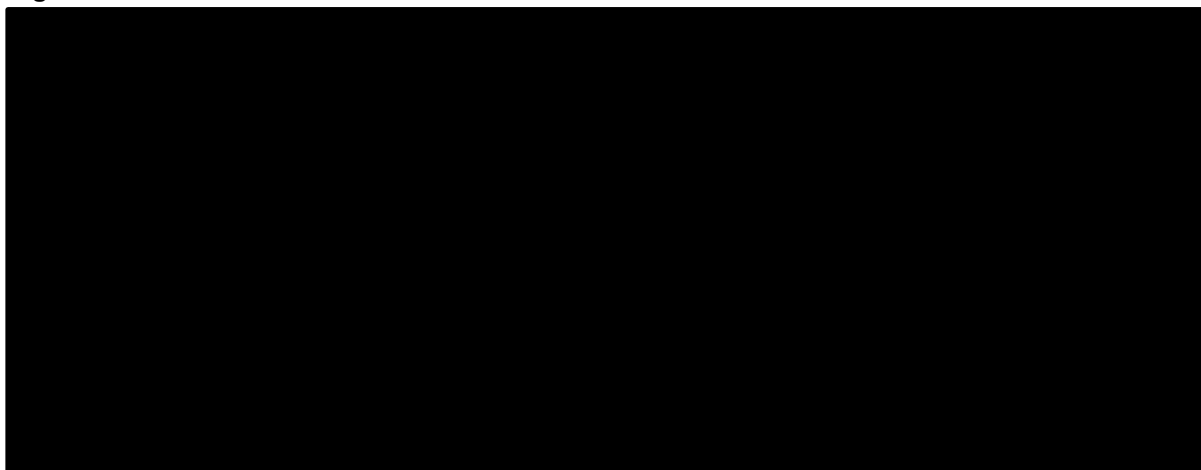
the difference between Ig and efgartigimod in aINCAT change from baseline Stage B to EoS visit, and the mean weight in the patient population. Table 87 details the DSA outputs with the change against the base case ICER.

Table 87: Percentage change in ICER in base case results following lower and upper variation in parameters

Parameter	Absolute value (£/QALY)		Percentage change in ICER vs base case	
	Lower value	Upper value	Lower value	Upper value
Time between IVIg cycles (weeks) - 1.0 - 1.99 g/kg				
Difference between Ig and Efgartigimod in aINCAT change from baseline Stage B to EoS visit				
Time between IVIg cycles (weeks) - 0.5-0.99 g/kg				
Time between IVIg cycles (weeks) - 2.0 g/kg				
Proportion of patients remaining in remission for one additional year after the first 6-month period in remission				
Among patients undergoing dependency test, proportion remaining clinically stable for at least 6 months				
Population characteristics- Weight (kg)				
Among patients on stable maintenance dose ($\geq 12m$), proportion eligible and willing to undergo Ig dependency test				
Average dose per treatment cycle - 1.0 - 1.99 g/kg				
Efgartigimod response rate				

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; EoS: End of study visit; ICER: Incremental cost-effectiveness ratio; Ig: Immunoglobulin; ToT: Time on treatment.

Figure 22: Results of the OWSA



Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; EoS: End of study visit; Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; ToT: Time on-Treatment.

3.11.3 Scenario analysis

Various structural assumptions were examined, encompassing both optimistic and pessimistic exploratory analyses. Table 93 provides the results of the different scenarios explored. The description of the scenarios is reported below.

3.11.3.1 Extrapolation of TPs in efgartigimod maintenance

In the base case, the continuity/identity matrix is applied after Cycle 4 in the efgartigimod cohort receiving maintenance (see Section 3.3.1). A scenario analysis is conducted where the last set of TP (based on transitions from week 72 to week 92) is recycled after Cycle 4.

3.11.3.2 Extrapolation of TPs in Ig maintenance

In the base case, the identity matrix is recycled after Cycle 4 in the proportion of the cohort receiving Ig maintenance (see Section 3.3.3.3). A scenario analysis is conducted where TP for months 18-24 were recycled.

3.11.3.3 Treatment effect of efgartigimod vs Ig

In the base case, the treatment effect of efgartigimod vs Ig is applied for two years (up to Cycle 4) based on the observed period of pooled ADHERE and ADHERE+ data. A scenario analysis is conducted where the treatment effect of efgartigimod vs Ig is applied for only six months (one Cycle). A second scenario analysis is conducted where more conservative treatment effect estimates are used (mean [95% CI] difference vs Ig: [REDACTED]). These are based on a pooled effect estimate from MAIC analysis against a set of three comparator studies^{57,60,144}.

3.11.3.4 Extrapolation of time on treatment with efgartigimod

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

In the base case, time on treatment with efgartigimod is modelled through a parametric function (exponential) up to Cycle 3, while no discontinuation is assumed from Cycle 4 onwards (to align with time on treatment with Ig maintenance). A scenario is conducted where the time on treatment for the efgartigimod cohort is extrapolated based on an exponential curve for the entire time horizon.

3.11.3.5 Caregiver disutilities

As mentioned in Section 3.4.9, caregiver disutilities from Gani et al¹⁷³ are used in the base case. A scenario analysis is conducted assuming no caregiver disutility.

3.11.3.6 Time of eligibility for treatment dependency test

In the base case, the cohort receiving efgartigimod maintenance becomes eligible for treatment dependency tests starting from Cycle 3 (after at least 12 months on treatment with efgartigimod). In contrast, the cohort receiving Ig maintenance is eligible from simulation start. Two scenarios are conducted that explore alternative assumptions:

- the cohort on efgartigimod maintenance is eligible for dependency tests from simulation start
- the cohort on Ig maintenance is eligible for dependency test starting from Cycle 3

3.11.3.7 Deterioration upon returning to active disease state

In the base case, the cohort that re-enter the active disease state do not deteriorate during the transition. This is based on the fact that patients are regularly monitored and expected to restart treatment before any clinically meaningful worsening occurs. A scenario is conducted where half of the cohort deteriorate by one health state upon return to active disease.

3.11.3.8 No induction costs for efgartigimod

As mentioned in Section 3.5.2, a one-off induction cost of [REDACTED] is applied in the first cycle of the Markov trace. A scenario is conducted where no induction costs for efgartigimod are applied. This simulates a scenario in which efgartigimod induction is sponsored by the manufacturer for all patients.

3.11.3.9 Alternative source: UK chart review data

The UK chart review study provided alternative values to inform the distribution of the cohort across different Ig schedules, as well as the average dose and the average time between Ig-treatment cycles.²³ These were used in a scenario analysis. Moreover, it provided alternative values for the distribution of the cohort across treatments post-Ig discontinuations. The alternative inputs sourced from the UK chart review study, compared to the base case of the values sourced from UK clinical experts, are detailed in Table 88 to Table 90 below.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Table 88: Alternative inputs for distribution of Ig cohort across different posology's

Product	Posology	Distribution of the cohort across treatments	
		Base case – SEE with UK clinical experts ¹⁶	Scenario – UK Chart review study ²³
IVIg	<0.50 g/kg	0.17%	
	0.50 – 0.99 g/kg	15.51%	
	1.00 – 1.99 g/kg	60.30%	
	2.00 g/kg	24.03%	
SCIg (Hizentra)	0.50 – 0.99 g/kg	15.67%	
	1.00 – 1.99 g/kg	84.33%	

Abbreviations: Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin; SEE: Structured Expert Elicitation.

Table 89: Alternative inputs for average dose per Ig-treatment cycle

Product	Posology	Average dose per Ig treatment-cycle	
		Base case – SEE with UK clinical experts ¹⁶	Scenario – UK Chart review study ²³
IVIg	<0.50 g/kg	250.0 mg/kg	
	0.50 – 0.99 g/kg	750.0 mg/kg	
	1.00 – 1.99 g/kg	1500.0 mg/kg	
	2.00 g/kg	2000.0 mg/kg	
SCIg (Hizentra)	0.50 – 0.99 g/kg	187.50 mg/kg (weekly)	
	1.00 – 1.99 g/kg	375.00 mg/kg (weekly)	

Abbreviations: Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin; SEE: Structured Expert Elicitation.

Table 90: Alternative inputs for average time between Ig-treatment cycles

Product	Posology	Average time between Ig-treatment cycles (weeks)	
		Base case – SEE with UK clinical experts ¹⁶	Scenario – UK Chart review study ²³
IVIg	<0.50 g/kg	3.63	
	0.50 – 0.99 g/kg	3.79	
	1.00 – 1.99 g/kg	4.08	
	2.00 g/kg	4.11	
SCIg (Hizentra)	0.50 – 0.99 g/kg	1.00 (time between single administrations)	
	1.00 – 1.99 g/kg	1.00 (time between single administrations)	

Abbreviations: Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin; SEE: Structured Expert Elicitation.

Table 91: Alternative distributions across treatments post-Ig discontinuation

	Base case – SEE with UK clinical experts ¹⁶	Scenario – UK Chart review study ²³
PLEX	22.90%	
Corticosteroids	76.97%	
Immunosuppressants	0.13%	

Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange.

3.11.3.10 Alternative distributions across treatments post-efgartigimod discontinuation

During the SEE process, the participating clinical experts debated that if patients who are on stable Ig maintenance decide to change their treatment for efgartigimod, they have strong reasons to do so, i.e., the burden of administration has likely become unbearable to them. Therefore, it is reasonable to assume that if they later need to discontinue efgartigimod, 31% revert to Ig treatment. This is used to inform the base case. However, other clinical experts highlighted during qualitative interviews that if patients responded to Ig before commencing efgartigimod, they were likely to return on Ig after discontinuing efgartigimod. To account for these different views, the CEM allows to test different input values for the proportion of the cohort on Ig post-efgartigimod discontinuation, as detailed in Table 92.

Table 92: Alternative distributions across treatments post-efgartigimod discontinuation

	Base case	Same distribution as post-Ig discontinuation	Upper confidence interval from SEE	60% of cohort restarts Ig	95% of cohort restarts Ig
Ig	30.96%	0.00%	47.99%	59.99%	95.00%
PLEX	14.46%	22.90%	10.89%	8.38%	1.05%
Corticosteroids	49.91%	76.97%	37.60%	28.93%	3.62%
Immunosuppressants	4.66%	0.13%	3.51%	2.70%	0.34%

Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange.

3.11.3.11 Alternative health-state utility values

In the base case, health state utility values for all health states have been sourced from ADHERE data. However, utility estimates for the most severe health state are based on a limited of observations and are therefore uncertain. To explore this uncertainty, a scenario analysis is conducted where health state utility values for the severe and very severe impairment states are linearly extrapolated from the values used for the very limited to moderate impairment states.

3.11.3.12 Alternative assumptions on discount on Ig list price

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Scenarios have been included which focus on the range of discounts that can be applied to the Ig list price. The values used include: [REDACTED]

Table 93: Results of the scenario analyses

Number	Scenario	Incremental cost (£)	Incremental QALY	ICER (£)
0	Base case	[REDACTED]	[REDACTED]	[REDACTED]
1	Extrapolation of TPs in efgartigimod maintenance	[REDACTED]	[REDACTED]	[REDACTED]
2	Extrapolation of TPs in Ig maintenance	[REDACTED]	[REDACTED]	[REDACTED]
3	Shorter treatment effect of efgartigimod vs Ig (6 months)	[REDACTED]	[REDACTED]	[REDACTED]
4	Alternative treatment effect estimate from analysis of pooled comparator studies	[REDACTED]	[REDACTED]	[REDACTED]
4	Extrapolation of time on treatment with efgartigimod over the entire time horizon (exponential curve)	[REDACTED]	[REDACTED]	[REDACTED]
5	No caregiver disutilities	[REDACTED]	[REDACTED]	[REDACTED]
6	Time of eligibility for treatment dependency test: efgartigimod cohort eligible from simulation start	[REDACTED]	[REDACTED]	[REDACTED]
7	Time of eligibility for treatment dependency test: Ig cohort eligible from Cycle 3 onwards	[REDACTED]	[REDACTED]	[REDACTED]
8	Deterioration upon returning to active disease state	[REDACTED]	[REDACTED]	[REDACTED]
9	No induction costs for efgartigimod	[REDACTED]	[REDACTED]	[REDACTED]
10	Alternative source: UK chart review data	[REDACTED]	[REDACTED]	[REDACTED]
11	Alternative distributions across treatments post-efgartigimod discontinuation (same distribution as post-Ig discontinuation)	[REDACTED]	[REDACTED]	[REDACTED]
12	Alternative distributions across treatments post-efgartigimod discontinuation (SEE upper bound)	[REDACTED]	[REDACTED]	[REDACTED]
13	Alternative distributions across treatments post-efgartigimod discontinuation (60% of the cohort restarts Ig)	[REDACTED]	[REDACTED]	[REDACTED]
14	Alternative distributions across treatments post-efgartigimod discontinuation (95% of the cohort restarts Ig)	[REDACTED]	[REDACTED]	[REDACTED]
15	Health state utility values – Utility for Severe and Very severe health state linearly extrapolated from utility values of Very limited to Moderate health state	[REDACTED]	[REDACTED]	[REDACTED]
16	[REDACTED] discount on Ig list price	[REDACTED]	[REDACTED]	[REDACTED]
17	[REDACTED] discount on Ig list price	[REDACTED]	[REDACTED]	[REDACTED]
18	[REDACTED] discount on Ig list price	[REDACTED]	[REDACTED]	[REDACTED]
19	[REDACTED] discount on Ig list price	[REDACTED]	[REDACTED]	[REDACTED]
20	[REDACTED] discount on Ig list price	[REDACTED]	[REDACTED]	[REDACTED]

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Abbreviations: GBP: Great British Pounds; ICER: Incremental cost-effectiveness ratio; Ig: Immunoglobulin; PLEX: Plasma exchange; QALY: Quality-adjusted life year; ToT: Time on treatment.

3.12 Subpopulation analysis

Results of the subpopulation analysis are in Sections 3.12.1 to 3.12.3.

3.12.1 Subpopulation 1 – patients on Ig maintenance

In Subpopulation 1, the total discounted lifetime cost of the pathway with efgartigimod amounts to [REDACTED], and it is higher than the total discounted cost observed in the pathway without efgartigimod, [REDACTED]. The Intervention arm also has the treatment with the highest total QALYs, which discounted amount to 6.26 compared with 1.71 in the Ig arm.

Considering the ratio between the incremental cost and the incremental QALY gain, the CEM yields a discounted ICER per QALY for efgartigimod vs Ig of [REDACTED] (Table 94).

Table 94: Subpopulation 1 - Results

	Total Costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)
Intervention - pathway with efgartigimod	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Comparator - pathway without efgartigimod	[REDACTED]	[REDACTED]	-	-	-

Abbreviations: ICER: Incremental cost-effectiveness ratio; Ig: Immunoglobulin; QALY: Quality-adjusted life-year

3.12.2 Subpopulation 2 – Ig dependent patients

In Subpopulation 2, the total discounted lifetime cost of the pathway with efgartigimod amounts to [REDACTED] and it is higher than the total discounted cost observed in the pathway without efgartigimod, [REDACTED]. The main driver of the higher total cost in the Intervention arm is the drug cost of efgartigimod. The Intervention arm also has the treatment with the highest total QALYs, which discounted amount to [REDACTED] compared with [REDACTED] in the Ig arm.

Considering the ratio between the incremental cost and the incremental QALY gain, the CEM yields a discounted ICER per QALY for efgartigimod vs Ig of [REDACTED] (Table 95).

Table 95: Subpopulation 2 - Results

	Total Costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)
Intervention - pathway with efgartigimod	██████	██████	██████	██████	██████
Comparator - pathway without efgartigimod	██████	██████	██████	██████	██████

Abbreviations: ICER: Incremental cost-effectiveness ratio; Ig: Immunoglobulin; QALY: Quality-adjusted life-year.

3.12.3 Subpopulation 3 – patients dependent on ultra-high dose of Ig

In Subpopulation 3, the total discounted lifetime cost of the pathway with efgartigimod amounts to ██████, and it is lower than the total discounted cost observed in the pathway without efgartigimod, ██████. The Intervention arm also has the treatment with the highest total QALYs, which discounted amount to ██████ compared with ██████ in the Ig arm.

Considering the ratio between the incremental cost and the incremental QALY gain, the CEM yields a discounted ICER per QALY for efgartigimod vs Ig is dominant (**Table 96**).

Table 96: Subpopulation 3 – Results

	Total Costs (£)	Total QALYs	Inc. Costs	Inc. QALYs	ICER versus baseline (£/QALY)
Intervention - pathway with efgartigimod	██████	██████	██████	██████	██████
Comparator - pathway without efgartigimod	██████	██████	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; Ig: immunoglobulin; QALY: Quality-adjusted life-year.

3.13 Benefits not captured in the QALY calculation

The QALY framework captures changes in HRQoL but does not fully account for several important benefits of efgartigimod in CIDP. Improved disease control and reduced treatment burden can have broader effects on patients, caregivers, and the healthcare system that are not fully reflected in EQ-5D utilities.

Patient productivity and independence: Patients with CIDP often experience fluctuating weakness, pain, and fatigue that limit employment and daily activities.^{10,15} Stabilisation of disease with efgartigimod may enable greater work participation, reduce sickness absence, and support return to productive roles within families and communities. These gains are not fully captured by EQ-5D mobility and self-care domains.

Caregiver productivity and wellbeing: As shown in Section 3.4.9, caregiver disutilities are substantial in severe CIDP. Improvements in patient function can translate to fewer hours of

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

informal care, lower absenteeism, and improved emotional wellbeing for family members. These indirect benefits are not included in the base-case cost-effectiveness analysis.

Reduced treatment and service burden: Efgartigimod, administered subcutaneously via pre-filled syringes over 20-30 seconds, will significantly decrease reliance on hospital infusion units, lessening travel demands, waiting times, and lost working hours compared with IVIg. This will also ease pressure on NHS infusion capacity and allow redeployment of resources to other patients. This system benefit beyond CIDP is not captured.

System resilience and supply security: by offering a non-plasma-derived mechanism of action, efgartigimod contributes to diversification of CIDP treatment supply, reducing vulnerability to plasma shortages, an external impact not reflected in the model. Given CIDP is the most significant indication for Ig this has potential to benefit a range of other diseases (see section 1.3.8).

Taken together, these elements indicate that the overall value of efgartigimod to patients, caregivers, and the NHS may be underestimated when assessed solely through QALYs and direct healthcare costs.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

The economic model was developed in accordance with NICE preferred methods and aligned with the NICE reference case. It adopted an NHS PSS perspective and applied a lifetime horizon to ensure that all relevant costs and QALY gains associated with the intervention were fully captured.

Quality-control procedures were implemented to ensure that the programming and technical implementation of the conceptual model were accurate and robust. These procedures included verification of all the input data against original sources, and model validation, covering consistency checks, formula and calculation verification, cross referencing data inputs, review of the model interface, and audit of the visual basic for application code.

Wherever appropriate, UK clinical expert opinion was sought during the model development process to ensure face validity of the model structure, assumptions and parameter inputs supporting the credibility and clinical relevance of the economic model.

3.15 Interpretation and conclusions of economic evidence

This de novo economic evaluation has estimated the cost-effectiveness of efgartigimod for the treatment of patients with CIDP. The results of the evaluation show that efgartigimod is associated with an increase in QALYs of [REDACTED] compared to the pathway without efgartigimod. The pathway with efgartigimod is associated with an increase in costs of [REDACTED] versus the pathway without efgartigimod. This results in an ICER of [REDACTED].

Scenario analysis was performed to assess the impact of key modelling assumptions, with the findings including the pathway with efgartigimod achieving dominance over the pathway

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

without efgartigimod when the extrapolation of time on treatment with efgartigimod was extended to the entire time horizon, and the extrapolation of transition probabilities in Ig maintenance. Overall, the majority of scenario analyses performed were cost-effective at the £30,000 WTP threshold.

The OWSA showed that the main drivers of cost-effectiveness are those that are related to the Ig schedule and dose, the comparative efficacy of efgartigimod vs Ig, and the mean weight in the patient population.

The PSA showed that the pathway with efgartigimod is cost-effective at a WTP threshold of £20,000. The ICER in the PSA is [REDACTED], which shows dominance for the pathway with efgartigimod over the pathway without efgartigimod. At a WTP threshold of £30,000, the pathway with efgartigimod is associated with a [REDACTED] probability of being cost-effective.

3.15.1 Strengths and limitations

The CEA was developed in line with international and NICE guidelines. It captures disease progression in CIDP and the related benefits and costs as realistically as possible, without adding unnecessary complexity. Treatment patterns were built to reflect real clinical practice, including periodic dependency tests and remission phases, as described by UK clinical experts. Inputs were informed by the best available evidence and when limited evidence was available from the literature, a SEE process was conducted, ensuring that uncertain parameters were informed as much as possible through unbiased clinical opinion.

The CEA also has some limitations. There are uncertainties around some key parameters, most notably regarding how patients are managed after discontinuation of efgartigimod, where limited evidence is available. Moreover, efficacy data from the ADHERE trial were extrapolated over a life-long time horizon, which is necessary to estimate long-term outcomes but introduces further uncertainty given the relatively short duration of observed data. These uncertainties introduce potential variability in the results, though they have been addressed by testing alternative assumptions through a series of scenario analyses.

3.15.2 Conclusions

The results of the CEA indicate that efgartigimod is a cost-effective treatment when assessed against the NICE WTP threshold of £30,000 per QALY. It can be considered cost-effective versus the pathway without efgartigimod, which contains a basket of treatments denoting SoC, for the treatment of chronic inflammatory demyelinating polyneuropathy from the perspective of the UK NHS and PSS. This conclusion was consistent across the PSA, DSA and the majority of scenario analyses.

4. References

1. Van Den Bergh PYK, Van Doorn PA, Hadden RDM, Avau B, Vankrunkelsven P, Allen JA, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision. *Euro J of Neurology*. 2021;28:3556–83.
2. Summary of product characteristics - Vyvgart [Internet]. European Medicines Agency. [cited 2025 Aug 27]. Available from: https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf
3. Merkies ISJ, Kieseier BC. Fatigue, Pain, Anxiety and Depression in Guillain-Barré Syndrome and Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *Eur Neurol*. 2016;75:199–206.
4. Bunschoten C, Blomkwist-Markens PH, Horemans A, van Doorn PA, Jacobs BC. Clinical factors, diagnostic delay, and residual deficits in chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst*. 2019;24:253–9.
5. Lunn MP, Manji H, Choudhary PP, Hughes RA, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. *J Neurol Neurosurg Psychiatry*. 1999;66:677–80.
6. Allen JA. The Misdiagnosis of CIDP: A Review. *Neurol Ther*. 2020;9:43–54.
7. Population estimates for England and Wales: mid-2024 [Internet]. Office for National statistics. 2025. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/populationestimatesforenglandandwales/mid2024>
8. Allen JA, Butler L, Levine T, Haudrich A. A Global Survey of Disease Burden in Patients Who Carry a Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy. *Adv Ther*. 2021;38:316–28.
9. CIDP Healthcare Resource Use Survey - Redacted Summary. Data on file. argenx; 2025.
10. argenx. Caregiver research survey report - Experiences of individuals supporting adults living with chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. Data on file. 2025.
11. Mengel D, Fraune L, Sommer N, Stettner M, Reese JP, Dams J, et al. Costs of illness in chronic inflammatory demyelinating polyneuropathy in Germany. *Muscle Nerve*. 2018;58:681–7.
12. Mahdi-Rogers M, McCrone P, Hughes RAC. Economic costs and quality of life in chronic inflammatory neuropathies in southeast England. *Euro J of Neurology*. 2014;21:34–9.
13. Guptill J, Blein C, Arvin-Berod C, Deborah G, Sergio BS, Hashmath UTAS, et al. Burden of illness for adults with chronic inflammatory demyelinating polyneuropathy in the United States [Internet]. ISPOR; 2024 May 5; Atlanta, USA. Available from: <https://argenxmedical.com/content/dam/medical-affairs/congress-posters/neurology/cidp/isor/Burden-Demyelinating-Polyneuropathy.pdf>
14. Guptill JT, Runken MC, Eaddy M, Lunacsek O, Fuldeore RM. Treatment Patterns and Costs of Chronic Inflammatory Demyelinating Polyneuropathy: A Claims Database Analysis. *Am Health Drug Benefits*. 2019;12:127–35.
15. argenx. Patient survey research report - Patient experiences living with chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. 2025.
16. Qualitative clinical validation and structured expert elicitation. Data on file. argenx;
17. argenx. Market research survey report - Treatment patterns for chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. Data on file. 2025.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

18. England NHS. NHS England » Fit for the Future: 10 Year Health Plan for England [Internet]. [cited 2025 Oct 13]. Available from: <https://www.england.nhs.uk/long-term-plan/>
 19. NHS Framework Agreement for the supply of Human Normal Immunoglobulin and Anti-D Immunoglobulin (modification notice) [Internet]. NHS England. 2024. Available from: <https://www.find-tender.service.gov.uk/Notice/040401-2024>
 20. Human normal immunoglobulins - supply shortage | European Medicines Agency (EMA) [Internet]. 2024 [cited 2025 Oct 13]. Available from: <https://www.ema.europa.eu/en/medicines/human/shortages/human-normal-immunoglobulins>
 21. Changes in immunoglobulin product supply in 2025 [Internet]. Immunodeficiency UK. 2025. Available from: <https://www.immunodeficiencyuk.org/immunoglobulin-replacement-therapy/changes-in-immunoglobulin-product-supply-in-2025/>
 22. argenx. Data on file: UK advisory board report.
 23. UK Chart review protocol. Data on file. argenx; 2025.
 24. Ripellino P, Fleetwood T, Cantello R, Comi C. Treatment of chronic inflammatory demyelinating polyneuropathy: from molecular bases to practical considerations. *Autoimmune Dis.* 2014;2014:201657.
 25. Heo YA. Efgartigimod: First Approval. *Drugs.* 2022;82:341–8.
 26. Yang Y, Shen Z, Shi F, Wang F, Wen N. Efgartigimod as a novel FcRn inhibitor for autoimmune disease. *Neurol Sci.* 2024;45:4229–41.
 27. NIHR. Health Technology Briefing December 2023: Efgartigimod PH20 SC for treating chronic inflammatory demyelinating polyradiculoneuropathy [Internet]. 2023 [cited 2024 Aug 23]. Available from: <https://www.io.nihr.ac.uk/wp-content/uploads/2023/12/29647-Efgartigimod-PH20-SC-for-Chronic-Inflammatory-Demyelinating-Polyradiculoneuropathy-V1.0-DEC2023-NON-CONF.pdf>
 28. Efgartigimod alfa and hyaluronidase-qvfc (subcutaneous route) - Side effects & dosage [Internet]. Mayo Clinic. [cited 2025 Oct 10]. Available from: <https://www.mayoclinic.org/drugs-supplements/efgartigimod-alfa-and-hyaluronidase-qvfc-subcutaneous-route/description/drg-20552453>
 29. UK grants promising innovative medicine status to CIDP drug - PharmaTimes [Internet]. 2024 [cited 2025 Oct 10]. Available from: <https://pharmatimes.com/news/scientists-join-forces-to-speed-up-vaccine-development-with-new-technology/>
 30. CIDP & the associated chronic variant [Internet]. Gain Charity; Available from: <https://gaincharity.org.uk/wp-content/uploads/2017/10/CIDP-the-chronic-variants-rebrand.interim.pdf#:~:text=Chronic>
 31. Cox SZ, Gwathmey KG. Chronic Immune-Mediated Polyneuropathies. *Clinics in Geriatric Medicine.* 2021;37:327–45.
 32. Dyck PJB, Tracy JA. History, Diagnosis, and Management of Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *Mayo Clinic Proceedings.* 2018;93:777–93.
 33. Lewis RA, Van Doorn PA, Sommer C. Tips in navigating the diagnostic complexities of chronic inflammatory demyelinating polyradiculoneuropathy. *Journal of the Neurological Sciences.* 2022;443:120478.
 34. Van den Bergh PYK, Hadden RDM, Bouche P, Cornblath DR, Hahn A, Illa I, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision. *Eur J Neurol.* 2010;17:356–63.
 35. Roman-Guzman RM, Martinez-Mayorga AP, Guzman-Martinez LD, Rodriguez-Leyva I. Chronic Inflammatory Demyelinating Polyneuropathy: A Narrative Review of a Systematic Diagnostic Approach to Avoid Misdiagnosis. *Cureus [Internet].* 2025 [cited 2025 Oct 16]; Available from: <https://www.cureus.com/articles/299844-chronic->
- Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

inflammatory-demyelinating-polyneuropathy-a-narrative-review-of-a-systematic-diagnostic-approach-to-avoid-misdiagnosis

36. Gogia B, Rocha Cabrero F, Khan Suheb M, Lui F, Rai P. Chronic Inflammatory Demyelinating Polyradiculoneuropathy. [Updated 2024 Mar 4]. In Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Aug 22]. (StatPearls [Internet].). Available from: <https://www.ncbi.nlm.nih.gov/books/NBK563249/>
37. Van Doorn I, Eftimov F, Wieske L, Van Schaik I, Verhamme C. Challenges in the Early Diagnosis and Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy in Adults: Current Perspectives. *TCRM*. 2024;Volume 20:111–26.
38. Querol L, Nogales-Gadea G, Rojas-Garcia R, Diaz-Manera J, Pardo J, Ortega-Moreno A, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. *Neurology*. 2014;82:879–86.
39. Doppler K, Appeltshauser L, Villmann C, Martin C, Peles E, Krämer HH, et al. Auto-antibodies to contactin-associated protein 1 (Caspr) in two patients with painful inflammatory neuropathy. *Brain*. 2016;139:2617–30.
40. Kouton L, Boucraut J, Devaux J, Rajabally YA, Adams D, Antoine JC, et al. Electrophysiological features of chronic inflammatory demyelinating polyradiculoneuropathy associated with IgG4 antibodies targeting neurofascin 155 or contactin 1 glycoproteins. *Clin Neurophysiol*. 2020;131:921–7.
41. Manso C, Querol L, Lleixà C, Poncelet M, Mekaouche M, Vallat JM, et al. Anti-neurofascin-155 IgG4 antibodies prevent paranodal complex formation in vivo. *The Journal of Clinical Investigation*. 2019;129:2222.
42. Yan WX, Taylor J, Andrias-Kauba S, Pollard JD. Passive transfer of demyelination by serum or IgG from chronic inflammatory demyelinating polyneuropathy patients. *Ann Neurol*. 2000;47:765–75.
43. Hahn AF, Bolton CF, Pillay N, Chalk C, Benstead T, Bril V, et al. Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy. A double-blind, sham-controlled, cross-over study. *Brain*. 1996;119 (Pt 4):1055–66.
44. Dyck PJ, Litchy WJ, Kratz KM, Suarez GA, Low PA, Pineda AA, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol*. 1994;36:838–45.
45. Filomena CA, Filomena AP, Hudock J, Ballas SK. Evaluation of serum immunoglobulins by protein electrophoresis and rate nephelometry before and after therapeutic plasma exchange. *Am J Clin Pathol*. 1992;98:243–8.
46. Mehndiratta MM, Hughes RAC, Pritchard J. Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev*. 2015;2015:CD003906.
47. Zinman LH, Sutton D, Ng E, Nwe P, Ngo M, Bril V. A pilot study to compare the use of the Excorim staphylococcal protein immunoadsorption system and IVIG in chronic inflammatory demyelinating polyneuropathy. *Transfus Apher Sci*. 2005;33:317–24.
48. Bunschoten C, Jacobs BC, Van Den Bergh PYK, Cornblath DR, Van Doorn PA. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. *The Lancet Neurology*. 2019;18:784–94.
49. Hughes R a. C, Bouche P, Cornblath DR, Evers E, Hadden RDM, Hahn A, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol*. 2006;13:326–32.
50. Eftimov F, Lucke IM, Querol LA, Rajabally YA, Verhamme C. Diagnostic challenges in chronic inflammatory demyelinating polyradiculoneuropathy. *Brain*. 2020;143:3214–24.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

51. Guo Y, Tian X, Wang X, Xiao Z. Adverse Effects of Immunoglobulin Therapy. *Front Immunol*. 2018;9:1299.
52. Gorson KC, van Schaik IN, Merkies ISJ, Lewis RA, Barohn RJ, Koski CL, et al. Chronic inflammatory demyelinating polyneuropathy disease activity status: recommendations for clinical research standards and use in clinical practice. *J Peripher Nerv Syst*. 2010;15:326–33.
53. Broers MC, Bunschoten C, Nieboer D, Lingsma HF, Jacobs BC. Incidence and Prevalence of Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Systematic Review and Meta-Analysis. *Neuroepidemiology*. 2019;52:161–72.
54. Swart G, Skolka MP, Shelly S, Lewis RA, Allen JA, Dubey D, et al. Distinguishing Chronic Inflammatory Demyelinating Polyneuropathy From Mimic Disorders: The Role of Statistical Modeling. *J Peripher Nerv Syst*. 2025;30:e12682.
55. Allen JA, Lin J, Basta I, Dysgaard T, Eggers C, Guptill JT, et al. Safety, tolerability, and efficacy of subcutaneous efgartigimod in patients with chronic inflammatory demyelinating polyradiculoneuropathy (ADHERE): a multicentre, randomised-withdrawal, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2024;23:1013–24.
56. Breiner A, Barnett C, Bril V. INCAT disability score: a critical analysis of its measurement properties. *Muscle Nerve*. 2014;50:164–9.
57. Hughes RAC, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol*. 2008;7:136–44.
58. Katzberg HD, Latov N, Walker FO. Measuring disease activity and clinical response during maintenance therapy in CIDP: from ICE trial outcome measures to future clinical biomarkers. *Neurodegener Dis Manag*. 2017;7:147–56.
59. Léger JM, De Bleecker JL, Sommer C, Robberecht W, Saarela M, Kamienowski J, et al. Efficacy and safety of Privigen® in patients with chronic inflammatory demyelinating polyneuropathy: results of a prospective, single-arm, open-label Phase III study (the PRIMA study). *J Peripher Nerv Syst*. 2013;18:130–40.
60. van Schaik IN, Bril V, van Geloven N, Hartung HP, Lewis RA, Sobue G, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2018;17:35–46.
61. Vanhoutte EK, Latov N, Deng C, Hanna K, Hughes R a. C, Bril V, et al. Vigorimeter grip strength in CIDP: a responsive tool that rapidly measures the effect of IVIG--the ICE study. *Eur J Neurol*. 2013;20:748–55.
62. Hughes R, Bensa S, Willison H, Van Den Bergh P, Comi G, Illa I, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Annals of Neurology*. 2001;50:195–201.
63. Khoo A, Frasca J, Schultz D. Measuring disease activity and predicting response to intravenous immunoglobulin in chronic inflammatory demyelinating polyneuropathy. *Biomark Res*. 2019;7:3.
64. van Nes SI, Vanhoutte EK, van Doorn PA, Hermans M, Bakkers M, Kuitwaard K, et al. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology*. 2011;76:337–45.
65. Vanhoutte EK, Faber CG, van Nes SI, Jacobs BC, van Doorn PA, van Koningsveld R, et al. Modifying the Medical Research Council grading system through Rasch analyses. *Brain*. 2012;135:1639–49.
66. Podsiadlo D, Richardson S. The timed 'Up & Go': a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39:142–8.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

67. EQ-5D-5L [Internet]. EuroQol. [cited 2024 Nov 5]. Available from: <https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/>
 68. Draak THP, Gorson KC, Vanhoutte EK, van Nes SI, van Doorn PA, Cornblath DR, et al. Correlation of the patient's reported outcome Inflammatory-RODS with an objective metric in immune-mediated neuropathies. *Eur J Neurol*. 2016;23:1248–53.
 69. Rajabally YA, Min YG, Nazeer KK, Englezou C. Treatment response amplitude and timing in chronic inflammatory demyelinating polyneuropathy with routine care: Study of a UK cohort. *Euro J of Neurology*. 2024;31:e16399.
 70. Chronic Inflammatory Demyelinating Polyneuropathy [Internet]. [cited 2024 Nov 7]. Available from: <https://www.thewaltoncentre.nhs.uk/patient-leaflets/chronic-inflammatory-demyelinating-polyneuropathy/486098>
 71. Orphanet: Chronic inflammatory demyelinating polyneuropathy [Internet]. [cited 2024 Nov 5]. Available from: <https://www.orpha.net/en/disease/detail/2932?name=CIDP&mode=name>
 72. EU/3/21/2555 - orphan designation for treatment of chronic inflammatory demyelinating polyneuropathy | European Medicines Agency (EMA) [Internet]. 2022 [cited 2025 Oct 10]. Available from: <https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-21-2555>
 73. Annual report 2023/2024 [Internet]. Immunoglobulin database; 2025. Available from: https://igd.mdsas.com/wp-content/uploads/Igd_AnnualReport_202324.pdf
 74. Said G, Krarup C. Chapter 22 - Chronic inflammatory demyelinating polyneuropathy. In: Said G, Krarup C, editors. *Handbook of Clinical Neurology* [Internet]. Elsevier; 2013 [cited 2024 Nov 7]. p. 403–13. (Peripheral Nerve Disorders; vol. 115). Available from: <https://www.sciencedirect.com/science/article/pii/B9780444529022000229>
 75. Findling O, Logt R van der, Nedeltchev K, Achtnichts L, Allum JHJ. A comparison of balance control during stance and gait in patients with inflammatory and non-inflammatory polyneuropathy. *PLoS ONE*. 2018;13:e0191957.
 76. Kuitwaard K, Bos-Eyssen ME, Blomkwist-Markens PH, van Doorn PA. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. *J Peripher Nerv Syst*. 2009;14:310–5.
 77. Querol L, Rinaldi S, Borsi A, Boggia GM, de Courcy J, Taylor Y, et al. Real-World Multinational Survey of Chronic Inflammatory Demyelinating Polyneuropathy: Disease Characteristics and Therapeutic Landscape. *J Peripher Nerv Syst*. 2025;30:e70047.
 78. Clinical Commissioning Policy for the use of therapeutic immunoglobulin (Ig) England (2025) [Internet]. NHS England; 2025 Apr [cited 2025 Oct 11]. Available from: <https://www.england.nhs.uk/publication/commissioning-criteria-policy-for-the-use-of-therapeutic-immunoglobulin-ig-in-england/>
 79. Cuvitru 200 mg/ml solution for subcutaneous injection - Summary of Product Characteristics (SmPC) - (emc) | 9191 [Internet]. [cited 2025 Oct 10]. Available from: <https://www.medicines.org.uk/emc/product/9191/smpc>
 80. Xembify 200 mg/mL solution for subcutaneous injection - Summary of Product Characteristics (SmPC) - (emc) | 15777 [Internet]. [cited 2025 Oct 10]. Available from: <https://www.medicines.org.uk/emc/product/15777/smpc?utm>
 81. Cutaquig, 165 mg/ml, solution for injection - Summary of Product Characteristics (SmPC) - (emc) | 12686 [Internet]. [cited 2025 Oct 11]. Available from: <https://www.medicines.org.uk/emc/product/12686/smpc>
 82. HyQvia 100 mg/ml solution for infusion for subcutaneous use - Summary of Product Characteristics (SmPC) - print friendly - (emc) [Internet]. [cited 2024 Nov 6]. Available from: <https://www.medicines.org.uk/emc/product/9197/smpc/print>
 83. Epland K, Suez D, Paris K. A clinician's guide for administration of high-concentration and facilitated subcutaneous immunoglobulin replacement therapy in patients with primary immunodeficiency diseases. *Allergy Asthma Clin Immunol*. 2022;18:87.
- Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

84. Bozovic I, Kacar A, Peric S, Nikolic A, Bjelica B, Cobeljic M, et al. Quality of life predictors in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol*. 2017;264:2481–6.
85. Querol L, Crabtree M, Herepath M, Priedane E, Viejo Viejo I, Agush S, et al. Systematic literature review of burden of illness in chronic inflammatory demyelinating polyneuropathy (CIDP). *J Neurol*. 2021;268:3706–16.
86. Fernandez M, Copley-Merriman C, Arvin-Berod C, Phillips G, Gelinas D, Weiss R, et al. CO85 Evidence Gap Analysis of the Burden of Illness and Treatment of Chronic Inflammatory Demyelinating Polyneuropathy. *Value in Health*. 2022;25:S34.
87. Santos PL dos, Almeida-Ribeiro GAN de, Silva DMD, Marques Junior W, Barreira AA. Chronic inflammatory demyelinating polyneuropathy: quality of life, sociodemographic profile and physical complaints. *Arq Neuropsiquiatr*. 2014;72:179–83.
88. Ryltoft AK, Al-Zuhairy A, Sindrup SH, Andersen H, Markvardsen LK. Quality of life in chronic inflammatory demyelinating polyneuropathy patients treated with subcutaneous immunoglobulin. *Acta Neurol Scand*. 2020;142:637–40.
89. Michaelides A, Hadden RDM, Sarrigiannis PG, Hadjivassiliou M, Zis P. Pain in Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Systematic Review and Meta-Analysis. *Pain Ther*. 2019;8:177–85.
90. Allen J, Butler L, Levine T, Bullinger A, Koski C. CIDP Disease Burden — Results of a US Nationwide Patient Survey [Internet]. GBS/CIDP Foundation International. 2019 [cited 2024 Nov 5]. Available from: <https://www.gbs-cidp.org/2019/03/cidp-disease-burden-results-of-a-us-nationwide-patient-survey/>
91. Shaikh A, Jaffry K, Trivedi R, Mandava K, Jaffry M, Ors M, et al. Effect of treatments on all-cause of mortality in chronic inflammatory demyelinating polyneuropathy [Internet]. American Academy of Neurology Annual Meeting - Session S19 - Neuroepidemiology; 2023. Available from: <https://www.aan.com/MSA/Public/Events/AbstractDetails/52825>
92. karkare S, C AB, F B, Mahajerin A, Nowacek D, Van de Veire L. The burden of illness in Chronic Inflammatory Demyelinating Polyneuropathy: results of a multinational real-world survey [Internet]. ISPOR 2025; 2025 May 13 [cited 2025 Aug 27]. Available from: https://www.ispor.org/docs/default-source/cti-meeting-21021-documents/0999e132-ea28-4ee8-9e48-d2767d639186.pdf?sfvrsn=987b7019_0
93. Al-Zuhairy A, Jakobsen J. Outcome in chronic inflammatory demyelinating polyneuropathy: A systematic review and meta-analysis. *Muscle Nerve*. 2023;68:388–96.
94. Overview | Suspected neurological conditions: recognition and referral | Guidance | NICE [Internet]. NICE; 2019 [cited 2024 Nov 6]. Available from: <https://www.nice.org.uk/guidance/ng127?UID=41118021420241167398>
95. Overview | Neuropathic pain in adults: pharmacological management in non-specialist settings | Guidance | NICE [Internet]. NICE; 2013 [cited 2024 Nov 6]. Available from: <https://www.nice.org.uk/Guidance/CG173>
96. Overview | Suspected neurological conditions: recognition and referral | Quality standards | NICE [Internet]. NICE; 2021 [cited 2024 Nov 6]. Available from: <https://www.nice.org.uk/guidance/QS198>
97. Project information | Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409 | Guidance | NICE [Internet]. NICE; [cited 2024 Nov 6]. Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-ta11508>
98. Clinical Commissioning Policy Rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) & vasculitis of the peripheral nervous system (adults) [NHS England URN: 170026/P]. NHS England; 2021 Nov. Report No.: 170026/P.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

99. Oaklander AL, Lunn MP, Hughes RA, van Schaik IN, Frost C, Chalk CH. Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIPD): an overview of systematic reviews. *Cochrane Database Syst Rev*. 2017;1:CD010369.
100. Lunn MP, Ellis L, Hadden RD, Rajabally YA, Winer JB, Reilly MM. A proposed dosing algorithm for the individualized dosing of human immunoglobulin in chronic inflammatory neuropathies. *J Peripheral Nervous Sys*. 2016;21:33–7.
101. Ramo-Tello C, Blanco Y, Brieva L, Casanova B, Martínez-Cáceres E, Ontaneda D, et al. Recommendations for the Diagnosis and Treatment of Multiple Sclerosis Relapses. *J Pers Med*. 2021;12:6.
102. Therapeutic apheresis units [Internet]. NHS Blood and transplant. Available from: <https://www.nhsbt.nhs.uk/what-we-do/diagnostic-and-therapeutic-services/therapeutic-apheresis/therapeutic-apheresis-units/>
103. Kuitwaard K, Fokkink WJR, Brusse E, Vrancken AFJE, Eftimov F, Notermans NC, et al. Maintenance IV immunoglobulin treatment in chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst*. 2017;22:425–32.
104. Kuitwaard K, Hahn AF, Vermeulen M, Venance SL, van Doorn PA. Intravenous immunoglobulin response in treatment-naïve chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry*. 2015;86:1331–6.
105. Brannagan TH, Khosro F, Kleyman I, Leitch M, Traub R, Ulane C. Existing and Emerging Approaches to Treating Chronic Inflammatory Demyelinating Polyneuropathy. 2019;15:33–9.
106. Watkins JM, Dimachkie MM, Riley P, Murphy E. Subcutaneous Immunoglobulin Therapy for Chronic Inflammatory Demyelinating Polyneuropathy: A Nursing Perspective. *J Neurosci Nurs*. 2019;51:198–203.
107. Fargeot G, Gitiaux C, Magy L, Pereon Y, Delmont E, Viala K, et al. French recommendations for the management of adult & pediatric chronic inflammatory demyelinating polyradiculoneuropathy (CIPD). *Rev Neurol (Paris)*. 2022;178:953–68.
108. Strengers PFW. Challenges for Plasma-Derived Medicinal Products. *Transfus Med Hemother*. 2023;50:116–22.
109. Allen JA, Gelinas DF, Freimer M, Runken MC, Wolfe GI. Immunoglobulin administration for the treatment of CIPD: IVIG or SCIG? *J Neurol Sci*. 2020;408:116497.
110. Beydoun SR, Sharma KR, Bassam BA, Pulley MT, Shije JZ, Kafal A. Individualizing Therapy in CIPD: A Mini-Review Comparing the Pharmacokinetics of Ig With SCIG and IVIG. *Frontiers in Neurology*. 2021;12:638816.
111. Octagam 5%, solution for infusion - Summary of Product Characteristics (SmPC) - (emc) | 6555 [Internet]. [cited 2025 Oct 11]. Available from: <https://www.medicines.org.uk/emc/product/6555/smpc>
112. Gamunex 10%, 100 mg/ml, solution for infusion - Summary of Product Characteristics (SmPC) - print friendly - (emc) [Internet]. [cited 2024 Nov 7]. Available from: <https://www.medicines.org.uk/emc/product/4854/smpc/print>
113. Intratect 100g/l, solution for infusion - Summary of Product Characteristics (SmPC) - (emc) | 3222 [Internet]. [cited 2025 Oct 11]. Available from: <https://www.medicines.org.uk/emc/product/3222/smpc>
114. KIOVIG 100 mg/ml solution for infusion - Summary of Product Characteristics (SmPC) - (emc) | 9198 [Internet]. [cited 2025 Oct 12]. Available from: <https://www.medicines.org.uk/emc/product/9198/smpc>
115. Gamten, 100 mg/ml solution for infusion - Summary of Product Characteristics (SmPC) - (emc) | 15958 [Internet]. [cited 2025 Oct 12]. Available from: <https://www.medicines.org.uk/emc/product/15958/smpc>
116. Panzyga 100 mg/ml solution for infusion - Summary of Product Characteristics (SmPC) - (emc) | 7317 [Internet]. [cited 2025 Oct 12]. Available from: <https://www.medicines.org.uk/emc/product/7317/smpc>

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

117. Muley SA, Parry GJ. Inflammatory demyelinating neuropathies. *Curr Treat Options Neurol.* 2009;11:221–7.
118. Robertson EE, Donofrio PD. Treatment of chronic inflammatory demyelinating polyneuropathy. *Curr Treat Options Neurol.* 2010;12:84–94.
119. Adrichem ME, Eftimov F, Van Schaik IN. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyradiculoneuropathy, a time to start and a time to stop. *J Peripheral Nervous Sys.* 2016;21:121–7.
120. Jung SM, Kim WU. Targeted Immunotherapy for Autoimmune Disease. *Immune Netw.* 2022;22:e9.
121. Yoon MS, Chan A, Gold R. Standard and escalating treatment of chronic inflammatory demyelinating polyradiculoneuropathy. *Ther Adv Neurol Disord.* 2011;4:193–200.
122. Dalakas MC, Medscape. Advances in the diagnosis, pathogenesis and treatment of CIDP. *Nat Rev Neurol.* 2011;7:507–17.
123. Dalakas MC. 67 - Autoimmune Peripheral Neuropathies. In: Rich RR, Fleisher TA, Schroeder HW, Weyand CM, Corry DB, Puck JM, editors. *Clinical Immunology (Sixth Edition)* [Internet]. New Delhi: Elsevier; 2023 [cited 2024 Nov 7]. p. 854–65. Available from: <https://www.sciencedirect.com/science/article/pii/B9780702081651000678>
124. Cocito D, Paolasso I, Antonini G, Benedetti L, Briani C, Comi C, et al. A nationwide retrospective analysis on the effect of immune therapies in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *Eur J Neurol.* 2010;17:289–94.
125. Hodgens A, Sharman T. Corticosteroids. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Nov 7]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK554612/>
126. Yasir M, Goyal A, Sonthalia S. Corticosteroid Adverse Effects. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Nov 7]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK531462/>
127. Allen JA, Pasnoor M, Dimachkie MM, Ajroud-Driss S, Brannagan TH, Cook AA, et al. Quantifying Treatment-Related Fluctuations in CIDP: Results of the GRIPPER Study. *Neurology.* 2021;96:e1876–86.
128. Bus SRM, Broers MC, Lucke IM, Bunschoten C, van Lierloo GGA, Adrichem ME, et al. Clinical outcome of CIDP one year after start of treatment: a prospective cohort study. *J Neurol.* 2022;269:945–55.
129. Toth J. OHE's submission to a parliamentary inquiry on UK drug shortages - OHE [Internet]. 2025 [cited 2025 Oct 13]. Available from: <https://www.ohe.org/insights/ohes-submission-to-a-parliamentary-inquiry-on-uk-drug-shortages/>
130. Faith issues and treatment for immunodeficiency [Internet]. Immunodeficiency UK. Available from: <https://www.immunodeficiencyuk.org/immunodeficiency/treatment/faithissuesandtreatmentforpids/?utm>
131. argenx. Clinical study report ARGX-113-1802, Efgartigimod PH20 SC—CIDP. Data on file. 2023.
132. Open-label Extension of the ARGX-113-1802 Trial to Investigate the Long-term Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Patients With Chronic Inflammatory Demyelinating Polyneuropathy (ADHERE+) [Internet]. ClinicalTrials.gov. [cited 2025 Aug 28]. Available from: <https://clinicaltrials.gov/study/NCT04280718>
133. Allen JA, Lin J, Stettner M, Guptill J, Istas G. ADHERE+ Trial Interim Analysis: Long-Term Safety and Efficacy of Efgartigimod in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. Presented at the 2025 Peripheral Nerve Society (PNS) Annual Meeting; May 17–20, 2025; Edinburgh, UK. In 2025.
134. Substudy ARGX-113-1902 - IA2 : Substudy of Phase 2 OLE of ARGX-113-1802 in CIDP with efgartigimod PH20 SC. Data on file. argenx; 2025.
135. Clinical trial protocol ARGX-113-1902 (ADHERE+). Data on file. argenx; Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

136. Siddiqi Z, Allen J, Basta I, Eggers C, Guptill J, Gwathmey K, et al. Efficacy, Safety, and Tolerability of Subcutaneous Efgartigimod in Chronic Inflammatory Demyelinating Polyneuropathy: Results From the ADHERE Trial [Internet]. 2024 Canadian Neurological Sciences Federation's (CNSF) Congress; 2024 May 20; Toronto, Canada. Available from: https://argenxmedical.com/content/dam/medical-affairs/congress-posters/neurology/cidp/cnsf-2024/CNSF%202024_Efficacy_%20Safety_%20and%20Tolerability%20%20of%20Subcutaneous%20Efgartigimod%20in%20%20Chronic%20Inflammatory%20Demyelinating%20%20Polyneuropathy%20Results%20From%20the%20ADHERE%20Trial.pdf
137. Dewilde S, Brackx F, Arvin-Berod C, Istas G, De Roeck A, Hofman E, et al. The Effect of Efgartigimod on Treatment Convenience, Effectiveness, and Overall Satisfaction in CIDP Patients. ISPOR Europe; 2024 Nov; Barcelona, Spain.
138. Brackx F, Istas G, Van Hoorick B. The effect of efgartigimod on pain, mental health and fatigue in CIDP patients. Presented at the International Congress on Neuromuscular Disorders (ICNMD). In Perth; 2024.
139. Brackx F, Istas G, Van Hoorick B. The association between utility scores and pain, fatigue and mental health in CIDP patients. Presented at the International Congress of Neuromuscular Disorders (ICNMD). In 2024.
140. Allen J, Lin J, Stettner M, Merkies I, Guptill J, Gwathmey K, et al. Treatment Impact of Efgartigimod PH20 SC on I-RODS Daily Activity Assessment in Patients with Chronic Inflammatory Demyelinating Polyneuropathy: Post Hoc Analysis of the Registrational ADHERE Study (P10-11.025). *Neurology*. 2025;104:4890.
141. Efgartigimod for CIDP: Indirect Treatment Comparison. Data on file. argenx; 2024.
142. Cocito D, Peci E, Rigaldo S, Canavese C, Migliaretti G, Cossa FM. Manual push technique, an alternative route of subcutaneous immunoglobulin administration in chronic inflammatory demyelinating polyradiculoneuropathy: A proof-of-concept study. *Clinical Neurology and Neurosurgery*. 2020;198:106240.
143. Katzberg HD, Rasutis V, Bril V. Home IVIG for CIDP: A Focus on Patient Centred Care. *Can J Neurol Sci*. 2013;40:384–8.
144. Bril V, Hadden RDM, Brannagan TH, Bar M, Chroni E, Rejdak K, et al. Hyaluronidase-facilitated subcutaneous immunoglobulin 10% as maintenance therapy for chronic inflammatory demyelinating polyradiculoneuropathy: The ADVANCE-CIDP 1 randomized controlled trial. *J Peripher Nerv Syst*. 2023;28:436–49.
145. Population-adjusted indirect comparisons (MAIC and STC) [Internet]. 2025 [cited 2025 Oct 13]. Available from: <https://sheffield.ac.uk/nice-dsu/tsds/population-adjusted>
146. Health Survey for England, 2021: Data tables [Internet]. NHS England Digital. [cited 2025 Oct 13]. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2021/health-survey-for-england-2021-data-tables>
147. Tibshirani R, Walther G, Hastie T. Estimating the Number of Clusters in a Data Set Via the Gap Statistic. *J R Stat Soc Ser B Stat Methodol*. 2001;63:411–23.
148. Development and validation of a cost-effectiveness model concept of chronic inflammatory demyelinating polyneuropathy. Data on file. argenx; 2024.
149. NICE. NICE health technology evaluations: the manual. Process & methods (PMG36) [Internet]. 2022 Jan. Available from: <https://www.nice.org.uk/process/pmg36>
150. 5 The reference case | Guide to the methods of technology appraisal 2013 | Guidance | NICE [Internet]. NICE; 2013 [cited 2025 Oct 12]. Available from: <https://www.nice.org.uk/process/pmg9/chapter/the-reference-case>
151. Koay S, Chen YC, Ransley G, Compton L, Lunn MP, Carr AS. Safety and Cost Analysis of Immunoglobulin Cessation Trials in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *J Peripher Nerv Syst*. 2025;30:e70007.
152. argenx. Input from clinical experts. Data on file. 2025.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

153. van Schaik IN, Mielke O, Bril V, van Geloven N, Hartung HP, Lewis RA, et al. Long-term safety and efficacy of subcutaneous immunoglobulin IgPro20 in CIDP: PATH extension study. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e590.
154. Office for National Statistics. UK population estimates [Internet]. Office for National Statistics. 2024; Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/ukpop/pop>
155. Hernández-Alava M, Pudney S. Mapping between EQ-5D-3L and EQ-5D-5L: A survey experiment on the validity of multi-instrument data. *Health Econ*. 2022;31:923–39.
156. Analysis of Adelphi dataset on patients with CIDP in support of NICE submission. Data on file. argenx; 2025.
157. Hernandez M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. 2018.
158. Mielke O, Bril V, Cornblath DR, Lawo JP, van Geloven N, Hartung HP, et al. Restabilization treatment after intravenous immunoglobulin withdrawal in chronic inflammatory demyelinating polyneuropathy: Results from the pre-randomization phase of the Polyneuropathy And Treatment with Hizentra study. *J Peripher Nerv Syst*. 2019;24:72–9.
159. Waheed W, Ayer GA, Jadoo CL, Badger GJ, Aboukhatwa M, Brannagan TH, et al. Safety of intravenous immune globulin in an outpatient setting for patients with neuromuscular disease. *Muscle and Nerve*. 2019;60:528–37.
160. Dorst J, Fillies F, Dreyhaupt J, Senel M, Tumani H. Safety and Tolerability of Plasma Exchange and Immunoadsorption in Neuroinflammatory Diseases. *J Clin Med*. 2020;9:2874.
161. Narayanaswami P, Sanders DB, Thomas L, Thibault D, Blevins J, Desai R, et al. Comparative effectiveness of azathioprine and mycophenolate mofetil for myasthenia gravis (PROMISE-MG): a prospective cohort study. *The Lancet Neurology*. 2024;23:267–76.
162. Dychter SS, Gold DA, Carson D, Haller M. Intravenous therapy: a review of complications and economic considerations of peripheral access. *J Infus Nurs*. 2012;35:84–91.
163. Marsh N, Larsen EN, Ullman AJ, Mihala G, Cooke M, Chopra V, et al. Peripheral intravenous catheter infection and failure: A systematic review and meta-analysis. *Int J Nurs Stud*. 2024;151:104673.
164. Mallick R, Carlton R, Van Stiphout J. A Budget Impact Model of Maintenance Treatment of Chronic Inflammatory Demyelinating Polyneuropathy with IgPro20 (Hizentra) Relative to Intravenous Immunoglobulin in the United States. *PharmacoEconomics Open*. 2023;7:243–55.
165. Overview | Ozanimod for treating relapsing–remitting multiple sclerosis | Guidance | NICE [Internet]. NICE; 2021 [cited 2025 Sept 24]. Available from: <https://www.nice.org.uk/guidance/ta706>
166. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. 2011;31:800–4.
167. Overview | Teduglutide for treating short bowel syndrome | Guidance | NICE [Internet]. NICE; 2022 [cited 2025 Sept 24]. Available from: <https://www.nice.org.uk/guidance/ta804>
168. Brewer S, Kennedy-Martin T. Interrogating Social Media Sources to Gain Insight on Opioid-Induced Constipation Symptoms as Reported By Patients. *Value in Health*. 2017;20:A637–8.
169. Matza LS, Cong Z, Chung K, Stopeck A, Tonkin K, Brown J, et al. Utilities associated with subcutaneous injections and intravenous infusions for treatment of patients with bone metastases. *Patient Prefer Adherence*. 2013;7:855–65.

Company evidence submission template for efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

170. Dosing and Administration - CIDP Treatment - GAMUNEX®-C HCP [Internet]. [cited 2025 Sept 24]. Available from: <https://www.gamunex-c.com/en/hcp/cidp/dosing-administration>
171. Dosing and Infusion Rates - PRIVIGEN Immune Globulin Intravenous (Human), 10% Liquid [Internet]. [cited 2025 Sept 24]. Available from: <https://www.privigen.com/hcp/dosing>
172. NICE. Inotersen for treating hereditary transthyretin amyloidosis (HST9). 2019; Available from: <https://www.nice.org.uk/guidance/hst9>
173. Gani R, Giovannoni G, Bates D, Kembal B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *Pharmacoeconomics*. 2008;26:617–27.
174. National Cost Collection for the NHS [Internet]. NHS England. [cited 2025 Oct 13]. Available from: <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>
175. Hizentra 200 mg/ml solution for subcutaneous injection - Summary of Product Characteristics (SmPC) - (emc) | 4643 [Internet]. [cited 2025 Oct 13]. Available from: <https://www.medicines.org.uk/emc/product/4643/smpc#gref>
176. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2024 Manual [Internet]. Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2025 [cited 2025 Sept 26]. Available from: <https://kar.kent.ac.uk/id/eprint/109563>
177. Nobile-Orazio E, Cocito D, Jann S, Uncini A, Beghi E, Messina P, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. *Lancet Neurol*. 2012;11:493–502.
178. Bedi G, Brown A, Tong T, Sharma KR. Chronic inflammatory demyelinating polyneuropathy responsive to mycophenolate mofetil therapy. *J Neurol Neurosurg Psychiatry*. 2010;81:634–6.
179. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2023 Manual [Internet]. Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2024 [cited 2025 Oct 14]. Available from: <https://kar.kent.ac.uk/id/eprint/105685>
180. Madihi Y, Mostofizadeh N, Shamsipour Dehkordi H, Riahinezhad M, Hovsepian S, Rostampour N, et al. Prevalence of nephrocalcinosis in children with congenital adrenal hyperplasia. *J Res Med Sci*. 2022;27:16.
181. 2025/26 NHS Payment Scheme – Annex D: Prices and cost adjustments [Internet]. NHS England. [cited 2025 Oct 13]. Available from: <https://www.england.nhs.uk/long-read/25-26-nhsps-annex-d-prices-and-cost-adjustments/>
182. NHS England. 2023-25 NHS Payment Scheme (amended). [Internet]. 2024 [cited 2025 Oct 7]. Available from: <https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/>

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy ID6409

Summary of Information for Patients (SIP)

October 2025

File name	Version	Contains confidential information	Date
ID6409_efgartigimod CIDP_SIP	V1	No	17 October 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the Company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Efgartigimod alfa with recombinant human hyaluronidase PH20 (Vyvgart)
Referred to in this SIP as 'efgartigimod'

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Efgartigimod should be considered for patients with chronic inflammatory demyelinating polyneuropathy (CIDP) who have a confirmed diagnosis according to guidelines¹ but for whom Immunoglobulin (Ig) treatment is unsatisfactory. Unsatisfactory Ig treatment may be defined by at least one of the following criteria:

1. High burden of Ig treatment: patients who have received at least six months of treatment with Igs (intravenous immunoglobulin [IVIg] or subcutaneous immunoglobulin [SCIg] for whom ongoing Ig infusions or injections significantly impact daily life, work, or caregiving responsibilities). Within this category, includes patients who remain symptomatic or require high doses or frequency of Ig to maintain benefit and avoid peri-dose fluctuations.
2. Patients who are intolerant or refractory to Ig: patients unable to continue Ig due to adverse events, safety concerns (e.g. bloods clots and heart failure), or relevant co-existing conditions.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Efgartigimod is indicated as monotherapy for the treatment of adult patients with progressive or relapsing active chronic inflammatory demyelinating polyneuropathy (CIDP) after prior treatment with corticosteroids or immunoglobulins.²

Efgartigimod received European Medicines Agency approval on 19 June 2025 and is anticipated to receive marketing authorisation in the UK in February 2026.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

As a responsible pharmaceutical company, argenx works closely with patient organisations to improve care for patients living with CIDP and to deepen understanding of the condition. In the UK, the Company partnered with Inflammatory Neuropathies UK (INUK). In 2025, the Company commissioned an independent research agency to carry out a nationwide online survey of patients and carers. The charity helped refine the questions and promoted the survey to its members, while the agency managed recruitment, data collection, and analysis. All responses were anonymised before review. Insights from this collaboration inform the patient-based evidence in our submission, and all activities were conducted in line with the Association of the British Pharmaceutical Industry (ABPI) Code of Practice, and the charity's partnership policies.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is CIDP?:

CIDP is a rare, long-term illness in which the body's own immune system mistakenly attacks the protective covering (called myelin) of the nerves outside the brain and spinal cord.²⁻⁵ When this covering is damaged, nerve messages slow down or stop working properly. Early signs typically include tingling, numbness and heaviness in the feet or hands. Over time many patients notice weakness in the legs and arms, poor balance, pain and severe tiredness, all of which make everyday tasks much harder.

How common is CIDP?:

CIDP can begin at any age and can affect children, however the average age when patients are diagnosed is 60 years old.⁶ CIDP is diagnosed about twice as often in men than in women.⁶ A large review of studies from Europe, Japan, Australia and the United States found that only about three people in every 100,000 are living with CIDP at any time.⁷ The charity INUK believes up to 650 people are newly-diagnosed with CIDP in the UK each year.⁸

What is the everyday impact on patients living with CIDP?:

Diagnosis: CIDP does not follow a single pattern. Some patients have slow but steady worsening of symptoms, others have periods where they get better and then worse over and over again (called relapse and remission), and a smaller group have an initial flare followed by stability that can last months or years.⁹ Delays and misclassification of CIDP are common in practice: in the joint Company-INUK UK patient survey, almost half of patients reported an initial misdiagnosis and many described variable diagnostic communication.¹⁰ This may result in patients being treated wrongly or delays in receiving the right treatment.

Impact of disease: Even after treatment, patients report varied problems with daily activities:

- A Dutch study found that almost nine in ten patients still had troublesome symptoms after starting treatment, most often changes in touch, tiredness, muscle weakness and pain.¹¹

- Nerve damage can slow walking speed and affect balance, which increases the risk of trips and falls.¹²
- Pain and severe tiredness are common; one study found that almost one patient in five described their pain as “severe”.¹³
- Although CIDP rarely shortens life, the gradual build-up of nerve damage can cause lasting and progressive disability. Even when treated, fewer than half of patients in one long-term study got back to what doctors considered a good level of everyday function.¹⁴

Impact of treatment: The main treatment for CIDP is Ig therapy, given either through a drip (IVIg) or under the skin (SCIg).¹ These treatments work by helping to calm or balance the immune system, so it stops producing the antibodies that attack the nerves; they are made from healthy antibodies donated by blood donors.^{1,15}

Even after treatment, patients report varied problems with daily activities:

- About a third of patients do not respond to Ig treatment.¹⁶ Others respond well but need large or frequent doses that increase the chance of side effects.^{1,17}
- Common infusion-related side effects include headache, nausea, malaise (feeling generally unwell), fatigue, fever and chills; these are often linked to higher infusion rates and volumes.^{5,17–20}
- A joint Company-INUK UK patient survey found that almost all IVIg users (96.7%) received their infusions in hospital, with almost one third reporting travel times of more than an hour.¹⁰ These frequent hospital visits can be a significant logistical burden, especially for patients with mobility problems or those living in remote areas.¹⁰
- Ig supply challenges remain a risk due to rising demand from expanding clinical indications (e.g. neurology, haematology, autoimmune diseases) which is expected to further strain supply over the coming years.¹⁵

What is the everyday impact on those who provide care to patients living with CIDP?:

Many patients need regular support from a partner or spouse, and the demands of caregiving often extend well beyond the home.²¹ UK survey data also show that most caregiving is provided informally, creating sustained pressures on time, health and finances:

- Caregivers often dedicate many hours each week to support, frequently while balancing employment or other responsibilities, which contributes to stress and loss of personal time.²¹
- A large proportion report problems with their own physical and mental health, as well as financial strain, underscoring that positive aspects of caregiving often coexist with significant challenges.²¹

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Specialist neurologists (doctors who specialise in illnesses affecting the nervous system) follow international guidelines when they suspect CIDP. This guidance helps them to make the correct diagnosis and rule out other disorders that may look like CIDP.¹

Specialist neurologists start by examining the patient and asking about their symptoms. In the most common type of CIDP, weakness and numbness appear on both sides of the body and become steadily worse over several weeks. Patients’ reflexes are often absent or much weaker than normal.²² Even though these forms look different, the underlying damage to the nerve covering happens in the same way and they usually respond to the same type of treatments.^{1,22}

Because many other conditions can look like CIDP, diagnosis relies on tests that measure whether nerves are working normally.¹ The main test is called a nerve conduction study, where tiny electrical pulses are sent through the nerves and sensors record how quickly the signal travels. Guidelines recommend checking more than four nerves and, if the results aren't clear, repeating the test later, as changes may be more obvious with time.¹ Other tests may also be needed, since relying only on how someone feels after a treatment can lead to mistakes and unnecessary therapies.²³ In practice, the path to diagnosis can often be prolonged and confusing: in a joint Company-INUK UK patient survey, 49.2% (n=31/63) reported an initial misdiagnosis and 38.1% (24/63) said the diagnosis was not clearly explained, which may contribute to uncertainty and delayed access to appropriate treatment.¹⁰

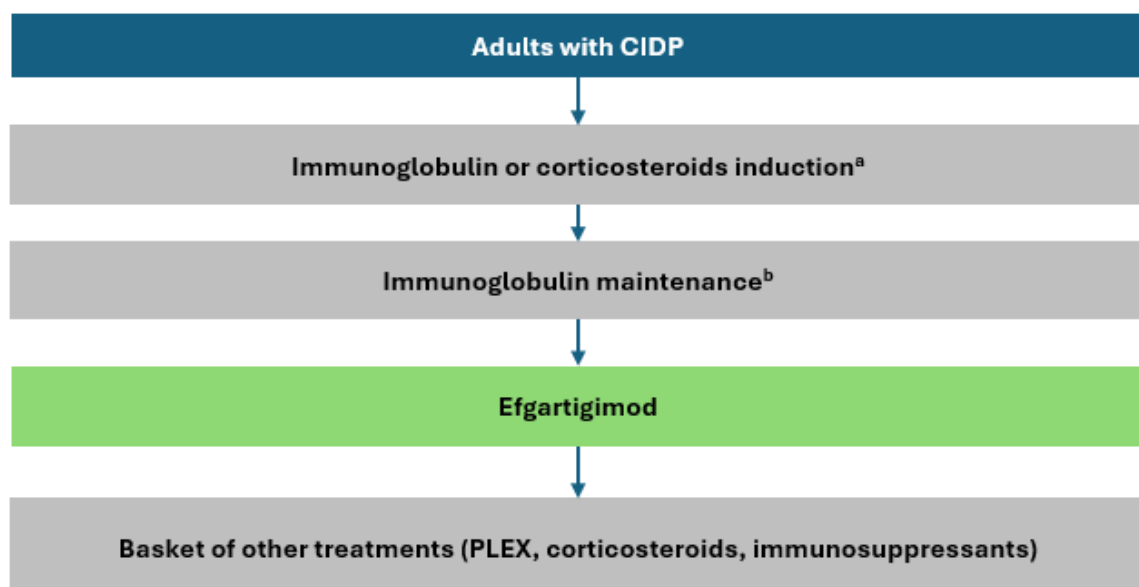
Efgartigimod, the new medicine being assessed, does not need any extra tests or procedures compared with established options such as Igs or corticosteroids. Patients begin treatment based on the usual clinical examination and nerve-conduction tests, and their progress is followed using the same strength and disability assessments that are already part of routine CIDP care. For patients, this means no extra hospital visits or tests beyond normal diagnosis and monitoring of CIDP.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Figure 1: Proposed position of efgartigimod in the treatment pathway



a. Approximately 35% of patients will be initiated on corticosteroids and 65% of patients on Ig.²⁴

b. Approximately 87.7% of patients are maintained on Ig treatment.²⁵

Adapted from Van der Bergh et al. (2021) and validated with UK clinical experts^{1,24}

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; Ig: Immunoglobulin; PLEX: Plasma exchange.

The care of CIDP usually follows two steps: an 'induction' phase that gets symptoms under control, and a 'maintenance' phase that keeps symptoms stable.

Treatment - induction:

During the induction phase most patients receive high-dose IVIg or corticosteroids (see Figure 1) to get control of symptoms.²⁴ In the usual form of CIDP, doctors may use either of these medicines but for some specific types of CIDP they choose IVIg because corticosteroids can make that type worse.¹

Treatment - maintenance:

Once strength and feeling have improved, for most patients, treatment moves to the maintenance phase; patients started on corticosteroids will move to Ig treatment, or IVIg can be continued for those who were initiated on it.^{1,26} Doctors then gradually increase the gap between doses or lower the dose to find the smallest amount that still works, which can reduce treatment burden and likelihood/severity of side effects.¹ For patients who respond well to a relatively lower dose and frequency of IVIg, they could potentially be switched to SCIg that patients can take at home. It is of note however, that the use of SCIg is low in the UK (14%) due to the higher frequency of doses (compared to IVIg), issues with patients adhering to the treatment plan, time taken for nurses to train patients at home, discomfort of self-administering high-volumes under the skin and the practicalities of requiring at-home infusion equipment.^{26,27} If patients do not get a good response from Ig, plasma exchange (PLEX), a treatment that cleans the blood, can be tried. Although it can work for CIDP, PLEX is used very infrequently (<5% of patients) because the procedure is very complex and needs specialist equipment that not all centres have access to.^{1,26} Immunosuppressants or immunomodulatory agents may be added to the treatment plan, despite not being licensed for CIDP and having limited supporting evidence.¹

The best choice of treatment depends on each patient's response, any co-existing health conditions (such as diabetes, osteoporosis, or cardiovascular disease that can affect tolerance to steroids), and practical considerations including ability to attend hospital for infusions, confidence with self-injection, and the fit with work or family commitments.¹

A Company-commissioned survey was carried out in the UK with nine doctors who are currently treating patients diagnosed with CIDP.²⁶ This study confirmed that the majority of patients receive IVIg for maintenance treatment (63%), while only a small proportion receive SCIg (14%), PLEX (<5%) or immunosuppressive therapies (<5%).²⁶ The lower use of SCIg, PLEX and immunosuppressive agents are owing to the difficulties highlighted above for SCIg, the procedural complexity and resource demands of PLEX, and to the limited, largely off-licence evidence base for most immunosuppressants in CIDP.^{1,26}

Challenges of current therapies:

Every current treatment option for CIDP has significant practical challenges. IVIg needs hospital or day-unit visits for an infusion that may last several hours, and the effect can begin to wear off after three weeks, which means regular top-ups are required.^{5,17,28,29} These repeated hospital visits can add to the overall burden of treatment, particularly for patients who face long travel times or difficulties with mobility.¹⁰ Some patients find repeated infusions difficult because of poor veins, and in such cases a permanent central venous line or port may need to be placed.²⁸ This adds extra risk during the procedure, ongoing maintenance burden, and a risk of line-related infection or thrombosis.²⁰

IVIg can also cause headaches, nausea that can last for days following infusion or, rarely, blood-clot complications that make it not safe for patients with heart failure or a history of thromboembolism.^{17,19,30} In addition, the production of Ig is complex in nature: it depends on plasma pooled from many thousands of individual donations, and increasing global demand means that supply shortages can and do occur.³¹

SCIg can be taken at home for patients who respond well to a relatively lower dose and frequency of Ig; however, uptake in the UK is low (14%) due to the issues discussed above.^{26,27} Long-term corticosteroids can cause reversible side effects like weight gain, high blood pressure, and high blood sugar. In some cases, high blood sugar may lead to diabetes, which doesn't always go away after stopping treatment. More serious, long-term effects of steroids include potentially irreversible risks such as weak bones (osteoporosis) and cataracts.^{1,32-35}

PLEX removes harmful antibodies from the blood very quickly and can improve symptoms, but is used very infrequently (<5% of patients) because the procedure is complex, benefits often fade within days, and it requires easy and convenient access to a patient's veins which can be difficult after prolonged IVIg use, close monitoring and specialist equipment that not all centres can access.^{1,26,36}

Where we could use efgartigimod:

About a third of patients do not achieve stability of their disease with Ig treatment.¹⁶ Others respond well but need large or frequent doses that increase the chance of side effects.^{1,17} It is in this maintenance phase, after Ig treatment, that efgartigimod is expected to be used. Efgartigimod should be considered for the following patients:

1. High burden of Ig treatment: patients who have received at least 6 months of treatment with Igs (IVIg or SCIg) for whom ongoing Ig infusions or injections significantly impact daily life, work, or caregiving responsibilities. This category includes patients who remain symptomatic or require high doses or frequency of Ig to maintain benefit and avoid peri-dose fluctuations.
2. Patients who are intolerant or refractory to Ig: patients unable to continue Ig due to adverse events, safety concerns (e.g. blood clots and heart failure), or relevant co-existing conditions.

Efgartigimod has been shown to improve symptoms in patients with CIDP who have responded to Ig treatment, and its rapid (20-30 second), low-volume (5ml) under-the-skin weekly self-administration may help reduce the treatment burden associated with infusions or long-term corticosteroid use.^{2,37,38}

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Several research surveys ask those patients living with CIDP about their physical ability, social life, and emotional wellbeing. Patients living with CIDP score lower than healthy adults of the same

age, particularly on questions about physical tasks.^{3,39–44} Difficulties with self-care are very common, and feelings of anxiety or low mood affected more than one in three patients in one study.⁴⁴ One study also showed that difficulty with walking is closely linked with lower quality-of-life scores.⁴³ In a large real-world survey that included the UK, 47.3% of people with CIDP were using a mobility aid, most often a walking stick (35.3%), with others using wheeled walkers (8.0%), walking frames (4.9%) or manual wheelchairs (4.9%), which highlights the day-to-day impact on mobility.⁴⁵

As part of this review the Company carried out two independent online surveys in the UK in collaboration with the Patient Group (INUK); one of adults with CIDP, and another survey of caregivers caring for someone living with CIDP.^{10,21} Most patients with CIDP reported relying on long-term IVIg, yet the ‘wearing-off’ effect before each infusion, repeated infusions, and travel to hospital caused dissatisfaction with current treatment.¹⁰ Average quality-of-life scores, as measured by the ‘EQ-5D’ (a standard tool for assessing health status), were lower than UK population norms.¹⁰

Direct patient quotes from the joint Company-INUK UK surveys further highlight the persistent effects of CIDP on independence, energy, and participation in everyday life:¹⁰

- *“CIDP robs you of your livelihood, independence, energy and at times enthusiasm for life... it imposes so many life-limiting restrictions upon you.”*
- *“Everything takes so much longer to do. Tiredness makes life difficult, as does pain. I hate being the one with the disability so I try not to talk about CIDP, but this is isolating.”*
- *“My whole world changed overnight. From being a fit active sociable 64-year-old I became an immobile dependent person living with constant pain.”*

The caregiver survey showed that caregiving was mostly provided by family members, usually by a spouse or partner, and requires about 20 hours of hands-on help every week.²¹ The survey also showed that being a caregiver frequently affects carers’ own health, drains their energy, and increases anxiety, while also putting pressure on household finances, work commitments, and personal relationships.²¹ Despite overall quality of life being similar to “normal” controls, carers commonly reported specific problems with mental health (66.7%); physical health (81.0%); and difficulty with daily activities (61.9%).²¹ Carers reported receiving no formal support for their physical or emotional needs, leaving them at risk of exhaustion and social isolation.²¹

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Efgartigimod is given as a ready-to-use injection that is administered weekly and contains two parts in one syringe: ‘efgartigimod alfa’ (the main medicine) and ‘hyaluronidase’, the helper ingredient, in a total volume of 5ml.²

Our bodies naturally make antibodies called immunoglobulin G (IgG) to help fight infections.⁴⁶ Normally, these antibodies are recycled by a recycling protein (called the neonatal Fc receptor), which keeps them working in the blood longer.⁴⁶ In CIDP, some IgG antibodies mistakenly attack

the nerves sheaths, causing damage.⁴⁶ The nerve sheaths are very important in maintaining fast and effective conduction of nerve signals. Efgartigimod is a small antibody fragment that sticks more strongly to the recycling protein than ordinary IgG antibodies.⁴⁷ By sticking to the recycling protein, this blocks it, preventing it from recycling IgG antibodies.⁴⁷ The unrecycled antibodies are then removed from the body, lowering overall IgG antibody levels and reducing the immune attack on the nerves.^{46,47}

Hyaluronidase is the helper ingredient. It temporarily loosens the tissue just under the skin so that the dose spreads quickly and can be given in 20-30 seconds.^{2,48}

Efgartigimod works differently from other treatments for CIDP. Instead of adding antibodies from donated blood (like Ig therapy) or broadly weakening the immune system (like steroids or other immune-suppressing drugs), it helps to remove the harmful antibodies that cause nerve damage.^{46,47} This makes it the first CIDP medicine to work in this way.⁴⁹ Its quick under-the-skin delivery means most patients can avoid hours-long infusions and the practical burden those create for patients with CIDP and their families and caregivers.

Further details, including the full dosing schedule, possible side effects, and guidance on driving or work after an injection are set out in the Summary of Product Characteristics (SmPC) published by the European Medicines Agency (EMA). Note that the UK marketing authorisation for efgartigimod is expected in February 2026 but the EMA SmPC can be consulted for further information at this time: https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Efgartigimod is designed to be used on its own as a maintenance treatment after a patient has already tried Igs. In the Phase II ADHERE clinical trial, patients stopped their regular CIDP treatment before starting efgartigimod and received no other CIDP-specific treatment during the study.³⁷

Although efgartigimod is taken without any other CIDP medications, many patients may still be taking other medicines for unrelated conditions (such as blood-pressure tablets or diabetes medication).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Efgartigimod is given as a once-weekly injection under the skin. Each syringe contains the right dose for one week. Treatment starts with this weekly dosing schedule and may be changed to every other week based on how a patient responds. The four first doses will usually be given under the supervision of a doctor or nurse so that injection technique and possible reactions can

be checked, but most patients with CIDP or their caregivers can then be trained to give the medicine at home.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Efgartigimod was studied in two clinical trials called ADHERE and ADHERE+. ^{37,50} An overview of the ADHERE and ADHERE+ trials is detailed in the table below. ADHERE tested the effectiveness (how well a treatment works) and safety of efgartigimod by comparing it to a placebo (dummy treatment). ³⁷ ADHERE+ is following the same patients long-term to show how long-lasting those benefits are and to collect more safety data. ⁵⁰ Both studies used efgartigimod on its own; patients stopped other treatments when joining the study. ^{37,50} This was done so the results reflect real-world use as a single weekly injection.

Study	ADHERE ³⁷ (NCT04281472)	ADHERE+ ⁵⁰ (NCT04280718)
Study design	Phase 2 study at several hospitals with two parts: everyone first receives the medicine, then some are randomly switched to a placebo without knowing which they receive.	An open-label extension of the ADHERE study to assess the long-term safety, tolerability and effectiveness of weekly efgartigimod, with all participants continuing on the same treatment.
Population	Adults ≥ 18 years with probable or definite CIDP, active disease (CDAS ≥ 2) despite treatment, were included after stopping their Ig or steroid therapy, patients who weren't currently on treatment were also included	ADHERE responders or restabilised patients continuing weekly efgartigimod
Geography	216 sites in North America, Europe, and Asia-Pacific	147 sites in North America, Europe, and Asia-Pacific
Intervention	Efgartigimod 1,000 mg weekly	Efgartigimod 1,000 mg weekly, with optional fortnightly dosing sub-study
Comparator	Placebo (Stage B only)	None (single arm)
Number of patients	Stage A: 322; Stage B: 221 (efgartigimod 111, placebo 110)	228 enrolled at interim analysis
Status of completion	Completed	Ongoing, interim data cut-off February 2024
Main reported outcomes	- Symptoms and function: evidence of clinical improvement in aINCAT disability score, I-RODS daily-activity scale, grip-strength test, timed-up-and-go walking test - Relapse control: time to first worsening on the INCAT scale (primary endpoint of Stage B) - Quality of life: EQ-5D-5L self-rating scale - Blood tests: total IgG levels over time	- Long-term durability: repeat measurements of INCAT, I-RODS and dominant-hand grip strength every three months - Safety over time: ongoing monitoring of ordinary and serious side effects, infections and injection-site reactions - Optional dosing schedule: exploratory sub-study assessing whether some patients can move to less-frequent dosing once stable

	Safety: treatment-emergent side effects, serious events, withdrawals	
Key inclusion and exclusion criteria	Inclusion - Age ≥ 18 years with probable or definite CIDP - Active disease after stopping immunoglobulin or steroids, or treatment-naïve - aINCAT ≥ 2 and CDAS ≥ 2 Exclusion - Other immune, hereditary or toxic neuropathies - Uncontrolled medical conditions judged unsafe for trial participation	Inclusion - Completed ADHERE and showed clinical benefit or were restabilised - Willing and able to follow weekly injection schedule Exclusion - Serious adverse event during ADHERE that led to permanent discontinuation
Further information	Further information can be found on clinicaltrials.gov using the reference NCT04281472	Further information can be found on clinicaltrials.gov using the reference NCT04280718

Abbreviations: aINCAT: adjusted Inflammatory Neuropathy Cause and Treatment score; CDAS: CIDP Disease Activity Status scale; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; I-RODS: Inflammatory Rasch-built Overall Disability Scale; IgG: immunoglobulin G; SC: subcutaneous

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Efgartigimod is already approved for CIDP in the United States, European Union, Japan and China. Reviews are under way in the UK, Canada, Australia, Israel and Switzerland.

The ADHERE study was done in patients with CIDP who had active disease with noticeable symptoms after stopping their normal treatment of either corticosteroids or Ig.³⁷

The ADHERE study had two parts which tested how effective efgartigimod is in treating the symptoms of CIDP:³⁷

- Open-label stage (Stage A): After coming off their usual treatment every patient received a weekly injection of efgartigimod under-the-skin for up to 12 weeks.³⁷ ('Open label' means that everyone knew they were getting the real medicine). Because all patients in this stage knew they were getting efgartigimod, this stage tested whether efgartigimod could help at all. Proof of improvement was measured by a scale that looks at walking and everyday hand-arm use. In this stage of the trial, 214 out of 322 patients showed evidence of clinical improvement compared to when they weren't receiving any treatment, which is 66% of everyone treated with efgartigimod in Stage A.³⁷ The medicine appeared to work quickly, with 40% of patients showing evidence of clinical improvement by week four.³⁷
- Double-blind stage (Stage B): Only the patients who had already improved on efgartigimod moved on to Stage B of the trial. These patients were split at random: 111 patients kept taking efgartigimod and 110 patients switched to a placebo (a dummy injection with no medicine) for up to 48 weeks.³⁷ Neither the patients, their doctors, nor the study team knew who had which injection, so the results would be fair and

unbiased.³⁷ In this stage of the trial, a relapse (symptoms getting worse again) occurred in 31 of 111 patients on efgartigimod (28%) compared with 59 of 110 on placebo (54%), showing a 61% relative reduction in relapse risk on efgartigimod.³⁷ This corresponds to an absolute risk reduction of 25.7% (95% CI 11.4% to 38.0%).³⁷

The ADHERE study also looked beyond response and relapse to see whether efgartigimod helped patients keep their strength, dexterity, mobility and overall wellbeing in their daily lives.³⁷ The figures below all come from the 48-week double-blind stage (Stage B), when patients either stayed on efgartigimod or switched to placebo:

- Everyday tasks: There was a 46% lower risk of losing function; 40 of 111 patients on efgartigimod (36%) versus 57 of 110 on placebo (52%), an absolute risk reduction of 16%. This analysis was based on time to a ≥ 4 -point drop on the I-RODS; HR 0.54 (95% CI 0.35 to 0.81).³⁷
- Overall disability: On average the level of overall disability held steady in the efgartigimod group until week 48, while the placebo group's overall disability increased.³⁷
- Hand strength: Grip strength in both hands improved with efgartigimod but fell on placebo.³⁷
- Walking and balance: On a test which measures how quickly someone can stand, walk three metres and sit again, time increased by only 0.8 seconds on efgartigimod versus 1.9 seconds on placebo.³⁷
- Quality of life: Patients rated their health from 0 to 100 on a scale. After Stage A of the trial this score had improved for all patients who were taking efgartigimod. In Stage B of the trial, it stayed almost unchanged for those patients on efgartigimod but fell for those on placebo, suggesting that patients felt worse once the medicine was withdrawn.³⁷

These results show that a weekly injection of efgartigimod can preserve the strength, steadiness and everyday independence that patients regain during the first weeks of treatment with the medicine, while also reducing the risk of a relapse by more than half over 48 weeks (28% on efgartigimod vs 54% on placebo; absolute risk reduction 25.7%).³⁷ Patients who switched to placebo lost much of that early progress, felt worse overall, and relapsed sooner.³⁷

These results suggest that efgartigimod gives a level of improvement and relapse protection that is similar to other therapies. For example, a clinical trial of IVIg in the treatment of CIDP, called the ICE study, showed that 54% of patients improved on measure of walking and everyday hand-arm use score compared with 21% on placebo. Another clinical trial of subcutaneous Ig in CIDP, called the PATH study, reported relapse or withdrawal of drug in 33-39% of treated patients, versus 63% on placebo.^{51,52}

No direct comparison has yet compared efgartigimod directly with IVIg or SCIg, so the exact size of any difference remains to be confirmed.

What does the ADHERE+ extension tell us about longer-term use of efgartigimod?:

Nearly every eligible patient from ADHERE (99%) chose to continue into ADHERE+, an open-label study designed to see how patients do on weekly efgartigimod for up to 2 years.⁵⁰ Results so far show:

- Benefits from efgartigimod lasted and improvements continued over time: By week 36 of ADHERE+, average grip strength in the main hand had increased, measures of walking and everyday hand-arm use had increased, and overall disability had decreased.⁵⁰
- Infections remained low: Low infection rates in ADHERE+ suggest the immune system keeps working well and the infections were generally mild, suggesting that the selective reduction of IgG antibodies has not led to increased risk so far.⁵⁰

These results confirm: The strength, dexterity, and everyday function gained during the initial 12-week course, shown in ADHERE can be maintained or further improved over a longer time period, as demonstrated by ADHERE+. ⁵⁰

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality-of-life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

What did the ADHERE trial show?:

Stage A (all participants received efgartigimod for up to 12 weeks):

- Average quality-of-life scores improved after only a few weekly injections, which shows that participants rated their overall health as better after taking efgartigimod.³⁷ At the beginning of Stage A in the ADHERE study, patients rated their overall health at an average of 50.8 out of 100 on the EQ-VAS scale. After treatment, this improved to 61.7, an improvement nearly 11 points (SD 22.3), which suggests patients felt noticeably better.³⁷

Stage B (48-week double-blind stage):

- In Stage B, EQ-VAS quality of life assessment, the improvement seen in Stage A was mainly maintained for patients on efgartigimod (+0.5; SD 17.4) but went back down for patients who were put on placebo (−10.2; SD 23.5).³⁷ These quality-of-life results were analysed descriptively and were not tested for statistical significance.³⁷
- Patients who stayed on efgartigimod were more likely to feel an improvement in their overall disability and were less likely to get worse than those who received placebo, based on I-RODS: 45% (50/111) improved vs 36% (40/110) on placebo; 36% (40/111) worsened vs 52% (57/110 on placebo).³⁷

What did the ADHERE+ open-label extension show:

After the initial ADHERE trial concluded, continued weekly treatment with efgartigimod (in the ADHERE+ open-label extension trial) led to further improvements in quality of life: average grip strength in the main hand had increased, measures of walking and everyday hand-arm use had increased, and overall disability had decreased.⁵⁰

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Efgartigimod was well tolerated in clinical trials, and its safety information has been studied in the 60-week ADHERE study, as well as in the ongoing open-label extension ADHERE+. ^{37,50} In both studies, most side effects were mild to moderate and very few patients stopped treatment because of them. ^{37,50}

In ADHERE Stage A (≤ 12 weeks, open label, $n=322$), 63% of ($n=204/322$) patients reported at least one treatment-emergent adverse event (TEAEs) and 7% (21) reported at least one serious TEAE.³⁷ The most commonly reported TEAEs during stage A of the ADHERE trial were injection site irritation (10% [33]), CIDP worsening (5% [17]), and headache (5% [16]).³⁷

In ADHERE Stage B (48 weeks, double-blind, $n=221$), 64% of ($n=74/111$) patients in the efgartigimod group and 56% of ($n=62/110$) patients in the placebo group reported a TEAE.³⁷ There was no clinically significant difference between the efgartigimod and placebo groups in the occurrence of TEAEs and serious adverse events (SAEs).³⁷ The most common TEAEs for the efgartigimod group were COVID-19 (17% [19]), injection site bruising (5% [6]), and injection site irritation (5% [6]) and for the placebo group were COVID-19 (13% [14]) and upper respiratory tract infections (10% [11]).³⁷ Note that the ADHERE trial took place during the COVID-19 pandemic.³⁷ Efgartigimod was well tolerated in the ADHERE+ open-label extension trial, and the nature, frequency, and severity of adverse events were consistent with the preceding controlled study phases.⁵⁰

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- **Early and sustained clinical benefit:** In ADHERE, two-thirds (66%) of patients on efgartigimod reported meaningful improvements in walking and everyday hand-arm use within the first few weeks.³⁷ Among those who improved, staying on treatment for 48 weeks lowered relapse to 28% compared with 54% on placebo. Strength and daily function followed the same encouraging pattern.³⁷
- **Consistent safety with few withdrawals:** Over 48 weeks, serious adverse events were similar to placebo.³⁷ Efgartigimod was well tolerated in the ADHERE+ open-label extension trial, and the nature, frequency, and severity of adverse events were consistent with the preceding controlled study phases.⁵⁰
- **Practical advantages for people already treated with Ig:** Weekly under-the-skin dosing of 5ml efgartigimod avoids intravenous chair or bed time and repeated venous access, and it removes the need for ports or lines that carry infection or clot risks.²⁰ IVIg maintenance is commonly given every 3–4 weeks (often every 3 weeks in trials), typically at hospital or day-unit infusions lasting several hours, so many patients make regular trips to hospital for ongoing treatment.^{5,10,17,28,29} SCIg can be taken at home and avoids hospital trips; it is generally offered to patients whose CIDP is controlled on relatively low doses and frequency of IVIg, and typically requires injections once or several times a week.^{18,26,27,29,51} Some people cannot continue Ig because of side effects or safety concerns such as thromboembolism or heart failure.^{17,19,30} For these groups, efgartigimod offers a non-blood-derived alternative that may fit better with daily life.
- **Benefits for families and caregivers:** Fewer lengthy hospital visits and steadier symptom control may reduce time away from work and caring for others, with potential savings on travel and a lower day-to-day support burden.²¹
- **Service and community impact:** Transitioning eligible patients from infusion chairs or beds to brief weekly or fortnightly injections (lasting just 20–30 seconds), initially administered in hospital and later self-injected at home, will ease pressure on day units, reduce travel and parking demands, and lessen reliance on plasma-derived therapies—products that can face supply challenges.³¹

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
 - Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
 - What is the impact of any disadvantages highlighted compared with current treatments
-
- Weekly injections and local injection-site reactions: Efgartigimod is given every week into the abdomen under the skin, as per the normal dosing schedule.² Although the injection is quick, some patients may dislike the need for a weekly injection or need help from a carer to give it. In ADHERE, injection site reactions were one of the most common side effects, however very few found the discomfort bad enough to stop treatment.³⁷
 - Not everyone responds well to efgartigimod: about one patient in three did not achieve enough improvement during the first part of the study and would therefore need to go back on other treatments.³⁷

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition:

The Company has developed an economic model for efgartigimod which it is presenting to NICE as part of its assessment. This looks at the benefits and costs of efgartigimod against the other treatments NICE has determined to be standard of care extends over a life-time period. This means that all the quality of life benefits a patient experiences every year of their life (known as quality-of-life-year benefit, or 'QALY') a patient might expect from being treated with efgartigimod are added up over their lifetime, as are all the costs from treating the patient for that amount of time. This is the commonly accepted method for calculating cost effectiveness for a long-term chronic condition such as CIDP.

The group of patients considered in the cost-effectiveness model includes those who have a confirmed diagnosis of CIDP, have previously been treated with Ig, and are still struggling - either because their symptoms remain uncontrolled or because the treatment itself is burdensome. It also includes a small number of patients who cannot take Ig due to side effects or interactions with other medicines. This reflects how efgartigimod is expected to be licensed and aligns with

the view of both the company and doctors: that there is a real need for new treatment options in patients whose condition is not well managed with current therapies.

CIDP health states:

In the economic model, patients are grouped into different 'health states' that reflect how severe their CIDP symptoms are. These states are based on a scale called aINCAT, which measures how much CIDP affects a person's ability to move and carry out daily activities. This same scale was used in the ADHERE study to see how well efgartigimod worked. The model helps show how CIDP can change over time - sometimes getting worse, sometimes improving - and how this affects a person's quality of life. The way patients move between these health states is based on data from the ADHERE study and has been reviewed by CIDP experts in the UK.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Efgartigimod represents a genuine step forward for patients with CIDP: it is the first targeted treatment that works by removing the harmful antibodies that cause the disease, rather than adding other people's antibodies (how Ig works) or broadly damping down the immune system (how steroids/immunosuppressives work). Additionally, efgartigimod is not dependent on plasma donations, avoiding the supply challenges often associated with Ig.³¹ Because the full dose is delivered in a quick (20-30 second) weekly injection of 5ml efgartigimod under the skin, patients and caregivers can avoid the long hospital-based infusions that come with IVIg.² This should free up hospital time, reduce associated costs, and reduce the anxiety many patients feel as they wait for their next infusion.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

More men than women are expected to receive treatment because CIDP is more common in men.⁶ Religion or belief may also be relevant: some people choose to avoid blood products.⁵³ IVIg is made from donated human plasma, so individual patients may decline it.³¹ Efgartigimod may alleviate these concerns because it is a recombinant (non-plasma-derived) medicine. Care teams should offer sensitive discussion and document shared decisions to ensure equitable access to appropriate treatment.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be

useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Inflammatory Neuropathies UK resources:

- CIDP Information hub: <https://www.inflammatoryneuropathies.uk/cidp>

External resources:

- Rare diseases website: <https://rarediseases.org/rare-diseases/chronic-inflammatory-demyelinating-polyneuropathy/>
- Cleveland clinic website: <https://my.clevelandclinic.org/health/diseases/cidp-chronic-inflammatory-demyelinating-polyneuropathy>

Further information on NICE and the role of patients:

- Public Involvement at NICE: [Public involvement](#) | [NICE and the public](#) | [NICE Communities](#) | [About NICE](#)
- NICE's guides and templates for patient involvement in HTAs: [Guides to developing our guidance](#) | [Help us develop guidance](#) | [Support for voluntary and community sector \(VCS\) organisations](#) | [Public involvement](#) | [NICE and the public](#) | [NICE Communities](#) | [About NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

ARR (Absolute risk reduction): The simple difference in risk between two groups. It describes how many fewer people out of one hundred had the outcome with the treatment compared with control.

aINCAT (Adjusted Inflammatory Neuropathy Cause and Treatment score): A 0-to-10 scale clinicians use to rate how much arm-hand and walking function is lost in CIDP. A one-point change is considered a meaningful shift in day-to-day ability.

CI (Confidence interval): A CI shows the range of values that is likely to contain the true result. A 95% CI means we are reasonably confident the real number lies somewhere between the lower and upper limits; wider intervals mean more uncertainty, narrower intervals mean more precise estimates.

CarerQoL-7D (Caregiver Quality of Life, 7 domains): A questionnaire for carers that scores overall quality of life and asks about seven areas: fulfilment, relationship strain, mental health, physical health, difficulty with daily activities, financial pressure, and feeling supported. Higher scores mean better quality of life.

Double-blind: A study design in which neither the participants nor the research team know who is receiving the active treatment and who is receiving a comparator until the study ends.

EQ-5D-5L (EuroQol five-dimension, five-level questionnaire): A short questionnaire about health five areas: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each area has five response levels from no problems to extreme problems. Answers are combined into a single index score where higher scores mean better health.

EQ-VAS (EuroQol Visual Analogue Scale): A simple 0–100 scale to rate overall health today. 0 means the worst health you can imagine and 100 means the best.

HR (Hazard ratio): A way to compare how often something happens over time in two groups. HR 1.0 means no difference. HR below one means the treatment group had a lower risk at any given time. For example, HR 0.54 means about a 46% lower risk.

I-RODS (Inflammatory Rasch-built Overall Disability Scale): A patient questionnaire used in CIDP that asks about everyday activities and social participation. Scores reflect how much disability a patient has; higher scores mean better function.

Immunoglobulin (Ig): A medicine made from donated human plasma that contains antibodies. It helps strengthen the immune system and is used to treat certain infections or immune-related conditions such as CIDP.

Immunoglobulin G (antibodies): One class of antibodies in the blood that helps fight infection; in CIDP some IgG antibodies mistakenly attack the nerves.

Intravenous immunoglobulin (IVIg): Pooled antibodies taken from healthy blood donors and given through a drip into a vein to calm the immune system.

Induction: The first phase of treatment, given to bring an illness under control.

Maintenance: Ongoing treatment given after induction to keep symptoms stable.

Myelin: The fatty covering that wraps around nerves and helps electrical signals travel quickly from one part of the body to another.

Neonatal Fc receptor: A transport protein inside cells that normally protects IgG antibodies from being broken down, allowing them to stay in the bloodstream for weeks.

Open-label: A type of study in which everyone knows which treatment they are receiving.

Plasma exchange (PLEX): A hospital procedure that removes blood, separates out the liquid part (plasma) containing harmful antibodies, and returns the cleaned blood cells with a replacement fluid.

Placebo: An inactive substance or look-alike treatment used in trials to show whether the real medicine works better than no active treatment.

Subcutaneous immunoglobulin (SCIg): Pooled antibodies delivered by a small injection under the skin instead of by drip into a vein.

QALY (Quality-Adjusted Life Year): A way health economists combine length of life and quality of life into a single number; one QALY equals one year of life lived in perfect health.

4c) References

1. Van Den Bergh PYK, Van Doorn PA, Hadden RDM, Avau B, Vankrunkelsven P, Allen JA, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision. *Eur J Neurol.* 2021;28:3556–83.
2. Summary of product characteristics - Vyvgart [Internet]. European Medicines Agency. [cited 2025 Aug 27]. Available from: https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf
3. Merkies ISJ, Kieseier BC. Fatigue, Pain, Anxiety and Depression in Guillain-Barré Syndrome and Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *Eur Neurol.* 2016;75:199–206.

4. Lunn MP, Manji H, Choudhary PP, Hughes RA, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. *J Neurol Neurosurg Psychiatry*. 1999;66:677–80.
5. Bunschoten C, Jacobs BC, Van Den Bergh PYK, Cornblath DR, Van Doorn PA. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. *Lancet Neurol*. 2019;18:784–94.
6. Gogia B, Rocha Cabrero F, Khan Suheb M, Lui F, Rai P. Chronic Inflammatory Demyelinating Polyradiculoneuropathy. [Updated 2024 Mar 4]. In *Treasure Island (FL): StatPearls Publishing*; 2024 [cited 2024 Aug 22]. (StatPearls [Internet].). Available from: <https://www.ncbi.nlm.nih.gov/books/NBK563249/>
7. Broers MC, Bunschoten C, Nieboer D, Lingsma HF, Jacobs BC. Incidence and Prevalence of Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Systematic Review and Meta-Analysis. *Neuroepidemiology*. 2019;52:161–72.
8. CIDP & the associated chronic variant [Internet]. Gain Charity; Available from: <https://gaincharity.org.uk/wp-content/uploads/2017/10/CIDP-the-chronic-variants-rebrand.interim.pdf#:~:text=Chronic>
9. Van den Bergh PYK, Hadden RDM, Bouche P, Cornblath DR, Hahn A, Illa I, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision. *Eur J Neurol*. 2010;17:356–63.
10. argenx. Patient survey research report - Patient experiences living with chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. 2025.
11. Bunschoten C, Blomkwist-Markens PH, Horemans A, van Doorn PA, Jacobs BC. Clinical factors, diagnostic delay, and residual deficits in chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst JPNS*. 2019;24:253–9.
12. Findling O, Logt R van der, Nedeltchev K, Achtnichts L, Allum JHJ. A comparison of balance control during stance and gait in patients with inflammatory and non-inflammatory polyneuropathy. *PLoS ONE*. 2018;13:e0191957.
13. Gündüz A, Basci N, Tütüncü M, Uzun N. Clinical and Electrophysiologic Findings of Fatigue in Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Narrative Review. *Neurol Sci Neurophysiol*. 2024;41:121–8.
14. Al-Zuhairy A, Jakobsen J. Outcome in chronic inflammatory demyelinating polyneuropathy: A systematic review and meta-analysis. *Muscle Nerve*. 2023;68:388–96.
15. So-Osman C, Delaney M, Fung M, Lu W, Murphy M, Sasongko PL, et al. A global analysis of the use of immunoglobulin, shortages in supply, and mitigating measures: A survey of hospital providers (a BEST Collaborative study). *Transfusion (Paris)*. 2024;64:775–83.
16. Rajabally Y. Overview of the pathogenesis and treatment of chronic inflammatory demyelinating polyneuropathy with intravenous immunoglobulins. *Biol Targets Ther*. 2010;45.
17. Brannagan TH, Khosro F, Kleyman I, Leitch M, Traub R, Ulane C. Existing and Emerging Approaches to Treating Chronic Inflammatory Demyelinating Polyneuropathy. 2019;15:33–9.
18. Allen JA, Gelinas DF, Freimer M, Runken MC, Wolfe GI. Immunoglobulin administration for the treatment of CIDP: IVIG or SCIG? *J Neurol Sci*. 2020;408:116497.
19. Watkins JM, Dimachkie MM, Riley P, Murphy E. Subcutaneous Immunoglobulin Therapy for Chronic Inflammatory Demyelinating Polyneuropathy: A Nursing Perspective. *J Neurosci Nurs J Am Assoc Neurosci Nurses*. 2019;51:198–203.
20. Guo Y, Tian X, Wang X, Xiao Z. Adverse Effects of Immunoglobulin Therapy. *Front Immunol*. 2018;9:1299.
21. argenx. Caregiver research survey report - Experiences of individuals supporting adults living with chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. Data on file. 2025.

22. Lewis RA, Van Doorn PA, Sommer C. Tips in navigating the diagnostic complexities of chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Sci.* 2022;443:120478.
23. Eftimov F, Lucke IM, Querol LA, Rajabally YA, Verhamme C. Diagnostic challenges in chronic inflammatory demyelinating polyradiculoneuropathy. *Brain.* 2020;143:3214–24.
24. Qualitative clinical validation and structured expert elicitation. Data on file. argenx;
25. Chiò A, Cocito D, Bottacchi E, Buffa C, Leone M, Plano F, et al. Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. *J Neurol Neurosurg Psychiatry.* 2007;78:1349–53.
26. argenx. Market research survey report - Treatment patterns for chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. Data on file. 2025.
27. CIDP Healthcare Resource Use Survey - Redacted Summary. Data on file. argenx; 2025.
28. Immunoglobulin therapy and management of patient data [Internet]. Cambridge University Hospitals Foundation Trust. Available from: <https://www.cuh.nhs.uk/patient-information/immunoglobulin-therapy-and-management-of-patient-data/>
29. Beydoun SR, Sharma KR, Bassam BA, Pulley MT, Shiye JZ, Kafal A. Individualizing Therapy in CIDP: A Mini-Review Comparing the Pharmacokinetics of Ig With SCIg and IVIg. *Front Neurol.* 2021;12:638816.
30. Fargeot G, Gitiaux C, Magy L, Pereon Y, Delmont E, Viala K, et al. French recommendations for the management of adult & pediatric chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Rev Neurol (Paris).* 2022;178:953–68.
31. Strengers PFW. Challenges for Plasma-Derived Medicinal Products. *Transfus Med Hemotherapy Off Organ Dtsch Ges Transfusionsmedizin Immunhamatologie.* 2023;50:116–22.
32. Oaklander AL, Lunn MP, Hughes RA, van Schaik IN, Frost C, Chalk CH. Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews. *Cochrane Database Syst Rev.* 2017;1:CD010369.
33. van Lieverloo GGA, Peric S, Doneddu PE, Gallia F, Nikolic A, Wieske L, et al. Corticosteroids in chronic inflammatory demyelinating polyneuropathy : A retrospective, multicentre study, comparing efficacy and safety of daily prednisolone, pulsed dexamethasone, and pulsed intravenous methylprednisolone. *J Neurol.* 2018;265:2052–9.
34. Hodgens A, Sharman T. Corticosteroids. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Nov 7]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK554612/>
35. Yasir M, Goyal A, Sonthalia S. Corticosteroid Adverse Effects. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Nov 7]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK531462/>
36. Hahn AF, Bolton CF, Pillay N, Chalk C, Benstead T, Bril V, et al. Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy. A double-blind, sham-controlled, cross-over study. *Brain J Neurol.* 1996;119 (Pt 4):1055–66.
37. Allen JA, Lin J, Basta I, Dysgaard T, Eggers C, Guptill JT, et al. Safety, tolerability, and efficacy of subcutaneous efgartigimod in patients with chronic inflammatory demyelinating polyradiculoneuropathy (ADHERE): a multicentre, randomised-withdrawal, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol.* 2024;23:1013–24.
38. Allen JA, Van Doorn PA, Basta I, Dysgaard T, Eggers C, Guptill J. Efficacy and Safety of Subcutaneous (SC) Efgartigimod PH20 in CIDP: ADHERE/ADHERE+ Trials. *Peripheral Nerve Society (PNS);* 2024 June 22; Montréal, Quebec, Canada.
39. Bozovic I, Kacar A, Peric S, Nikolic A, Bjelica B, Cobeljic M, et al. Quality of life predictors in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol.* 2017;264:2481–6.
40. Querol L, Crabtree M, Herepath M, Priedane E, Viejo Viejo I, Agush S, et al. Systematic literature review of burden of illness in chronic inflammatory demyelinating polyneuropathy (CIDP). *J Neurol.* 2021;268:3706–16.

41. Fernandez M, Copley-Merriman C, Arvin-Berod C, Phillips G, Gelinas D, Weiss R, et al. CO85 Evidence Gap Analysis of the Burden of Illness and Treatment of Chronic Inflammatory Demyelinating Polyneuropathy. *Value Health*. 2022;25:S34.
42. Santos PL dos, Almeida-Ribeiro GAN de, Silva DMD, Marques Junior W, Barreira AA. Chronic inflammatory demyelinating polyneuropathy: quality of life, sociodemographic profile and physical complaints. *Arq Neuropsiquiatr*. 2014;72:179–83.
43. Ryltoft AK, Al-Zuhairy A, Sindrup SH, Andersen H, Markvardsen LK. Quality of life in chronic inflammatory demyelinating polyneuropathy patients treated with subcutaneous immunoglobulin. *Acta Neurol Scand*. 2020;142:637–40.
44. Mahdi-Rogers M, McCrone P, Hughes RAC. Economic costs and quality of life in chronic inflammatory neuropathies in southeast England. *Eur J Neurol*. 2014;21:34–9.
45. Querol L, Rinaldi S, Borsi A, Boggia GM, de Courcy J, Taylor Y, et al. Real-World Multinational Survey of Chronic Inflammatory Demyelinating Polyneuropathy: Disease Characteristics and Therapeutic Landscape. *J Peripher Nerv Syst JPNS*. 2025;30:e70047.
46. Yang Y, Shen Z, Shi F, Wang F, Wen N. Efgartigimod as a novel FcRn inhibitor for autoimmune disease. *Neurol Sci*. 2024;45:4229–41.
47. Heo YA. Efgartigimod: First Approval. *Drugs*. 2022;82:341–8.
48. NIHR. Health Technology Briefing December 2023: Efgartigimod PH20 SC for treating chronic inflammatory demyelinating polyradiculoneuropathy [Internet]. 2023 [cited 2024 Aug 23]. Available from: <https://www.io.nihr.ac.uk/wp-content/uploads/2023/12/29647-Efgartigimod-PH20-SC-for-Chronic-Inflammatory-Demyelinating-Polyradiculoneuropathy-V1.0-DEC2023-NON-CONF.pdf>
49. Caballero-Ávila M, Martin-Aguilar L, Collet-Vidiella R, Querol L, Pascual-Goñi E. A pathophysiological and mechanistic review of chronic inflammatory demyelinating polyradiculoneuropathy therapy. *Front Immunol*. 2025;16:1575464.
50. Jeffrey A A, Jie L, Stettner M, Guptill J, Istas G, Roeck AD, et al. ADHERE+ Trial Interim Analysis: Long-Term Safety and Efficacy of Efgartigimod in Chronic Inflammatory Demyelinating Polyradiculoneuropathy [Internet]. Poster presented at: Peripheral Nerve Society (PNS) annual meeting; 2025 May 17 [cited 2025 Aug 6]; Edinburgh, United Kingdom. Available from: https://argenxmedical.com/content/dam/medical-affairs/congress-posters/nerology/mmn/pns/posters2025/ADHERE+%20Trial%20Interim%20Analysis_%20Long-Term%20Safety%20and%20Efficacy%20of%20Efgartigimod%20in%20Chronic%20Inflammatory%20Demyelinating%20Polyneuropathy.pdf
51. van Schaik IN, Bril V, van Geloven N, Hartung HP, Lewis RA, Sobue G, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2018;17:35–46.
52. Hughes RAC, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol*. 2008;7:136–44.
53. Faith issues and treatment for immunodeficiency [Internet]. Immunodeficiency UK. Available from: <https://www.immunodeficiencyuk.org/immunodeficiency/treatment/faithissuesandtreatmentforpids/?utm>

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Clarification questions

November 2025

File name	Version	Contains confidential information	Date
ID6409 efgartigimod CIDP EAG clarification letter [redacted]	1.0	No	25 November 2025

argenx thanks the EAG for their questions and appreciates the opportunity to provide clarification where needed. In addition, following discussions with the EAG/NICE, argenx has also submitted an updated Appendix 2 accordingly.

Section A: Clarification on effectiveness data

ADHERE

A1. Priority question: There is limited information in the CS about the proportion of missing data. Please provide information on the proportion of missing data and how any missing data was handled.

For the primary endpoint in Stage A, all randomised participants were included in the efficacy analysis. Participants who discontinued treatment before completing 12 weeks or who did not achieve evidence of clinical improvement (ECI) within the prespecified assessment window were classified as non-responders. These participants were therefore not treated as missing data for the primary endpoint, and no imputation was applied.

For the primary endpoint in Stage B (time to first relapse based on adjusted Inflammatory Neuropathy Cause and Treatment score [aINCAT] deterioration), all randomised participants contributed to the time-to-event analysis according to prespecified methodology. Participants who experienced a relapse were assigned an event time at the visit at which the aINCAT deterioration met the relapse definition. Participants who discontinued the study or were lost to follow-up before Week 48 without a documented relapse were censored at the time of their last available aINCAT assessment. These participants were therefore not considered to have missing data for the primary endpoint; their data were handled via right censoring within the time-to-event framework, with no additional imputation.

The company confirms that, in line with the statistical analysis plan, no imputation was performed for missing values and analyses were based on observed cases. For continuous variables, descriptive statistics were generated using only non-missing observations.¹

A2. Priority question: The EAG notes that clinically meaningful deterioration in the run-in period, and evidence of clinical improvement in Stage A, was assessed based on change in either aINCAT, I-RODS or mean grip strength (i.e. whichever was used to assess deterioration was also used to assess improvement). In Stage B clinical deterioration/relapse was assessed solely on a change in aINCAT.

- a) Please clarify if aINCAT was assessed during the run-in phase for all patients, even if they showed deterioration during the run-in phase on one of the other measures?**
- b) Please confirm if all patients had an aINCAT assessment prior to Stage A and if all patients had an aINCAT assessment after Stage A? Please report the results for clinical improvement (after Stage A) solely based on aINCAT.**
- c) Please comment on the potential effects on the results of ADHERE if any patients experienced a deterioration in I-RODS or mean grip strength, but did not experience a change in aINCAT, and therefore were not classified as having relapsed.**

(a) The company confirms that aINCAT was assessed during the run-in phase for all participants, including those who demonstrated deterioration on Inflammatory Rasch-Built Overall Disability Scale (I-RODS) or mean grip strength (MGS).² All participants in the run-in were evaluated for clinical change using a composite of aINCAT, I-RODS and MGS, meaning that aINCAT was measured for every individual.² Eligibility also required an INCAT score of at least two at the first run-in visit or at the Stage A baseline, confirming that an aINCAT assessment was performed for all patients that entered the run-in.² The definition of the Stage A endpoint provided in the supplementary appendix of the key publication for ADHERE further differentiates participants who deteriorated in aINCAT during run-in from those who had no change in aINCAT but deterioration on I-RODS and/or MGS, confirming that aINCAT was consistently assessed during the run-in phase for all patients.²

(b) The company confirms that all participants who entered Stage A had an aINCAT assessment prior to treatment initiation, as Stage A baseline was defined for aINCAT and other endpoints as the last available value before the first administration in Stage A, with aINCAT then measured weekly during Stage A.² Table 1 below summarises Stage A clinical improvement based solely on aINCAT, presented according to the measure on which clinically meaningful deterioration was confirmed during the run-in period.

Table 1: Stage A clinical improvement based on aINCAT, by measure of clinically meaningful deterioration during run-in (Stage A safety analysis set)

	Way of ECMD during run-in						
Way of confirmed ECI during Stage A	ECMD on aINCAT only n (%)	ECMD on I-RODS only n (%)	ECMD on MGS only n (%)	ECMD on I-RODS and MGS n (%)	No ECMD on any parameter n (%)	Did not enter run-in n (%)	Total n (%)
ECI on adjusted INCAT	██████	██████	██████	██████	-	██████	██████

Source: argenx data on file - tables, figures and listings table 14.2.4.1.³

Abbreviations: aINCAT Inflammatory Neuropathy Cause And Treatment score; Adjusted ECI: Evidence of clinical improvement; ECMD: Evidence of clinically meaningful deterioration; INCAT: Inflammatory Neuropathy Cause And Treatment score; I-RODS: Inflammatory Rasch-Built Overall Disability Scale; MGS: Mean grip strength.

(c) The company understands that the EAG is querying whether defining relapse solely on aINCAT deterioration in Stage B might have underestimated relapse, given that earlier stages used a composite of aINCAT, I-RODS and MGS. In summary, the company notes that any such under-ascertainment would apply equally to both treatment arms because the same blinded aINCAT-based definition and visit schedule were used throughout Stage B, and this non-differential misclassification would be expected to attenuate rather than exaggerate the observed treatment difference.

In ADHERE, evidence of clinically meaningful deterioration (ECMD) in the run-in period was defined using a composite of aINCAT, I-RODS and MGS.² A composite of the same measures was then used to define ECI in Stage A.² This design maximised sensitivity to clinical change around treatment withdrawal and initial response. By contrast, in Stage B, the primary endpoint was prospectively defined as time to first aINCAT deterioration of at least one point from Stage B baseline, whereas I-RODS and MGS were assessed as secondary endpoints.²

Participants who experienced a clinically meaningful deterioration in I-RODS or MGS during Stage B, but without a concomitant increase of at least one point in aINCAT, would not have been counted as relapses in the primary Stage B endpoint.

Conceptually, this would lead to an underestimation of the absolute number of participants with any worsening in Stage B. However, the same aINCAT-based relapse definition, visit schedule and outcome assessments (aINCAT, I-RODS, MGS) were applied in a blinded manner to both treatment arms throughout Stage B. Any under-ascertainment of relapse due to reliance on aINCAT would therefore be expected, in general, to affect both arms similarly. Under usual statistical assumptions, such non-differential misclassification would be expected to attenuate the observed treatment difference rather than exaggerate it.

The available Stage B secondary endpoint results provide evidence on whether defining relapse using aINCAT alone could have obscured a different pattern of treatment effect. In the primary Stage B analysis, efgartigimod reduced the risk of relapse, defined as time to first aINCAT deterioration compared with placebo (hazard ratio [HR] 0.39, 95% confidence interval [CI]: 0.25 to 0.61, nominal $p < 0.0001$).² A prespecified secondary time-to-event analysis based on I-RODS alone, defined as the first decrease of at least four points from Stage B baseline, demonstrated a

consistent finding, with a HR of 0.54 (95% CI: 0.35 to 0.81, nominal $p=0.0034$).² The consistent treatment effects observed across both aINCAT (HR 0.39) and I-RODS (HR 0.54) provide reassurance that the aINCAT-based relapse definition did not obscure the underlying pattern of treatment benefit, as efgartigimod delayed clinical worsening regardless of whether progression was measured through disability or functional outcomes.

A3. Priority question: Table 10 in the CS reports the percentage of patients who discontinued Stage A of ADHERE early for ‘Other reasons’ than the trial ending. Please provide:

- a) A list of the other reasons for discontinuation;**
- b) The percentage of patients who discontinued for each of these reasons, separated by prior CIDP therapy (as reported in Table 10).**

(a) The company provides in Table 2 a summary of all reasons for study discontinuations during Stage A.

(b) Table 2 below also presents, for each of the three prior-treatment subgroups (corticosteroids, intravenous immunoglobulin/subcutaneous immunoglobulin [IVIg/SCIg] and treatment-naïve), the number and percentage of participants who discontinued Stage A for each reason.

Table 2: Study discontinuation by prior CIDP medication in Stage A (Stage A safety analysis set)

	Corticosteroids (N=63) n (%)	IVIg/SCIg (N=165) n (%)	Treatment- naïve (N=94) n (%)	Total (N=322) n (%)
Discontinued from trial				
Lack of efficacy at end of Stage A*				
All events required for primary analysis achieved				
Rolled over to ADHERE+				
Any other reason				
Adverse event				
Death				
Lack of efficacy before end of Stage A†				
Lost to follow-up				
Non-compliance with study drug				
Physician decision				
Prohibited medications				
Withdrawal by subject				
Other				
Randomised in Stage B				

Source: argenx data on file - tables, figures and listings table 14.4.1.5.³

*All participants who discontinued study due to lack of efficacy with completed Stage A treatment status.

†All participants who discontinued study due to lack of efficacy without completed Stage A treatment

status.

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; IVIg: Intravenous immunoglobulin; SCIg: Subcutaneous immunoglobulin.

A4. Priority question: Please provide information on the reasons for discontinuation in Stage B of ADHERE (as provided for Stage A in Table 10 of the CS)

Table 3 provides a summary of the reasons for discontinuation during Stage B of ADHERE. In Stage B, discontinuations attributed to lack of efficacy correspond to participants who experienced a confirmed aINCAT-defined relapse, which was the primary endpoint for this stage of the trial. Discontinuation due to adverse events was uncommon, and one death occurred during Stage B in the placebo arm. Other reasons for discontinuation, such as withdrawal by the patient or administrative reasons, occurred infrequently and with similar proportions to those observed in Stage A, where discontinuations were also primarily driven by clinically defined changes rather than tolerability issues.

Table 3: Reasons for discontinuation in Stage B of ADHERE

	Efgartigimod (N=111) n (%)	Placebo (N=110) n (%)	All participants (N=221) n (%)
Completed Stage B treatment without aINCAT deterioration	██████	██████	██████
Discontinued from treatment in Stage B	██████	██████	██████
Adverse event	██████	██████	██████
All events required for primary analysis achieved	██████	██████	██████
Death	██████	██████	██████
Lack of efficacy*	██████	██████	██████
Lost to follow-up	██████	██████	██████
Prohibited medications	██████	██████	██████
Protocol deviation	██████	██████	██████
Sponsor decision	██████	██████	██████
Withdrawal by subject	██████	██████	██████
Other	██████	██████	██████

Source: argenx data on file – tables, figures and listings table 14.1.1.8.2.³

*All participants, with or without clinical deterioration, in Stage B safety analysis set who discontinued from treatment in Stage B for reason of lack of efficacy.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score.

A5. Priority question: Section 2.3.1.1.3 of the CS reports thresholds for evidence of clinical improvement, including:

- **aINCAT: ≥ 1 point improvement;**
- **I-RODS: ≥ 4 points;**
- **Mean grip strength: ≥ 8 kPa.**

(a) Please confirm if these are established minimal clinically important differences (MCIDs) and provide any relevant references in support of these thresholds;

(b) Please clarify if there are any established MCIDs for the other secondary outcomes (MRC sum score and TUG test) and provide any relevant references.

(a) The company refers to the recent review by Rajabally et al in Muscle & Nerve (2025), which provides a detailed synthesis of minimal clinically important differences (MCIDs) for outcome measures used in CIDP.⁴ The review evaluates the derivation and validation of MCIDs for aINCAT, I-RODS and grip strength using both anchor- and distribution-based methods and summarises their application across clinical trials.⁴

- For aINCAT, a one-point change is considered an established and widely accepted MCID.⁴ This threshold has been supported by anchor-based analyses from the ICE study and subsequent validation studies, and it is consistently applied across CIDP clinical trials.⁴ Rajabally et al. report that aINCAT with a one-point cut-off was used in the majority of analyses reviewed (13/18 [72.2%]).⁴
- For I-RODS, Rajabally and colleagues report an MCID of eight centile points for the centile score using a distribution-based method, and highlight that different thresholds have been applied across CIDP studies.⁴ They note that the four-centile threshold used in several trials, including ADHERE, has not been formally derived but has been applied pragmatically in previous CIDP research.⁴ In complement, the 2021 European Academy of Neurology/ Peripheral Nerve Society (EAN/PNS) guideline cites an improvement of at least four centile points on I-RODS as a practical change threshold used in clinical trials.⁵ Taken together, these sources indicate that while alternative thresholds exist, the four-centile I-RODS criterion used in ADHERE is consistent with established clinical trial practice in CIDP and with guideline-referenced thresholds.

- The review by Rajabally et al. delineated that an 8 kPa change in MGS has been the most commonly used threshold in clinical studies.⁴ While anchor-based analyses in some studies have suggested thresholds up to 14 kPa, the 8-kPa threshold has been consistently applied as the standard across the CIDP trial literature and represents a conservative, widely-accepted benchmark that provides adequate sensitivity to detect clinically meaningful improvement while maintaining specificity.⁴

(b) As summarised in the review by Rajabally et al., several studies have derived minimal clinically important differences for the Medical Research Council (MRC) sum score, typically in the range of approximately two to four points, using a combination of anchor-based and distribution-based methods.⁴ These analyses, including the post-hoc ICE study work, suggest that a four-point change is a reasonable marker of clinically important worsening or improvement, whereas lower cut-offs (for example, two points) may be inadequately sensitive to measurement error and intra-rater variability.⁴ However, the review also highlights important methodological limitations and discrepancies between studies, and concludes that MCIDs for strength scores, including the MRC sum score, lack reliability and direct clinical relevance when used in isolation.⁴

For gait outcomes, a prospective observational study by Llauradó et al. proposed an optimal timed up and go (TUG) cut-off of at least one-second improvement, derived from receiver operating characteristic analysis and associated with a sensitivity of 82.6% for detecting clinical improvement.⁶ This work, together with the synthesis in the Rajabally et al. review, supports the concept that small TUG changes may reflect clinically relevant gait improvement.^{4,6} At the same time, both sources emphasise that such a narrow margin is vulnerable to measurement error and day-to-day fluctuations, and that data in CIDP remains limited; the review therefore considers MCIDs for walking tests, including TUG, to be methodologically uncertain and not yet robust enough for routine use as definitive responder thresholds.^{4,6}

In ADHERE, the prespecified thresholds used to define clinically meaningful deterioration or improvement (≥ 1 -point change in aINCAT, ≥ 4 -point change in I-RODS centile score and ≥ 8 kPa change in MGS) were aligned with the change criteria suggested in the 2021 EAN/PNS guideline, which recommends these values as guidance based on their use in CIDP clinical trials.^{2,7} In contrast, no formal MCID

cut-offs were applied to the MRC sum score or TUG test in ADHERE; these measures were analysed as continuous secondary endpoints to characterise changes in strength and gait alongside the disability and grip strength outcomes with more established MCIDs.^{2,7} Taking into consideration recent literature, in which proposed MCIDs for MRC and TUG are still considered exploratory and of uncertain validity in CIDP, this approach is consistent with existing evidence and avoids over-interpretation of thresholds that are not yet validated for regulatory decision-making.

A6. The EAG would like further details on how aINCAT at baseline affects the potential benefits of efgartigimod.

- a) Please provide details of the distribution of aINCAT change from baseline, disaggregated by aINCAT categories (as defined in the economic model) at baseline.**
- b) Please comment on whether patients' aINCAT score at baseline is likely to determine the benefit they can gain from efgartigimod; for example, is it less likely to have clinically meaningful change in aINCAT scores for less severe patients compared to severe patients.**

(a) The company provides below the descriptive summaries of change in aINCAT disability score from baseline, presented separately for Stage A and Stage B in Table 4 and Table 5 respectively. Table 4 reports change from Stage A baseline at the last Stage A assessment, stratified by baseline aINCAT category. Table 5 reports change from Stage B baseline at the last Stage B assessment, shown separately for efgartigimod and placebo, and stratified by Stage B baseline aINCAT.

Table 4: aINCAT disability score: change from Stage A baseline at the last Stage A assessment, by baseline aINCAT category (Stage A safety analysis set)

	Change from Stage A baseline to Stage A last assessment			
	INCAT 2–3	INCAT 4-6	INCAT 7–8	INCAT 9–10
	Efgartigimod (N=90)	Efgartigimod (N=179)	Efgartigimod (N=36)	Efgartigimod (N=12)
n	████	████	████	████
Mean (SE)	████	████	████	████
SD	████	████	████	████
Median	████	████	████	████
Q1; Q3	████	████	████	████
Min; Max	████	████	████	████

Source: argenx data on file – analyses for NICE clarification questions.⁸

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; INCAT: Inflammatory Neuropathy Cause and Treatment score; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error; Q1: First quartile; Q3: Third quartile.

Table 5: aINCAT disability score: change from Stage B baseline at the last Stage B assessment, by baseline aINCAT category (Stage B mITT analysis set)

	Stage B							
	INCAT 0-1		INCAT 2-3		INCAT 4-6		INCAT 7-8	
	Efgartigimod (N=15)	Placebo (N=13)	Efgartigimod (N=59)	Placebo (N=33)	Efgartigimod (N=34)	Placebo (N=39)	Efgartigimod (N=3)	Placebo (N=5)
n	████	████	████	████	████	████	████	████
Mean (SE)	████	████	████	████	████	████	████	████
SD	████	████	████	████	████	████	████	████
Median	████	████	████	████	████	████	████	████
Q1; Q3	████	████	████	████	████	████	████	████
Min; Max	████	████	████	████	████	████	████	████

Source: argenx data on file – analyses for NICE clarification questions.⁸

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; INCAT: Inflammatory Neuropathy Cause and Treatment score; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error; Q1: First quartile; Q3: Third quartile.

(b) Published analyses indicate that aINCAT is a well-established disability outcome in CIDP trials, and that its structure as a scale scored in whole-point categories means that the observable magnitude of change depends, in part, on baseline severity.⁹ A review by Rajabally and colleagues of MCIDs for CIDP outcome measures notes that the detection of change can be influenced by baseline score and measurement properties of the scale: aINCAT changes only in whole-point increments at the individual patient level, participants with lower baseline disability have less numerical scope to show improvement than those entering treatment with greater disability.⁴ Participants with milder baseline disability may therefore experience clinical benefit that is less readily captured as a one-point change on aINCAT. A separate review on measuring disease activity and treatment response in CIDP reported that the INCAT score was relatively insensitive to detecting improvement in patients with milder baseline disease in the ICE IVIg trial, indicating that smaller but clinically relevant gains may not always be reflected as a one-point change in less disabled patients.¹⁰

aINCAT is more relevant to the detectability of improvement on the aINCAT scale than to a patient's capacity to benefit from treatment. This interpretation is supported by the ADHERE Stage A results presented as part of the response to part (a) above in Table 4. Table 4 shows that participants with higher baseline aINCAT categories experienced larger mean improvements at the last Stage A assessment than those with lower baseline scores. This expected gradient reflects the numerical headroom available within the scale rather than implying reduced responsiveness in participants with mild baseline disability.

Benefit in CIDP also includes prevention of deterioration, which is clinically meaningful regardless of baseline severity. CIDP is a chronic, immune-mediated neuropathy in which preventing relapse and avoiding the accumulation of disability are key treatment goals.⁵ Prospective cohort data show that patients remain at risk of relapse and functional decline even when baseline disability is relatively mild, supporting the need for effective disease control across the full severity spectrum.¹¹ In ADHERE Stage B, the primary endpoint was time to first relapse, defined as a $\geq$ one-point worsening in aINCAT from the Stage B baseline.² A one-point deterioration represents loss of functional capacity at all starting severity levels.

Subcutaneous efgartigimod significantly reduced this risk compared with placebo, demonstrating benefit in maintaining stability and preventing clinical worsening across the overall population.²

Taken together, the company considers that baseline aINCAT influences how numerical improvement is expressed on the scale but does not determine whether patients can derive meaningful clinical benefit from efgartigimod. Participants with lower baseline disability can still benefit through improvement, which can be captured on complementary outcome measures and through stabilisation and relapse prevention.

A7. Priority question: Figure 13 of the CS provides the results of subgroup analyses for the change in aINCAT score in Stage B. Please provide similar subgroup analyses for the secondary outcomes in ADHERE (time to first CIDP progression, improved functional level, I-RODS score, mean grip strength, TUG test and EQ-5D-5L VAS).

Subgroup analyses for the secondary outcomes in ADHERE Stage B are summarised in two tables below. The time to first CIDP progression and the proportion of participants achieving an improved functional level are presented by stratification factors in Table 6. Further subgroup results for the remaining secondary endpoints (I-RODS score, MGS, TUG test and EQ-5D-5L VAS) are provided in Table 7.

Table 6: ADHERE Stage B - subgroup analyses for secondary outcomes (time to CIDP disease progression and improved functional level) by stratification factors (mITT analysis sets)

Secondary endpoint	Efgartigimod	Placebo
Corticosteroids		
Time to CIDP disease progression*		
Observed response, N [†]		
n [‡] , (% [§])		
Comparison of efgartigimod and placebo		
HR		
95% CI		
p-value**		
Improved functional level ^{††}		
Observed response, N ^b		
n ^c , (% ^d)		
Comparison of efgartigimod and placebo		
Odds ratio ^{††}		
95% CI ^{††}		
p-value ^{††}		
IVIg/SCIg		
Time to CIDP disease progression*		
Observed response, N [†]		
n [‡] , (% [§])		
Comparison of efgartigimod and placebo		
HR		
95% CI		
p-value**		
Improved functional level ^{††}		
Estimate (SE)		
Observed response, N [†]		
n [‡] , (% [§])		
Comparison of efgartigimod and placebo		
Odds ratio ^{††}		
95% CI ^{††}		
p-value ^{§§}		

Secondary endpoint	Efgartigimod	Placebo
Treatment-naïve		
Time to CIDP disease progression*		
Observed response, N [†]		
n [‡] , (%§)		
Comparison of efgartigimod and placebo		
HR		
95% CI ^{††}		
p-value ^{§§}		
Improved functional level ^{††}		
Observed response, N [†]		
n [‡] , (%§)		
Comparison of efgartigimod and placebo		
Odds ratio ^{††}		
95% CI ^{††}		
p-value ^{§§}		

Source: argenx data on file – tables, figures and listings table 14.2.6.2.1 and table 14.2.7.2.1.³

*Time to CIDP disease progression is defined as the time (days) from first Stage B dose to the first occurrence of a decrease of the I-RODS score of at least 4 points compared to Stage B baseline

†Total number of participants per treatment in the mITT analysis set.

‡Total number of participants per treatment in the mITT analysis set per secondary outcome in ADHERE.

§The denominator for the percentage calculations is the total number of participants per treatment in the mITT analysis set.

||Wald Chi-square p-value.

¶Cox proportional hazards regression model stratified for change of adjusted INCAT score during Stage A.

**Wald-type 95% CI.

Improved functional level means participant has at least one Stage B I-RODS assessment with an increase of 4 points or more compared to Stage B baseline.

††Exact logistic regression using change of adjusted INCAT score during Stage A as a covariate instead of stratification factor due to convergence issues.

§§Exact statistics with 2-sided exact p-value.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyneuropathy; HR: Hazard ratio; I-RODS: Inflammatory Rasch-built Overall Disability Scale; INCAT: Inflammatory Neuropathy Cause and Treatment; mITT: Modified intent-to-treat; SE: Standard error.

Table 7: ADHERE Stage B - subgroup analyses for secondary outcomes (I-RODS, mean grip strength, TUG test, and EQ-5D-5L VAS score) by stratification factors (mITT analysis sets)

Secondary endpoint	Stage B baseline*	Stage B last assessment†	Stage B baseline*	Stage B last assessment†
	Efgartigimod		Placebo	
Corticosteroids				
I-RODS				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min: Max				

Secondary endpoint	Stage B baseline*	Stage B last assessment†	Stage B baseline*	Stage B last assessment†
	Efgartigimod		Placebo	
CFB				
Mean grip strength – dominant hand (kPa)				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
Mean grip strength – non-dominant hand (kPa)				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
Time to complete TUG test (seconds)				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
EQ-5D-5L VAS score				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				

Secondary endpoint	Stage B baseline*	Stage B last assessment†	Stage B baseline*	Stage B last assessment†
	Efgartigimod		Placebo	
Min; Max				
CFB				
IVIg/SCIg				
I-RODS				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
Mean grip strength – dominant hand (kPa)				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
Mean grip strength – non-dominant hand (kPa)				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
Time to complete TUG test (seconds)				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				

Secondary endpoint	Stage B baseline*	Stage B last assessment†	Stage B baseline*	Stage B last assessment†
	Efgartigimod		Placebo	
Q1; Q3				
CFB				
Min; Max				
CFB				
EQ-5D-5L VAS score				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
Treatment-naïve				
I-RODS				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
Mean grip strength – dominant hand (kPa)				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
Mean grip strength – non-dominant hand (kPa)				
n				
Mean (SE)				
CFB				
SD				
CFB				

Secondary endpoint	Stage B baseline*	Stage B last assessment†	Stage B baseline*	Stage B last assessment†
	Efgartigimod		Placebo	
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
Time to complete TUG test (seconds)				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				
EQ-5D-5L VAS score				
n				
Mean (SE)				
CFB				
SD				
CFB				
Median				
CFB				
Q1; Q3				
CFB				
Min; Max				
CFB				

Source: argenx data on file – analyses for NICE clarification questions.⁸

*Stage B baseline: Last available value before or at the day of first study drug administration in Stage B (and after Stage A baseline).

†Stage B last assessment: The latest non-missing post-baseline value in Stage B.

Abbreviations: CFB: Change from baseline; EQ-5D-5L: EuroQol 5 Dimensions, 5 Levels; I-RODS: Individualised Rasch-built Overall Disability Scale; IVIg: Intravenous immunoglobulin; kPa: Kilopascal; Max: Maximum; Min: Minimum; mITT: Modified intent-to-treat; SCIg: Subcutaneous immunoglobulin; SD: Standard deviation; SE: Standard error; Q1: First quartile; Q3: Third quartile; TUG: Timed Up and Go; VAS: Visual analogue scale.

A8. The EAG is aware of a 2025 update to the Association of British Neurologists autoimmune myasthenia gravis management guidelines, which states that, “As both IVIg and FcRn monoclonal antibodies bind to the FcRn receptor, they cannot be given concurrently; a washout period of 4 weeks is required before starting an anti-FcRn following IVIg treatment”.

Based on this information, please provide a clinical rationale for why the company expects that patients who are refractory to Ig may respond to efgartigimod instead.

The company appreciates the EAG’s question regarding the clinical rationale for including Ig-refractory patients in the target population. This positioning is supported by:

- The distinct mechanism of action between IVIg and efgartigimod,
- Feedback from UK clinical experts that Ig-refractory patients represent a high unmet need group,
- Regulatory precedent that lack of response to one immunomodulatory agent does not predict non-response to mechanistically distinct therapies.

The 2025 Association of British Neurologists (ABN) autoimmune myasthenia gravis guidance advises that IVIg and FcRn monoclonal antibodies should not be administered concurrently, and that a four-week washout is recommended before initiating an anti-FcRn agent.¹² The company considers that this recommendation reflects a precautionary approach intended to avoid transient competition for the neonatal Fc receptor (FcRn), rather than an implication that IVIg and FcRn antagonists have equivalent mechanisms or interchangeable clinical effects.^{12,13}

The company considers that the expected benefit of efgartigimod in patients who are refractory to immunoglobulin (Ig) is supported by its distinct and more selective mechanism of action. IVIg exerts pleiotropic and short-lived immunomodulatory effects, including FcRn saturation, Fcγ-receptor modulation, complement effects and cytokine regulation, each varying between individuals and dependent on dose and timing.¹⁴ By contrast, efgartigimod is a selective FcRn antagonist that prevents FcRn-mediated IgG recycling and thereby increases lysosomal degradation of IgG.^{2,15} This mechanism produces a sustained and predictable reduction in

circulating IgG concentrations, including pathogenic IgG autoantibodies, without materially affecting other Ig classes or albumin.^{2,15} Evidence from other IgG-mediated autoimmune disorders further supports this mechanistic distinction, as IVIg has been shown to produce only modest reductions in pathogenic autoantibodies compared with the substantially deeper IgG depletion achieved through more targeted IgG-removal approaches.¹⁶

Findings from ADHERE are also consistent with this distinction in mechanistic action.² Efgartigimod produced rapid and marked IgG reduction during the first four weeks, with mean IgG concentrations maintained at approximately two-thirds below the Stage A baseline throughout treatment, with reductions of 67% (SD 10.4) to 72% (SD 6.1).² However, the company notes that ADHERE did not include a definable subgroup of patients who were refractory to Ig, and these individuals cannot be isolated within the off-treatment or prior-steroid cohorts. Ig-refractory patients represent a small group (<5% in the company sponsored market research survey¹⁷) with substantial unmet need, and clinical experts support their inclusion because the mechanism of FcRn blockade remains relevant irrespective of prior IVIg response.¹³ Emerging real-world evidence also provides supportive observations consistent with this mechanistic rationale. A 2025 single-centre case series from China reported clinical improvement in all five patients with CIDP treated with efgartigimod, including three previously classified as refractory to at least two standard therapies.¹⁸ Four patients met predefined effectiveness criteria within 8 weeks and reductions in total IgG of 27.5% to 65% were observed.¹⁸ Although the cohort was small and uncontrolled, these findings align with the expectation that FcRn blockade may benefit patients who do not respond adequately to IVIg.¹⁸ Furthermore, the company would like to note that UK CIDP specialists consulted informally during submission development confirmed that in clinical practice some patients who show inadequate response to IVIg are subsequently found to respond to other immunomodulatory approaches.

The company therefore emphasises that lack of response to IVIg does not imply refractoriness to FcRn blockade. Given the transient and heterogeneous nature of IVIg's immunomodulatory actions compared with the selective and sustained

reduction in IgG achieved with efgartigimod, it is biologically plausible that some patients who do not respond adequately to IVIg could respond to efgartigimod.

The company further notes that the ADHERE investigators stated that “the optimal approach to transition a patient from IgG therapy to subcutaneous efgartigimod is yet to be determined”.² This supports the company’s position that appropriate sequencing or washout is a practical consideration to avoid receptor overlap, not an indication of pharmacological redundancy. A dedicated transition study is underway to address this question and will provide further prospective evidence regarding the sequencing of IVIg and efgartigimod in CIDP (NCT06637072).¹⁹ The study will assess the proportion of participants who initiate efgartigimod within 1 week after stopping IVIg and who remain on treatment at the end of the 12-week period.

ADHERE+

A9. Priority question: Section 2.3.2.1 of the CS states that participants were eligible to enrol in ADHERE+ if they had:

- **completed Week 48 of the double-blind Stage B of ADHERE;**
- **experienced clinical deterioration during Stage B; or**
- **discontinued early once sufficient events for the primary endpoint in ADHERE had been reached and the trial had concluded.**

However, the EAG notes that 228 patients were enrolled in ADHERE+ but only 221 were included in Stage B of ADHERE.

- a) Please clarify if patients from Stage A of ADHERE were eligible to be enrolled in ADHERE+. If so, please clarify which of these patients could enter ADHERE+;**
- b) Please provide a breakdown of the percentage of patients who entered ADHERE+ due to:**
 - ii) Completing Week 48 of ADHERE;**
 - iii) Clinical deterioration during Stage B;**
 - iv) Early discontinuation of the trial once sufficient events were reached.**

Please report this information separately for patients who were randomised to the efgartigimod arm and patients who were randomised to the placebo arm of ADHERE.

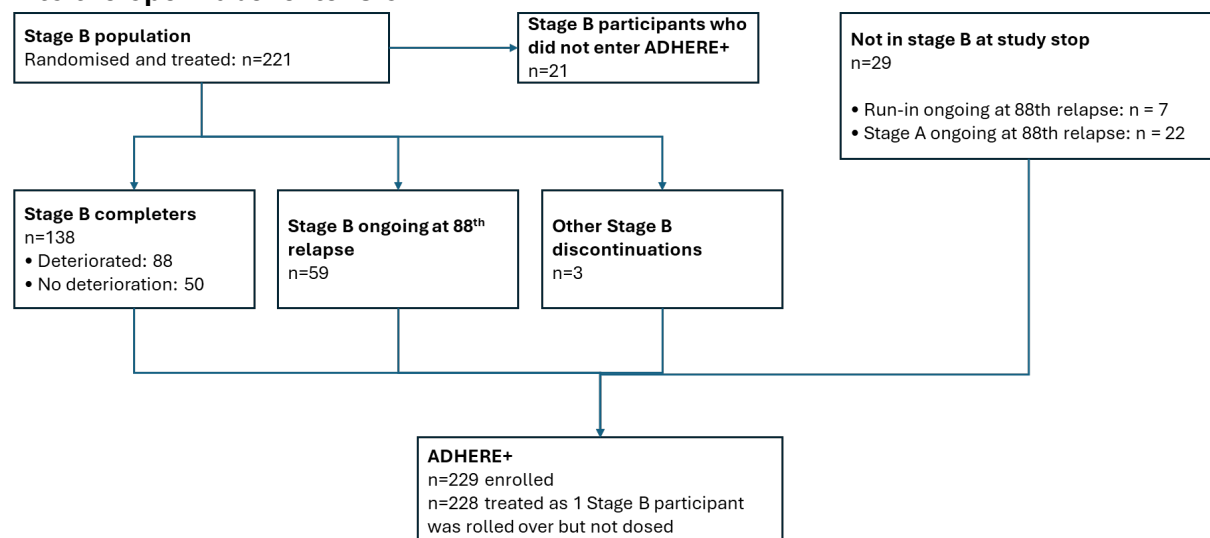
(a) The company confirms that patients from Stage A of ADHERE were eligible to enrol in the ADHERE+ open-label extension under specific, protocol-defined circumstances. Participants who were still ongoing in Stage A at the time ADHERE was stopped, namely when the prespecified 88 relapse events in Stage B had accrued, and the randomised-withdrawal phase was terminated, were permitted to roll over into ADHERE+ following an early-discontinuation visit and confirmation of eligibility for open-label efgartigimod treatment.

Participants who were still in the run-in at the time of study stop were also eligible to roll over into ADHERE+. Together with Stage B completers and Stage B participants who experienced clinical deterioration, these Stage A and run-in participants contributed to ADHERE+ enrolment. This explains why the number of participants enrolled and treated in ADHERE+ (229 enrolled, 228 treated) exceeded the number who had been randomised into Stage B (n=221).

In total, the rollover population included four protocol-consistent sources:

- (i) participants who completed Stage B (with or without clinical deterioration),
- (ii) participants who experienced clinical deterioration during Stage B,
- (iii) participants who were ongoing in Stage A at the time of the 88th relapse event, and
- (iv) participants who were ongoing in the run-in at the 88th relapse event.

Figure 1: Participant disposition from ADHERE to ADHERE+: Sources of enrolment into the open-label extension



Source: argenx data on file – ADHERE+ top-line results report – Interim analysis 2.²⁰

Note: One participant was rolled over but not dosed. One participant withdrew from ADHERE before receiving efgartigimod and was excluded from the safety and mITT analysis sets.

(b) Table 8 provides a breakdown of the percentage of patients who entered ADHERE+.

Table 8: Participant disposition in ADHERE+

	Stage B efgartigimod (N=99) n (%)	Stage B placebo (N=101) n (%)	Total (N=229)* n (%)
All enrolled participants in ADHERE+	████	████	████
Completed Stage B of ADHERE (Week 48)	████	████	████
Experienced clinical deterioration during Stage B	████	████	████
Ongoing at occurrence of 88 th event in Stage B	████	████	████
Discontinued treatment in ADHERE Stage B (without clinical deterioration)	████	████	████

Source: argenx data on file – ADHERE+ top-line results report – Interim analysis 2.²⁰

*Includes 7 participants from the run-in and 22 participants from Stage A who were ongoing and who were enrolled in ADHERE+ at the occurrence of the 88th event in Stage B.

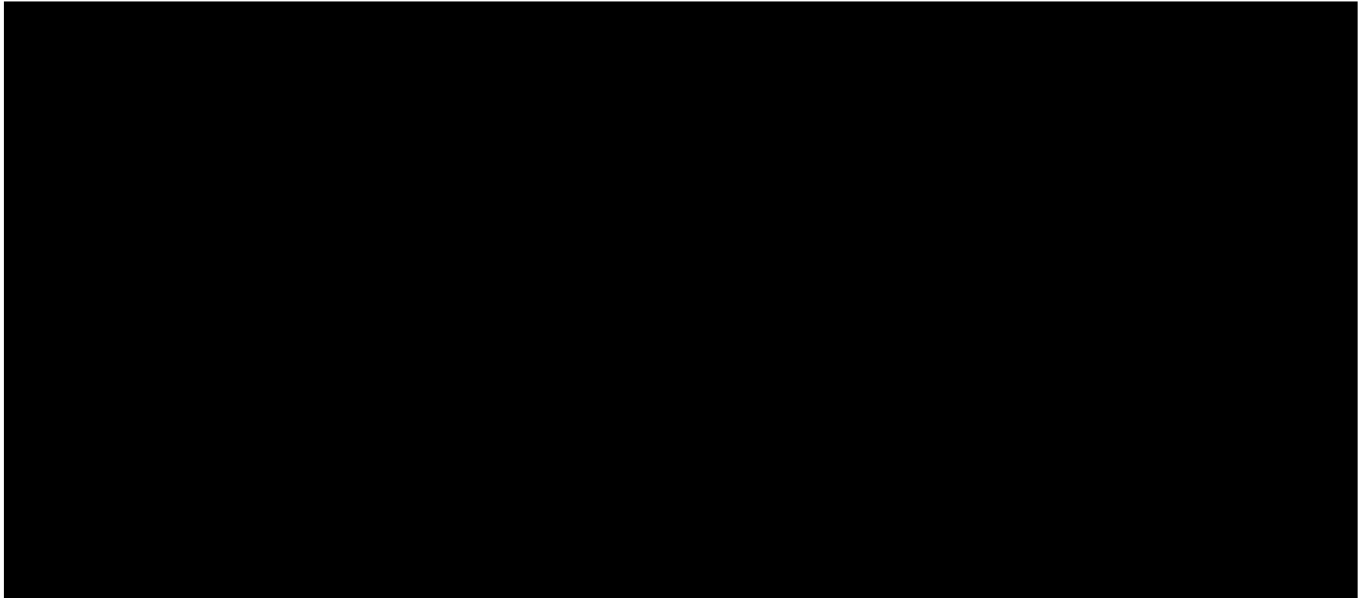
A10. Priority question: Please provide the results for the decline in adjusted INCAT scores from the interim analysis of ADHERE+, discussed in Section 2.6.2.2 of the CS.

Figure 2 presents the mean (standard error [SE]) absolute aINCAT scores in ADHERE+ by prior treatment group, and Figure 3 presents the corresponding mean (SE) change from open-label extension (OLE) baseline values. Interpretation should take into account that this is an interim analysis with a declining number of evaluable participants at later visits. As participants enter ADHERE+ on a rolling basis, the number of patients contributing to the later timepoints becomes small, and the resulting means are therefore more variable. This explains the upward fluctuations observed late in follow-up.

Across most of the follow-up period, absolute aINCAT values in Figure 2 remain broadly stable within each prior treatment group. Participants previously receiving placebo in Stage B show an initial decrease in absolute scores following their transition to active treatment, after which values stabilise. In Figure 2, participants entering from Stage A only show a reduction at entry followed by a modest increase, which is driven by very small numbers (n=1 patient) contributing to later timepoints. Participants previously treated with efgartigimod in Stage B maintain relatively stable scores throughout, consistent with sustained benefit before entering the extension.

In contrast, Figure 3 shows a consistent downward trajectory for change-from-baseline across all groups, indicating continued incremental improvement relative to the open-label extension baseline. Interpretation between the figures should account for the combination of the baseline reset at ADHERE+ entry (Figure 3) and increasing variability introduced by declining sample sizes at later visits (Figure 2 and Figure 3).

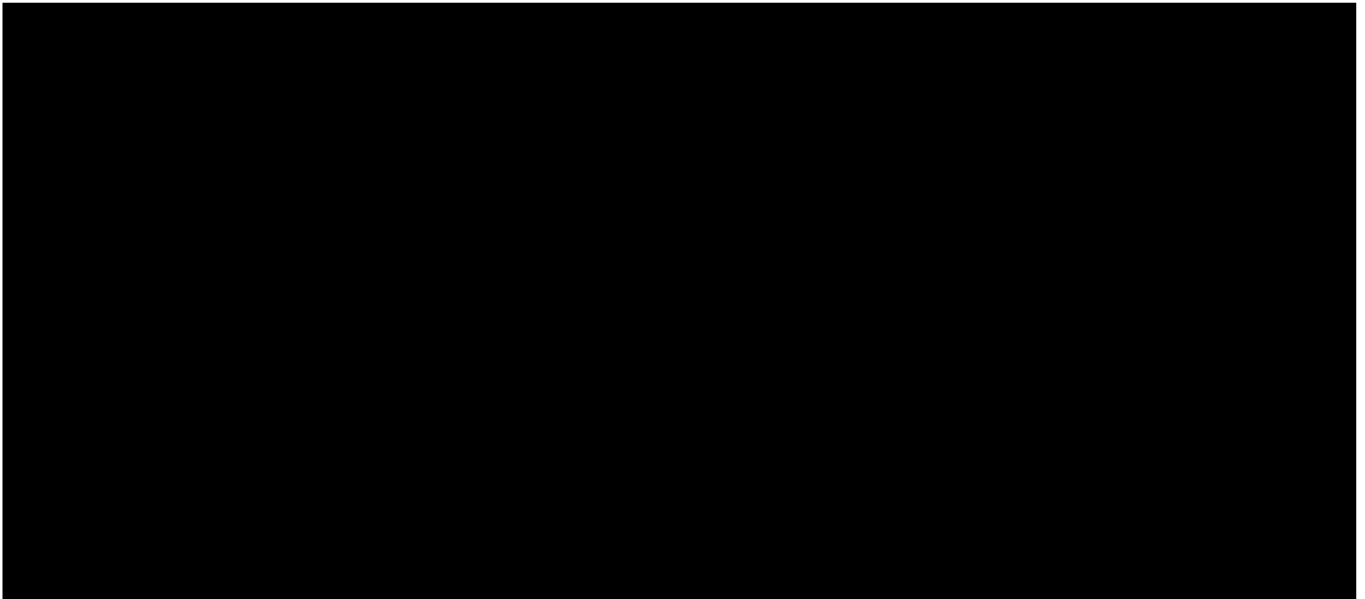
Figure 2: aINCAT Score: Mean (SE) Actual Values (mITT Analysis Set)



Source: argenx data on file – ADHERE+ top-line results report – Interim analysis 2.²⁰

Notes: ADHERE+ baseline corresponds to the last available value before the first efgartigimod administration in ADHERE+. Week 4 was the first time point at which efficacy assessments were measured. Abbreviations: aINCAT: adjusted INCAT disability score; EFG PH20 SC: Efgartigimod for subcutaneous administration coformulated with recombinant human hyaluronidase PH20; INCAT: Inflammatory Neuropathy Cause and Treatment; mITT: Modified intent-to-treat; PBO PH20 SC: Placebo for subcutaneous administration coformulated with recombinant human hyaluronidase PH20; RI: Run-in during ADHERE.

Figure 3: aINCAT Score: Mean (SE) changes From OLE Baseline (mITT Analysis Set)



Source: argenx data on file – ADHERE+ top-line results report – Interim analysis 2.20

Notes: ADHERE+ baseline corresponds to the last available value before the first EFG PH20 SC administration in ADHERE+. Week 4 was the first time point at which efficacy assessments were measured.

Abbreviations: aINCAT: Adjusted INCAT disability score; EFG PH20 SC: Efgartigimod for subcutaneous administration coformulated with recombinant human hyaluronidase PH20; INCAT: Inflammatory Neuropathy Cause and Treatment; mITT: Modified intent-to-treat; OLE: Open-label extension; PBO PH20 SC: Placebo for subcutaneous administration coformulated with recombinant human hyaluronidase PH20; RI: Run-in during ADHERE.

A11. Priority question: As discussed in question A4, the EAG notes that three patient groups were included in ADHERE+ (patients who completed 48 weeks of Stage B, patients who experienced clinical deterioration during Stage B or patients who were discontinued because the trial ended). Please provide the results of ADHERE+ for each of these groups separately for the following outcomes:

- **Change in adjusted INCAT score from ADHERE+ baseline;**
- **Change in I-RODS score from ADHERE+ baseline;**
- **Change in mean grip strength from ADHERE+ baseline.**

The company provides the results of ADHERE+ for the three patient groups specified by the EAG. Changes from ADHERE+ baseline in adjusted INCAT score, I-RODS score and MGS are summarised separately for: participants who completed 48 weeks of Stage B (Table 9); participants who experienced clinical deterioration during Stage B (Table 10); and participants who were ongoing in Stage B at the time the 88th relapse event was reached (Table 11). All analyses are based on the Stage B safety analysis set.

Table 9: Last assessment change from ADHERE+ baseline (aINCAT, I-RODS and grip strength) in participants who completed Week 48 of Stage B in ADHERE (Stage B safety analysis set)

	Stage B – Efgartigimod (N=33)	Stage B – Placebo (N=17)	All participants (N=50)
Change in adjusted INCAT score from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████
Change in I-RODS score from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████

	Stage B – Efgartigimod (N=33)	Stage B – Placebo (N=17)	All participants (N=50)
Change in mean grip strength (dominant hand, kPa) from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████
Change in mean grip strength (non-dominant hand, kPa) from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████

Source: argenx data on file – analyses for NICE clarification questions.⁸

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; I-RODS: Individualised Rasch-built Overall Disability Scale; INCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; kPa: Kilopascal; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error; Q1: First quartile; Q3: Third quartile.

Table 10: Last assessment change from ADHERE+ baseline (aINCAT, I-RODS and grip strength) in participants who experienced clinical deterioration during Stage B in ADHERE (Stage B safety analysis set)

	Stage B – Efgartigimod (N=30)	Stage B – Placebo (N=58)	All participants (N=88)
Change in adjusted INCAT score from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████
Change in I-RODS score from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
S.D.	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████

	Stage B – Efgartigimod (N=30)	Stage B – Placebo (N=58)	All participants (N=88)
Change in mean grip strength (dominant hand, kPa) from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████
Change in mean grip strength (non-dominant hand, kPa) from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████

Source: argenx data on file – analyses for NICE clarification questions.⁸

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; I-RODS: Individualised Rasch-built Overall Disability Scale; INCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; kPa: Kilopascal; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error; Q1: First quartile; Q3: Third quartile.

Table 11: Last assessment change from ADHERE+ baseline (aINCAT, I-RODS and grip strength) in participants who were ongoing at the occurrence of the 88th event in ADHERE Stage B (Stage B safety analysis set)

	Stage B – Efgartigimod (N=35)	Stage B – Placebo (N=23)	All participants (N=58)
Change in adjusted INCAT score from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████
Change in I-RODS score from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████

	Stage B – Efgartigimod (N=35)	Stage B – Placebo (N=23)	All participants (N=58)
Change in mean grip strength (dominant hand, kPa) from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████
Change in mean grip strength (non-dominant hand, kPa) from ADHERE+ baseline			
n	████	████	████
Mean (SE)	████	████	████
SD	████	████	████
Median	████	████	████
Q1; Q3	████	████	████
Min; Max	████	████	████

Source: argenx data on file – analyses for NICE clarification questions.⁸

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; I-RODS: Individualised Rasch-built Overall Disability Scale; INCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; kPa: Kilopascal; Max: Maximum; Min: Minimum; SD: Standard deviation; SE: Standard error; Q1: First quartile; Q3: Third quartile.

ITCs

A12. Priority question: Please provide data to justify the assumption that IVIg will have the same efficacy as SCIg.

The company considers the assumption of equal efficacy between IVIg and SCIg in CIDP to be supported by head-to-head comparative data and synthesis of the wider clinical evidence. In a randomised crossover trial in treatment-naïve CIDP, Markvardsen and colleagues compared weekly SCIg 0.4 g/kg for 5 weeks with a standard IVIg loading regimen of 0.4 g/kg/day for five days in a cohort of 20 patients before crossing them to the alternative treatment.²¹ Combined isokinetic muscle strength increased by $7.4 \pm 14.5\%$ during SCIg and $6.9 \pm 16.8\%$ during IVIg, with the treatment effect reported as similar ($p=0.80$), and the authors concluded that short-lasting SCIg and IVIg “improve motor performance to a similar degree” in CIDP.²¹ Further supportive evidence comes from the PATH randomised controlled trial, in which IVIg-stabilised patients were transitioned to weekly SCIg at doses of 0.2 g/kg or 0.4 g/kg.²² Both SCIg doses significantly reduced relapse risk compared with placebo, demonstrating that clinical stability achieved with IVIg can be maintained on SCIg and supporting the view that SCIg provides comparable efficacy for maintenance treatment in IVIg-responsive CIDP.²²

Narrative and systematic reviews of the Ig evidence base concur that IVIg and SCIg demonstrate comparable efficacy when used at equivalent maintenance doses. Goyal and colleagues report that long-term outcomes with IVIg and SCIg appear similar in CIDP, while differences in tolerability and convenience generally inform route selection rather than differences in treatment effect.²³ Cocito and colleagues, in a historical review of SCIg, further note that across switch studies from IVIg to dose-equivalent SCIg and in small prospective cohorts, clinical outcomes such as muscle strength, disability and grip strength are maintained without significant differences between IVIg and SCIg, and explicitly conclude that SCIg is as effective as IVIg while being better tolerated and easier to administer.²⁴

These data directly compare IVIg and SCIg, and reviews explicitly stating comparable or equal efficacy, support the company’s assumption that IVIg and SCIg can reasonably be assumed to have the same clinical efficacy in CIDP. The company also notes that regulatory approval of SCIg (Hizentra) for maintenance

treatment of adult CIDP following stabilisation with IVIg demonstrates that regulators consider SCIg to provide clinically meaningful efficacy in this setting.²⁵

A13. Priority question: Please provide the results of change in aINCAT from baseline for the placebo arm in ADHERE:

- a) Prior to weighting adjustments for the anchored MAIC;**
- b) After weighting adjustments for the anchored MAIC.**

Please comment on any reasons for discrepancies between the weighted placebo results from ADHERE and the placebo results from ADVANCE.

The mean change from baseline in aINCAT and I-RODS for the placebo arm in ADHERE Stage B, before and after matching-adjusted indirect comparison (MAIC) weighting, is presented alongside the corresponding placebo results from ADVANCE-CIDP 1 in Table 12.

The placebo arm in ADHERE shows a greater worsening from baseline than the placebo arm in ADVANCE-CIDP 1, and this difference persists, although attenuated, after weighting. This is likely driven by differences in trial design and in the underlying patient populations beyond the covariates included in the MAIC, as well as by unmeasured or imperfectly measured prognostic factors that influence absolute placebo responses and cannot be fully adjusted for.

The objective of the indirect comparison was to estimate the relative treatment effect versus placebo in each trial. In ADHERE, the contrast is efgartigimod versus placebo; in ADVANCE-CIDP 1, the contrast is SCIg versus placebo. Anchoring on within-trial placebo comparators allows the analysis to rely on randomisation to address both measured and unmeasured confounding affecting absolute outcomes, while the MAIC weighting is used to adjust for effect modifiers of the treatment–placebo contrast.

Accordingly, the observed differences in absolute placebo responses between ADHERE and ADVANCE-CIDP 1 do not undermine the validity of the anchored MAIC. Rather, they highlight the limitations of comparing absolute changes across trials and support the use of an anchored, population-adjusted approach that focuses on the relative treatment effect versus placebo, which is the estimate of interest for the indirect comparison between efgartigimod and Ig.

Table 12: Change from baseline in aINCAT and I-RODS in the placebo arm of ADHERE and ADVANCE-CIDP 1

	Placebo in comparator study	Placebo in ADHERE Stage B	
		Unweighted†	Weighted
Change in aINCAT from baseline, means (SE)			
Comparison vs ADVANCE-CIDP 1	0.2 (0.155*)	████████	████████
Change in I-RODS score from baseline, means (SE)			
Comparison vs ADVANCE-CIDP 1	-6.1 (1.640)	████████	████████

* Calculated from published SD=1.3 and n=70.

† After selection of patients to meet inclusion/exclusion criteria in ADVANCE-CIDP 1 study.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; I-RODS: Individualised Rasch-built Overall Disability Scale; SE: Standard error.

A14. Priority question: Please perform a simulated treatment comparison (STC) as a validation of the results of the anchored MAIC.

A simulated treatment comparison (STC) was performed on the change from baseline in aINCAT score, using patient-level data from the ADHERE Stage B subset and published data from the ADVANCE-CIDP 1 study (Bril et al. 2023).²⁶

The covariates used in the MAIC were considered in this analysis, namely baseline age, proportion male, disease duration, baseline aINCAT, baseline I-RODS, baseline MRC (0–60), and proportion on prior corticosteroids. An unadjusted regression model was first fitted in the ADHERE subset, with Week-32 change from baseline in aINCAT as the dependent variable and treatment as the main predictor, supplemented by these seven covariates and their interaction terms with treatment.

Among all treatment–covariate interaction terms, baseline aINCAT score and disease duration were found to be statistically relevant (p-values [REDACTED], respectively) (Table 13). All other interaction terms had p-values [REDACTED] and were therefore excluded from the final model to avoid overspecification. In the STC framework, least-squares means are estimated at covariate values corresponding to the external trial population. Including covariates without evidence of a treatment interaction would adjust the estimated treatment effect despite a lack of statistical support for such adjustment and could therefore introduce unnecessary noise.

The STC model was a generalised linear model including treatment, baseline aINCAT score, disease duration, and their interaction terms with treatment (Table 14). Least-squares means were then estimated at the average covariate values reported for the ADVANCE-CIDP 1 population. This STC yielded a mean difference in aINCAT change from baseline for efgartigimod versus Hyqvia of [REDACTED], indicating greater improvement in aINCAT with efgartigimod. The results of this analysis are presented in Table 15.

Overall, these STC results are broadly consistent with the findings of the anchored MAIC, supporting the robustness of the comparative efficacy estimates for efgartigimod versus Ig.

Table 13: Predictive model parameter estimates in the initial model

Predictive model parameter estimates	Estimate (SE), p-value
Intercept	
Treatment	
[Age (years)]	
[Male]	
[Disease Duration (years)]	
[aINCAT stage B baseline]	
[IRODS stage B baseline]	
[MRC (0-60) stage B baseline]	
[Prior corticosteroids]	
[Age (years)] x Treatment	
[Male] x Treatment	
[Disease Duration (years)] x Treatment	
[aINCAT stage B baseline] x Treatment	
[IRODS stage B baseline] x Treatment	
[MRC (0-60) stage B baseline] x Treatment	
[Prior corticosteroids] x Treatment	

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; CS6M: Change from baseline in the six-minute walk test; I-RODS: Inflammatory Rasch-built Overall Disability Scale; MRC: Medical Research Council; SE: Standard error.

Table 14: Predictive model parameter estimates, in the model used in STC

Predictive model parameter estimates	Estimate (SE), p-value
Intercept	
Treatment	
[Disease Duration (years)]	
[aINCAT stage B baseline]	
[Disease Duration (years)] x Treatment	
[aINCAT stage B baseline] x Treatment	

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; SE: Standard error; STC: Simulated treatment comparison.

Table 15: Results of the STC of aINCAT change from baseline versus ADVANCE-CIDP1

	ADVANCE-CIDP 1	Efgartigimod (ADHERE Stage B)	
		Unadjusted	Adjusted
Baseline characteristics			
Number			
Mean disease duration, years			
Mean total INCAT score			
STC analyses			
Difference in means (95% CI) vs placebo [¶]			
Difference in means (SE) [95% CI] for efgartigimod vs Hyqvia			
P-value			

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; CI: Confidence interval; SE: Standard error; STC: Simulated treatment comparison.

An anchored MAIC was selected as the primary approach for the ITC, given the relatively small sample size of the ADHERE subset and the relatively large number of candidate effect modifiers (seven covariates). In this context, MAIC is preferable, as it avoids fitting a potentially unstable outcome model and instead directly reweights the individual patient data (IPD) to match the aggregate data. In addition, the covariate means between ADHERE and ADVANCE-CIDP 1 do not differ substantially, resulting in a high effective sample size (ESS) and therefore good retention of statistical power.

By contrast, STC requires specifying and fitting a regression model and then predicting outcomes at a different covariate distribution. This can be problematic when predictions are made at the margins of the IPD covariate range, for example, if the aggregate data means differ materially from those in the IPD. Furthermore, the anchored MAIC, through its use of a common placebo comparator, allows adjustment for observed effect modifiers while preserving randomisation to placebo, thereby helping to mitigate the risk of residual confounding from unobserved covariates.

A15. Priority question: ITC results are only provided for the change in aINCAT score from baseline. Please perform anchored MAICs for the following outcomes, including any relevant studies identified in the SLR (e.g. ADVANCE-CIDP 1, PATH, PIMPA, Katzberg 2013 and the ICE trial) which report these outcomes:

- **Change in I-RODS score;**
- **Change in mean grip strength.**

For each comparison, please also provide information on the relative weight distributions (as provided in Appendix 8 of the ITC Technical Report) and the results from the adjusted placebo group of any comparator studies, as requested in question A13.

In outline, the company would like to highlight that there are key limitations associated with performing an indirect treatment comparison (ITC) comparing ADHERE, PATH and ICE trials. Key limitations in the comparisons versus the PATH study pertain to lack of published mean and SE from PATH, thus requiring normality assumptions when estimating these parameters from reported median, IQR and min/max values. This introduces bias which cannot be controlled for. The comparison versus the ICE trial is unlikely to be fully generalisable to the Ig pre-treated population targeted in this submission (as defined in the response to A20) and there are additional limitations associated with trial design and concomitant treatment which cannot be adjusted for. Thus, the results of ITC versus PATH and ICE should be interpreted with caution.

Despite the limitations highlighted above, the additional ITC analyses indicate that efgartigimod showed significantly greater improvement in I-RODS scores compared to low-dose Hizentra, high-dose Hizentra, Hyqvia, and pooled Ig. No data on I-RODS are available for Gamunex. For MGS scores in the dominant hand, efgartigimod demonstrated comparable or greater improvement to Hizentra and Gamunex, with pooled analyses indicating statistically significant benefits. Efgartigimod showed numerically greater improvement in non-dominant hand MGS compared to Hizentra and Gamunex, with this improvement reaching statistical significance in the pooled Ig analysis (due to increase in sample size by pooling). No data on MGS are

available for Hyqvia. Overall, efgartigimod consistently showed improvement compared with Ig therapies in improving functional outcomes. The detailed methods and results are summarised below.

As reported in the ITC Technical Report submitted with the CS, only five Ig studies included Ig pre-treated patients (ADHERE, ADVANCE-CIDP 1, PATH, PRIMA, Katzberg 2013).^{2,22,26–28} The ICE trial included treatment-naïve patients (who did not receive Ig, corticosteroid, or plasma exchange [PLEX] in the 3 months prior to study entry), however the extension part of the ICE was considered as part of the sensitivity analysis since it included Ig responders from the first and crossover period from the trial (see response to question A17). Among these studies, PRIMA and Katzberg 2013 were excluded due to multiple issues reported in the ITC Technical Report (see Table 17.1 of the ITC Technical Report). Therefore, the MAICs requested as a response to this question were conducted considering available data from ADVANCE-CIDP 1 (Hyqvia), PATH (low-dose and high-dose Hizentra), and ICE extension part (Gamunex). An overview of the feasible analysis is reported in Table 16. I-RODS was not reported in the ICE trial and grip strength was not reported in the ADVANCE CIDP 1 trial. The methods aligned with the anchored MAICs conducted on the change in aINCAT from baseline included in the CS. There are some important limitations associated with these MAICs:

- The PATH publication reports only the median, inter-quartile (IQR) and/or the min/max, and not the mean and SD.²² As discussed in more detail in the response to question A16, estimating the mean and SD from the median, IQR and min/max requires assuming an underlying distribution. This assumption cannot be verified using the available PATH data and may therefore introduce bias. To conduct the MAICs requested in this question, we assumed a Normal distribution to derive the mean and SD for the change in I-RODS and MGS from the reported median and IQR in PATH, using the approach published by Wan et al (2014).²⁹ Any comparison between ADHERE and PATH based on these derived values should therefore be interpreted with caution.
- The eligible population in the ICE study differs from the target population of interest in this submission, namely Ig pre-treated patients. For this reason, only the extension part of the trial was considered in the MAICs. However,

there remains substantial uncertainty about the comparability of the populations: patients in ICE were not receiving treatment with Ig, corticosteroid or PLEX for at least 3 months prior to enrolment, likely indicating a different level of disease burden than the target population in this submission. Unlike ADHERE, there was no run-in period in ICE, introducing heterogeneity that cannot be adjusted for in the MAIC. In addition, it is not clearly reported whether concomitant medications were permitted, which could influence the observed treatment effect. For these reasons, the MAICs between ADHERE and ICE should be interpreted with caution and are unlikely to be fully generalisable to the Ig pre-treated population targeted in this submission.

Table 16: Overview of feasible comparisons between efgartigimod and Ig on the change in I-RODS and change in mean grip strength

ADHERE			Comparator study				
Endpoint	Population	Timeframe	Comparator	Name	Population	Endpoint	Timeframe
Comparisons vs Stage B (Anchored MAIC) – Change from baseline in I-RODS							
Change from baseline Stage B in I-RODS*	Ig pre-treated	Stage B baseline to last assessment up to week 25	Hizentra low-dose	PATH	Ig pre-treated	Change from baseline in I-RODS	Baseline to last post-dose observation (up to week 25)
			Hizentra high-dose				
Change from baseline Stage B in I-RODS	Ig pre-treated	Stage B baseline to last assessment up to week 32	Hyqvia	ADVANCE-CIDP 1	Ig pre-treated	Change from baseline in I-RODS centile score	Baseline to end of study (up to week 32)
Comparisons vs Stage B (Anchored MAIC) – Change from baseline in mean grip strength (dominant hand)							
Change from baseline Stage B in mean grip strength (dominant hand)*	Ig pre-treated	Stage B baseline to last assessment up to week 25	Hizentra low-dose	PATH	Ig pre-treated	Change from baseline in grip strength – dominant hand	Baseline to last post-dose observation (up to week 25)
			Hizentra high-dose				
Change from baseline Stage B in mean grip	Ig pre-treated	Stage B baseline to last assessment up to week 24	Gamunex	ICE	Responded to IVIg during the First Period (treatment	Change from baseline in grip strength –	Baseline to last assessment in the Extension phase (up

strength (dominant hand) †					naïve in >=3 months from study entry)	dominant hand	to 24 weeks)
Comparisons vs Stage B (Anchored MAIC) – Change from baseline in mean grip strength (non-dominant hand)							
Change from baseline Stage B in mean grip strength (non-dominant hand) *	Ig pre-treated	Stage B baseline to last assessment up to week 25	Hizentra low-dose Hizentra high-dose	PATH	Ig pre-treated	Change from baseline in grip strength – non-dominant hand	Baseline to last post-dose observation (up to week 25)
Change from baseline Stage B in mean grip strength (non-dominant hand) †	Ig pre-treated	Stage B baseline to last assessment up to week 24	Gamunex	ICE	Responded to IVIg during the First Period	Change from baseline in grip strength – non-dominant hand	Baseline to last assessment in the Extension phase (up to 24 weeks)

* to be interpreted with caution due to lack of published mean and SE from PATH, thus requiring normality assumptions when estimating these parameters from reported median, IQR and min/max values.

† To be interpreted with caution as it is unlikely to be fully generalisable to the Ig pre-treated population targeted in this submission and there are additional limitations associated with trial design and concomitant treatment which cannot be adjusted for.

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; I-RODS: Inflammatory Rasch-built Disability Scale; Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; IQR: Interquartile range; MAIC: Matching-adjusted indirect comparison; SE: Standard error.

For change from baseline in I-RODS score, efgartigimod was associated with greater improvement than low-dose Hizentra (mean difference= [REDACTED]), high-dose Hizentra ([REDACTED]), Hyqvia ([REDACTED]), and pooled Ig (Hizentra and Hyqvia) ([REDACTED]).

For change from baseline in MGS, efgartigimod was associated with comparable or greater improvement than high-dose Hizentra (dominant: [REDACTED]; non-dominant: [REDACTED] and pooled Ig (dominant: [REDACTED]; non-dominant: [REDACTED]). Efgartigimod had numerically greater improvement compared with low-dose Hizentra (dominant: [REDACTED]; non-dominant: [REDACTED]) and Gamunex (dominant: [REDACTED] non-dominant: [REDACTED]).

A detail presentation of the results is included below for the change in I-RODS and change in MGS (dominant and non-dominant). The relative weights distribution is presented for each analysis.

Results on the change from baseline in I-RODS score

As requested, we included in Table 17 the change in I-RODS score from baseline in the placebo arm of the comparators trials (ADVANCE-CIDP 1 and PATH) and in the placebo arm of ADHERE (stage B), before and after weighting. Please note that the reason why the placebo effect in ADHERE before weighting differs in the comparisons versus the two trials is because patients in ADHERE were selected to match inclusion/exclusion criteria of the comparator trial (see ITC Technical Report).

There is some difference in the I-RODS score change from baseline between ADHERE and the comparator trials and this difference remains even after MAIC weighting, suggesting residual differences in trial design and patient populations, including factors that cannot be fully adjusted for. However, the purpose of the indirect comparison is to estimate the relative treatment effect versus placebo within each trial (efgartigimod versus placebo in ADHERE; SCIg versus placebo in ADVANCE-CIDP 1 and PATH), using randomisation to handle confounding and MAIC weighting to adjust for effect modifiers. Therefore, differences in absolute placebo responses across trials do not compromise the anchored MAIC; instead, they reinforce the need for an anchored, population-adjusted approach focused on the relative treatment effect versus placebo as the relevant estimand for comparing efgartigimod with Ig.

Table 17: Change from baseline in I-RODS in the placebo arm of ADHERE, ADVANCE-CIDP 1 and PATH studies

	Placebo in comparator study	Placebo in ADHERE Stage B	
		Unweighted ^a	Weighted
Change in I-RODS score from baseline, means (SE)			
Comparison vs ADVANCE-CIDP 1	██████████	██████████	██████████
Comparison vs PATH, low-dose Hizentra	██████████	██████████	██████████
Comparison vs high-dose Hizentra	██████████	██████████	██████████

^aAfter selection of patients to meet inclusion/exclusion criteria in ADVANCE-CIDP 1 and PATH studies.

^bThe mean and SE are not reported in the PATH published data. These were therefore calculated based on the sample number, the median and inter-quartile range using the approach published by Wan et al. (2014).²⁹

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; I-RODS: Individualised Rasch-built Overall Disability Scale; SE: Standard error.

Low-dose Hizentra (PATH)

The analysis indicates that efgartigimod was associated with a greater improvement in I-RODS score than low-dose Hizentra up to 25 weeks, with a difference in means (95% CI) of [REDACTED] after weighting (nominal p = [REDACTED]).

Table 18: Efgartigimod versus low-dose Hizentra for change from baseline in I-RODS in CIDP patients pre-treated with Ig.

	Low-dose Hizentra (PATH RCT)	Efgartigimod (ADHERE Stage B)	
		Unweighted*	Weighted†
Endpoint timing	Up to 25 weeks	Last visit up to 25 weeks	
Baseline characteristics‡			
Number/ESS§			
Female, %			
Mean age, years			
Mean disease/diagnosis duration, years			
Mean total INCAT score			
Mean I-RODS			
Mean grip strength (dominant hand)			
Anchored MAIC analyses			
Difference in means (95% CI) vs placebo			
Difference in means (95% CI) for efgartigimod vs Hizentra			
P-value			

Notes: All p-values are nominal.

*Based on restricted ADHERE population to align with comparator study.

†Adjusted for listed baseline characteristics.

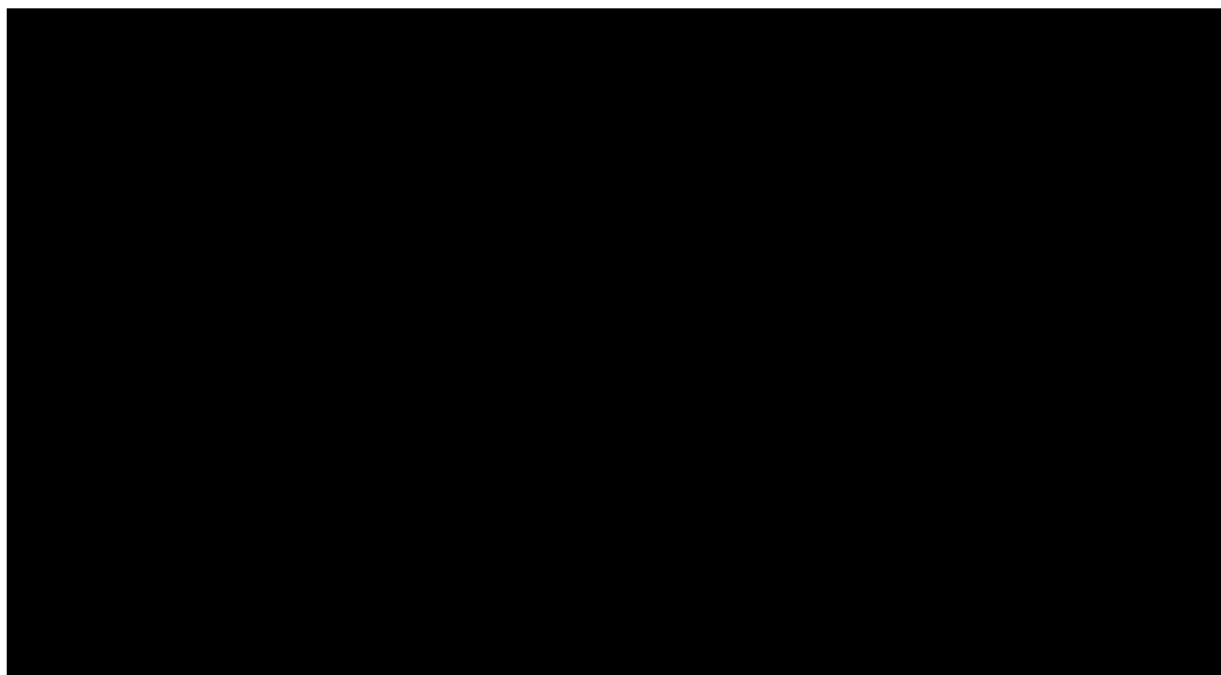
‡These baseline characteristics are limited to the factors that were consistently reported in ADHERE and the comparator study under evaluation.

§ESS is the effective sample size and is shown for the weighted analysis as count (%).

||Estimated using linear regression. A positive score shows improvement in I-RODS.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ESS: Effective sample size; Ig: Immunoglobulin; INCAT: Inflammatory neuropathy cause and treatment disability score; I-RODS: Inflammatory Rasch-built overall disability scale; MAIC: Matching-adjusted indirect comparison; RCT: Randomised controlled trial.

Figure 4: Relative weights distribution in the ITC on the change from baseline in I-RODS ADHERE Stage B versus PATH, low-dose Hizentra



Abbreviations: I-RODS: Inflammatory Rasch-built Overall Disability Scale; ITC: Indirect treatment comparison.

High-dose Hizentra (PATH)

The analysis indicates that efgartigimod was associated with a greater improvement in I-RODS score than high-dose Hizentra up to 25 weeks, with a difference in means of [REDACTED] after weighting (nominal $p = [REDACTED]$).

Table 19: Efgartigimod versus high-dose Hizentra for change from baseline in I-RODS in CIDP patients pre-treated with Ig

	High-dose Hizentra (PATH RCT)	Efgartigimod (ADHERE Stage B)	
		Unweighted*	Weighted†
Endpoint timing	Up to 25 weeks	Last visit up to 25 weeks	
Baseline characteristics‡			
Number/ESS§	████	████	████
Female, %	████	████	████
Mean age, years	████	████	████
Mean disease/diagnosis duration, years	████	████	████
Mean total INCAT score	████	████	████
Mean I-RODS	████	████	████
Mean grip strength (dominant hand)	████	████	████

	High-dose Hizentra (PATH RCT)	Efgartigimod (ADHERE Stage B)	
		Unweighted*	Weighted†
Anchored MAIC analyses			
Difference in means (95% CI) vs placebo ^{ll}			
Difference in means (95% CI) for efgartigimod vs Hizentra	Reference		
P-value			

Notes: All p-values are nominal.

*Based on restricted ADHERE population to align with comparator study.

†Adjusted for listed baseline characteristics.

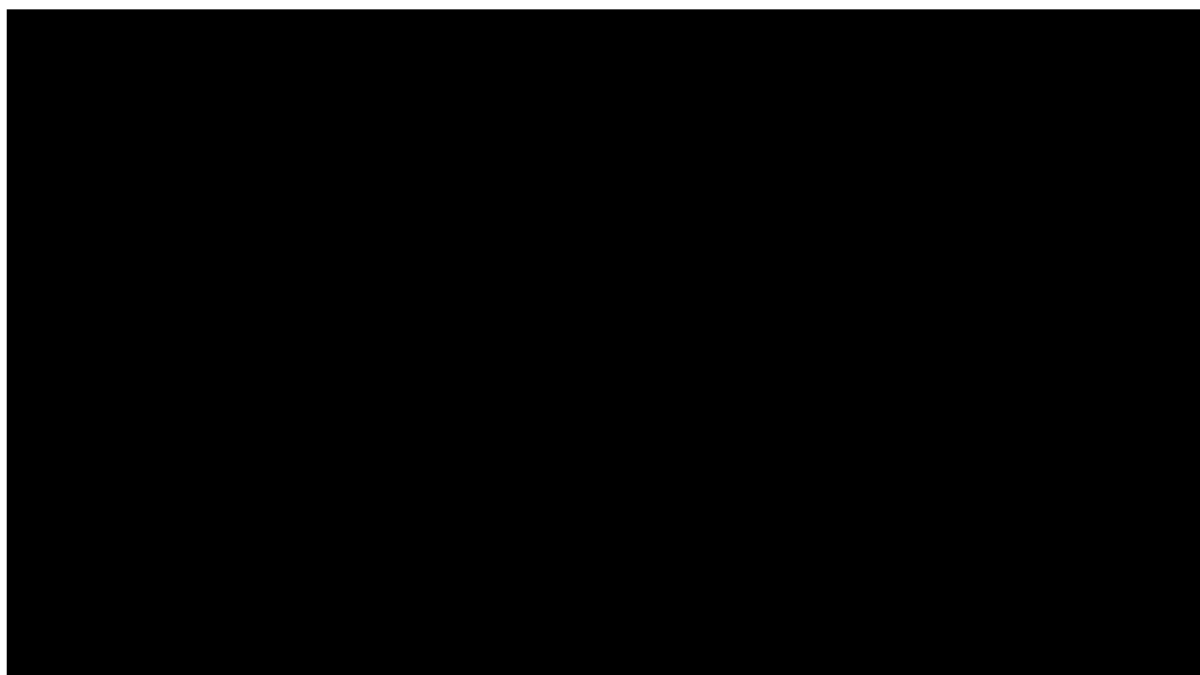
‡These baseline characteristics are limited to the factors that were consistently reported in ADHERE and the comparator study under evaluation.

§ESS is the effective sample size and is shown for the weighted analysis as count (%).

||Estimated using linear regression. A positive score shows improvement in I-RODS.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ESS: Effective sample size; Ig: Immunoglobulin; INCAT: Inflammatory neuropathy cause and treatment disability score; I-RODS: Inflammatory Rasch-built overall disability scale; MAIC: Matching-adjusted indirect comparison; RCT: Randomised controlled trial.

Figure 5: Relative weights distribution in the ITC on the change from baseline in I-RODS ADHERE Stage B versus PATH, high-dose Hizentra



Abbreviations: I-RODS: Inflammatory Rasch-built Overall Disability Scale; ITC: Indirect treatment comparison.

Hyqvia (ADVANCE-CIDP 1)

The analysis indicates that efgartigimod was associated with a greater improvement in I-RODS score than Hyqvia up to 32 weeks, with a difference in means (95% CI) of [REDACTED] after weighting (nominal p = [REDACTED]).

Table 20: Efgartigimod versus Hyqvia for change from baseline in I-RODS in CIDP patients pre-treated with Ig

	Hyqvia (ADVANCE-CIDP 1)		Efgartigimod (ADHERE Stage B)	
			Unweighted*	Weighted†
Endpoint timing	Up to 32 weeks		Last visit up to 32 weeks	
Baseline characteristics‡				
Number/ESS§				
Female, %				
Mean age, years				
Mean disease/diagnosis duration, years				
Mean aINCAT score				
Mean I-RODS				
Mean MRC Sum Score				
Received CS in 6 months before baseline, %				
Anchored MAIC analyses				
Difference in means (95% CI) vs placebo				
Difference in means (95% CI) for efgartigimod vs Hyqvia				
P-value				

Notes: All p-values are nominal.

*Based on restricted ADHERE population to align with comparator study.

†Adjusted for listed baseline characteristics.

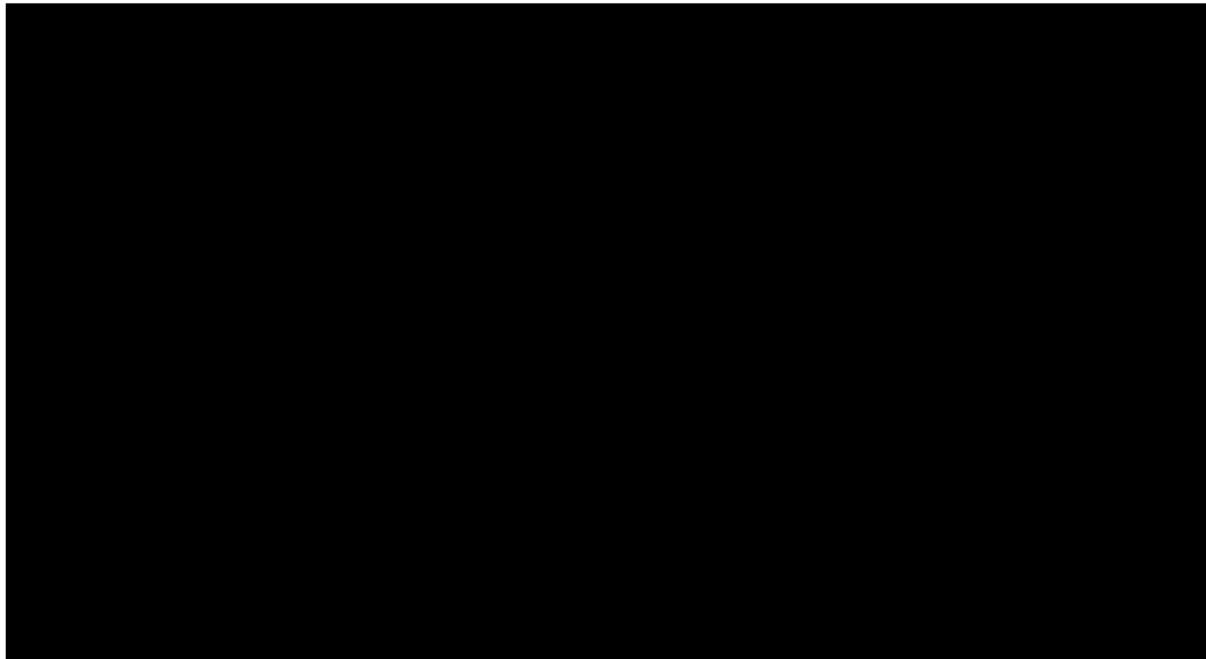
‡These baseline characteristics are limited to the factors that were consistently reported in ADHERE and the comparator study under evaluation.

§ESS is the effective sample size and is shown for the weighted analysis as count (%).

||Estimated using linear regression. A positive score shows improvement in I-RODS.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; CS: Corticosteroids; ESS: Effective sample size; Ig: Immunoglobulin; INCAT: Inflammatory neuropathy cause and treatment disability score; I-RODS: Inflammatory Rasch-built overall disability scale; MAIC: Matching-adjusted indirect comparison; RCT: Randomised controlled trial.

Figure 6: Relative weights distribution in the ITC on the change from baseline in I-RODS ADHERE Stage B versus ADVANCE-CIDP 1

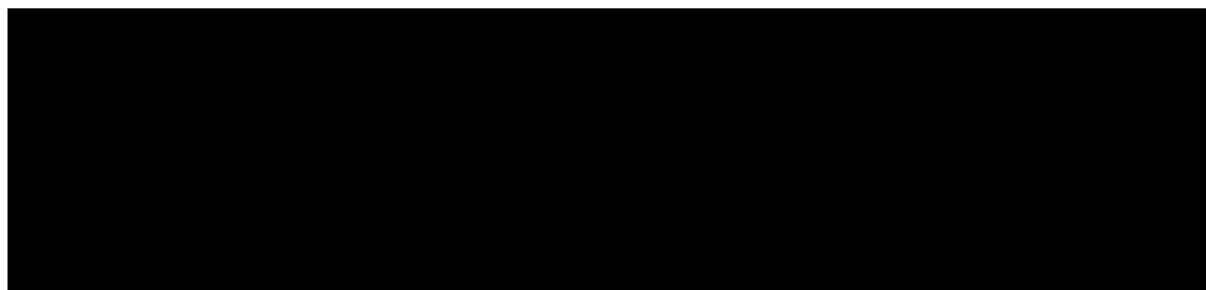


Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; I-RODS: Inflammatory Rasch-built Overall Disability Scale; ITC: Indirect treatment comparison.

Meta-analysis results (Change from baseline in I-RODS)

Figure 7 combines the MAIC results on the change from baseline in I-RODS for efgartigimod versus low-dose Hizentra, high-dose Hizentra and Hyqvia. The pooled difference in means indicates that efgartigimod was associated with a greater improvement in I-RODS score than SCIg (difference in means [95% CI] = [REDACTED]; nominal $p < [REDACTED]$).

Figure 7: Efgartigimod (ADHERE Stage B) versus pooled Hizentra (PATH) and Hyqvia (ADVANCE-CIDP 1) for change from baseline in I-RODS in CIDP patients pre-treated with Ig



Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; I-RODS: Inflammatory Rasch-built Overall Disability Scale; ITC: Indirect treatment comparison.

Results on the change from baseline in mean grip strength (dominant hand)

As requested, Table 21 presents the change in MGS (dominant and non-dominant hand separately) from baseline in the placebo arm of the PATH study and in the placebo arm of ADHERE (Stage B), before and after weighting.

There is some difference in the MGS change from baseline between ADHERE and the PATH and this difference appears to increase after MAIC weighting, suggesting residual differences in trial design and patient populations, including factors that cannot be fully adjusted for. However, the purpose of the indirect comparison is to estimate the relative treatment effect in terms of MGC change from baseline versus placebo within each trial (efgartigimod versus placebo in ADHERE; SCIg versus placebo in PATH). Therefore, differences in absolute placebo responses across trials do not compromise the anchored MAIC. As highlighted previously as part of this response, mean and SE on the MGS change from baseline in PATH study are not published. Thus, we estimated these parameters based on published median and IQR. For this reason, the results of these comparisons should be interpreted with caution.

Table 21: Change from baseline in MGS in the placebo arm of ADHERE and PATH studies

	Placebo in comparator study	Placebo in ADHERE Stage B	
		Unweighted*	Weighted
Change in MGS dominant hand from baseline, means (SE)			
Comparison vs PATH, low-dose Hizentra	-9.3 (2.206) [†]	██████	██████
Comparison vs high-dose Hizentra	-9.3 (2.206) [†]	██████	██████
Change in MGS non-dominant hand from baseline, means (SE)			
Comparison vs PATH, low-dose Hizentra	-10.4 (2.659) [†]	██████	██████
Comparison vs high-dose Hizentra	-10.4 (2.659) [†]	██████	██████

* after selection of patients to meet inclusion/exclusion criteria in PATH study.

† The mean and SE are not reported in the PATH published data. These were therefore calculated based on the sample number, the median and inter-quartile range using the approach published by Wan et al. (2014).²⁹ Abbreviations: SE: Standard error.

Abbreviations: MGS: Mean grip strength; SE: Standard error.

Low-dose Hizentra (PATH)

The change from baseline in MGS in the dominant hand up to 25 weeks was numerically greater for efgartigimod than in low-dose Hizentra.

Table 22: Efgartigimod versus low-dose Hizentra for change from baseline in mean grip strength (dominant hand) in CIDP patients pre-treated with Ig

	Low-dose Hizentra (PATH RCT)	Efgartigimod (ADHERE Stage B)	
		Unweighted*	Weighted†
Endpoint timing	Up to 25 weeks	Last visit up to 25 weeks	
Baseline characteristics‡			
Number/ESS§	████████	████████	████████
Female, %	████████	████████	████████
Mean age, years	████████	████████	████████
Mean disease/diagnosis duration, years	████████	████████	████████
Mean total INCAT score	████████	████████	████████
Mean I-RODS	████████	████████	████████
Mean grip strength (dominant hand)	████████	████████	████████
Anchored MAIC analyses			
Difference in means (95% CI) vs placebo	████████	████████	████████
Difference in means (95% CI) for efgartigimod vs Hizentra	Reference	████████	████████
P-value	-	████████	████████

Notes: All p-values are nominal.

*Based on restricted ADHERE population to align with comparator study.

†Adjusted for listed baseline characteristics.

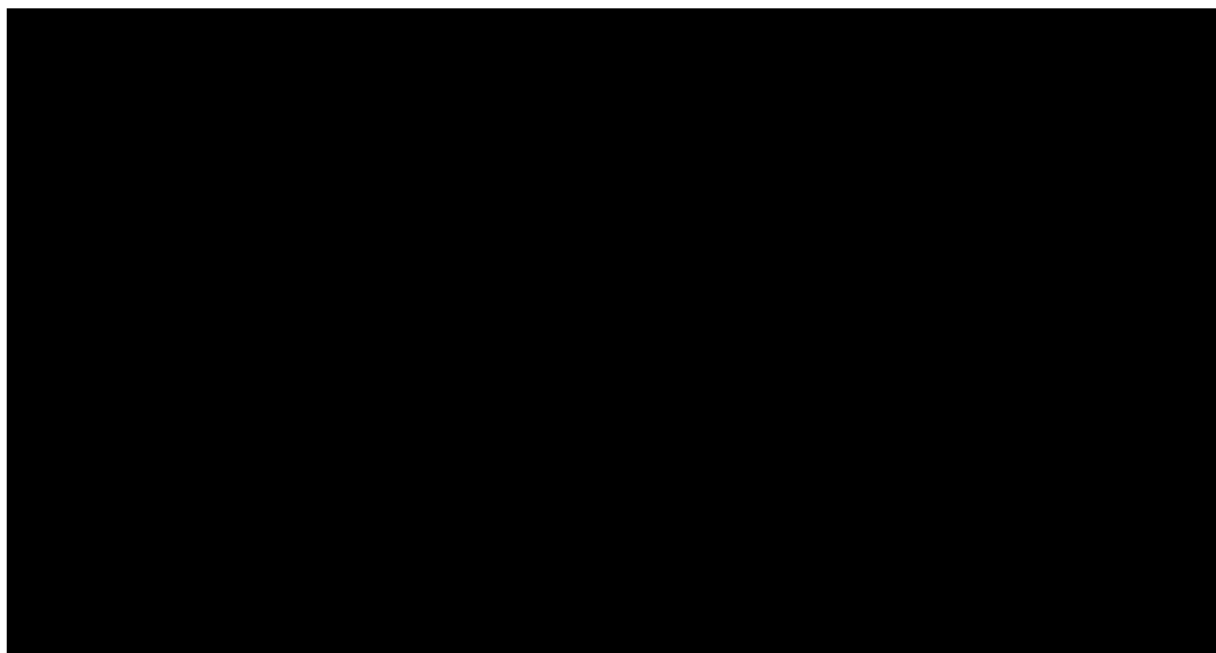
‡These baseline characteristics are limited to the factors that were consistently reported in ADHERE and the comparator study under evaluation.

§ESS is the effective sample size and is shown for the weighted analysis as count (%).

||Estimated using linear regression. A positive score shows improvement in mean grip strength.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ESS: Effective sample size; Ig: Immunoglobulin; INCAT: Inflammatory neuropathy cause and treatment disability score; I-RODS: Inflammatory Rasch-built overall disability scale; MAIC: Matching-adjusted indirect comparison; RCT: Randomised controlled trial.

Figure 8: Relative weights distribution in the ITC on the change from baseline in mean grip strength (dominant hand) ADHERE Stage B versus PATH, low-dose Hizentra



Abbreviations: ITC: Indirect treatment comparison.

High-dose Hizentra (PATH)

The analysis indicates that efgartigimod was associated with a greater improvement in MGS (dominant hand) than high-dose Hizentra up to 25 weeks, with a difference in means (95% CI) of [REDACTED] in weighted analyses (nominal p=[REDACTED]).

Table 23: Efgartigimod versus high-dose Hizentra for change from baseline in mean grip strength (dominant hand) in CIDP patients pre-treated with I

	High-dose Hizentra (PATH RCT)	Efgartigimod (ADHERE Stage B)			
		Unweighted*		Weighted†	
Endpoint timing	Up to 25 weeks	Last visit up to 25 weeks			
Baseline characteristics‡					
Number/ESS§					
Female, %					
Mean age, years					
Mean disease/diagnosis duration, years					
Mean total INCAT score					
Mean I-RODS					
Mean grip strength (dominant hand)					

	High-dose Hizentra (PATH RCT)	Efgartigimod (ADHERE Stage B)	
		Unweighted*	Weighted†
Anchored MAIC analyses			
Difference in means (95% CI) vs placebo ^{ll}			
Difference in means (95% CI) for efgartigimod vs Hizentra	Reference		
P-value	-		

Notes: All p-values are nominal.

*Based on restricted ADHERE population to align with comparator study.

†Adjusted for listed baseline characteristics.

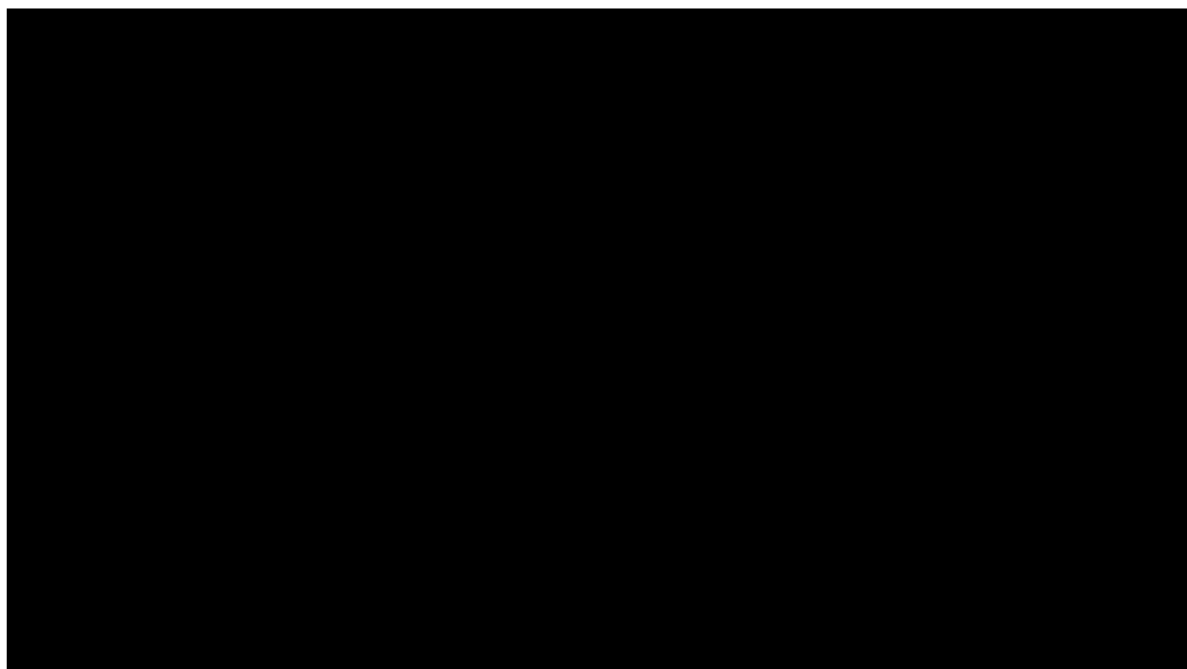
‡These baseline characteristics are limited to the factors that were consistently reported in ADHERE and the comparator study under evaluation.

§ESS is the effective sample size and is shown for the weighted analysis as count (%).

||Estimated using linear regression. A positive score shows improvement in mean grip strength.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ESS: Effective sample size; Ig: Immunoglobulin; INCAT: Inflammatory neuropathy cause and treatment disability score; I-RODS: Inflammatory Rasch-built overall disability scale; MAIC: Matching-adjusted indirect comparison; RCT: Randomised controlled trial.

Figure 9: Relative weights distribution in the ITC on the change from baseline in mean grip strength (dominant hand) ADHERE Stage B versus PATH, high-dose Hizentra



Abbreviations: ITC: Indirect treatment comparison.

Gamunex (ICE)

The change from baseline in MGS in the dominant hand up to 24 weeks was comparable between efgartigimod and Gamunex.

Table 24: Efgartigimod versus Gamunex for change from baseline in mean grip strength (dominant hand) in CIDP patients who responded to IVIg in the First Period

	Gamunex (ICE RCT)	Efgartigimod (ADHERE Stage B)	
		Unweighted*	Weighted†
Endpoint timing	Up to 24 weeks	Last visit up to 24 weeks	
Baseline characteristics‡			
Number/ESS§	████████	████████	████████
Mean aINCAT score	████████	████████	████████
Anchored MAIC analyses			
Difference in means (95% CI) vs placebo	████████	████████	████████
Difference in means (95% CI) for efgartigimod vs Gamunex	Reference	████████	████████
P-value	-	████████	████████

Notes: All p-values are nominal.

*Based on restricted ADHERE population to align with comparator study.

†Adjusted for listed baseline characteristics.

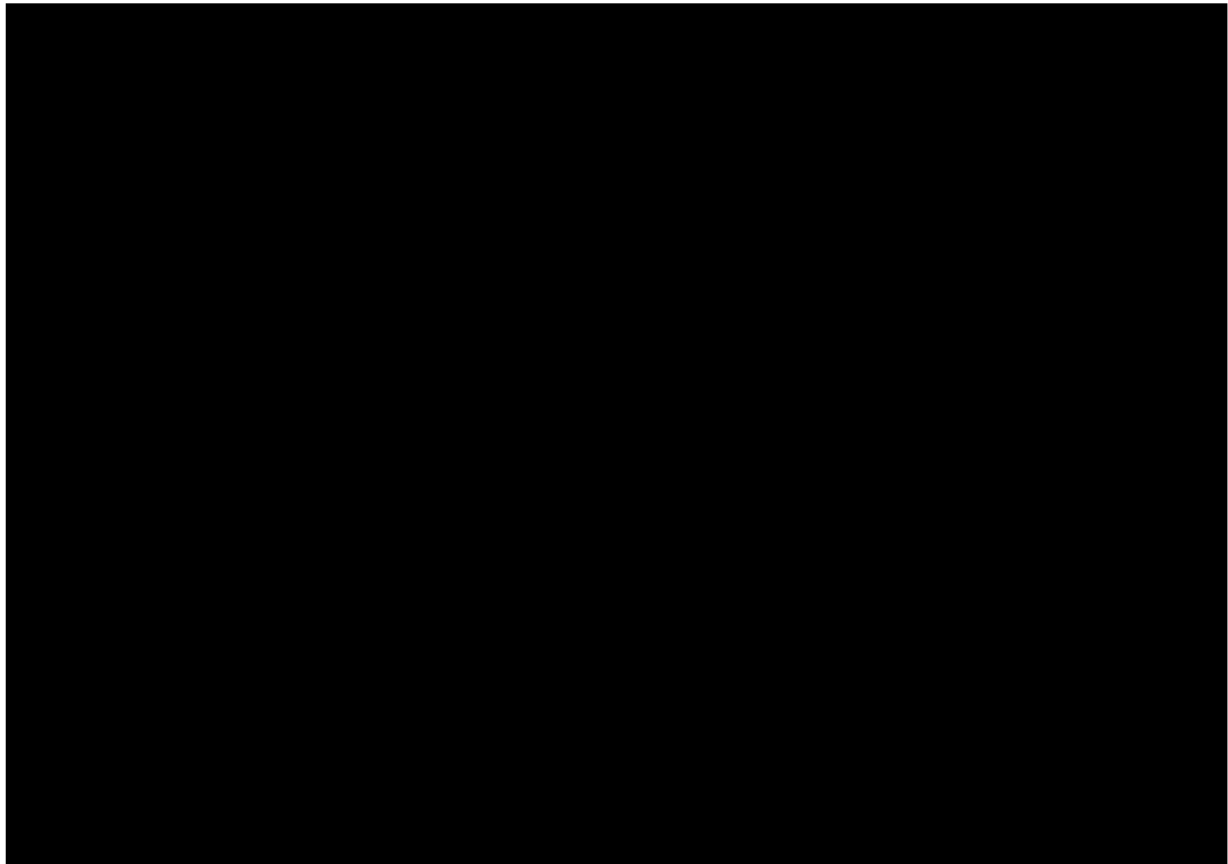
‡These baseline characteristics are limited to the factors that were consistently reported in ADHERE and the comparator study under evaluation.

§ESS is the effective sample size and is shown for the weighted analysis as count (%).

||Estimated using linear regression. A positive score shows improvement in mean grip strength.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ESS: Effective sample size; Ig: Immunoglobulin; INCAT: Inflammatory neuropathy cause and treatment disability score; I-RODS: Inflammatory Rasch-built overall disability scale; MAIC: Matching-adjusted indirect comparison; RCT: Randomised controlled trial.

Figure 10: Relative weights distribution in the ITC on the change from baseline in mean grip strength (dominant hand) ADHERE Stage B versus ICE extension part

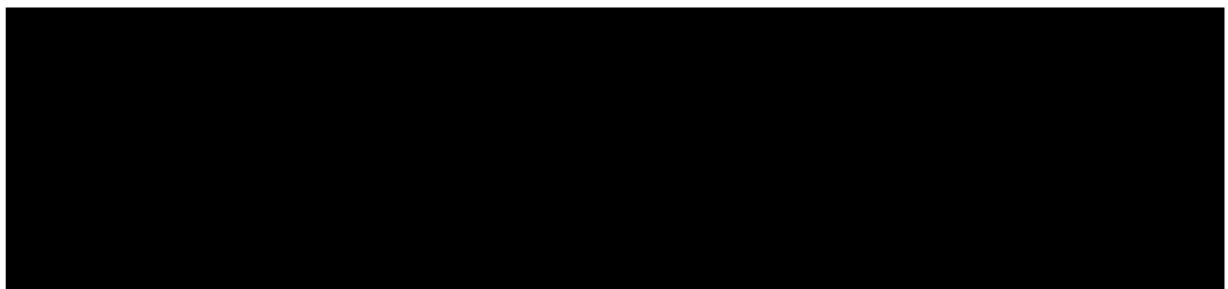


Abbreviations: ITC: Indirect treatment comparison.

Meta-analysis results

Figure 11 combines the MAIC results for the analysed Igs (Hizentra, Gamunex). The pooled difference in means indicates that efgartigimod was associated with a greater improvement from baseline in MGS of the dominant hand than Ig (difference in means [95% CI] = ██████████ nominal p = ████████).

Figure 11: Efgartigimod (ADHERE Stage B) versus Hizentra (PATH) and Gamunex (ICE extension part) for change from baseline in mean grip strength (dominant hand) in CIDP patients who were pre-treated with Ig.



Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; Ig: Immunoglobulin.

Results on the change from baseline in mean grip strength (non-dominant hand)

Low-dose Hizentra (PATH)

The change from baseline in MGS in the non-dominant hand up to 25 weeks was comparable between efgartigimod and low-dose Hizentra.

Table 25: Efgartigimod versus low-dose Hizentra for change from baseline in mean grip strength (non-dominant hand) in CIDP patients pre-treated with Ig

	Low-dose Hizentra (PATH RCT)		Efgartigimod (ADHERE Stage B)	
			Unweighted*	Weighted†
Endpoint timing	Up to 25 weeks		Last visit up to 25 weeks	
Baseline characteristics‡				
Number/ESS§				
Female, %				
Mean age, years				
Mean disease/diagnosis duration, years				
Mean total INCAT score				
Mean I-RODS				
Mean grip strength (dominant hand)				
Anchored MAIC analyses				
Difference in means (95% CI) vs placebo¶				
Difference in means (95% CI) for efgartigimod vs Hizentra	Reference			
P-value	-			

Notes: All p-values are nominal.

*Based on restricted ADHERE population to align with comparator study.

†Adjusted for listed baseline characteristics.

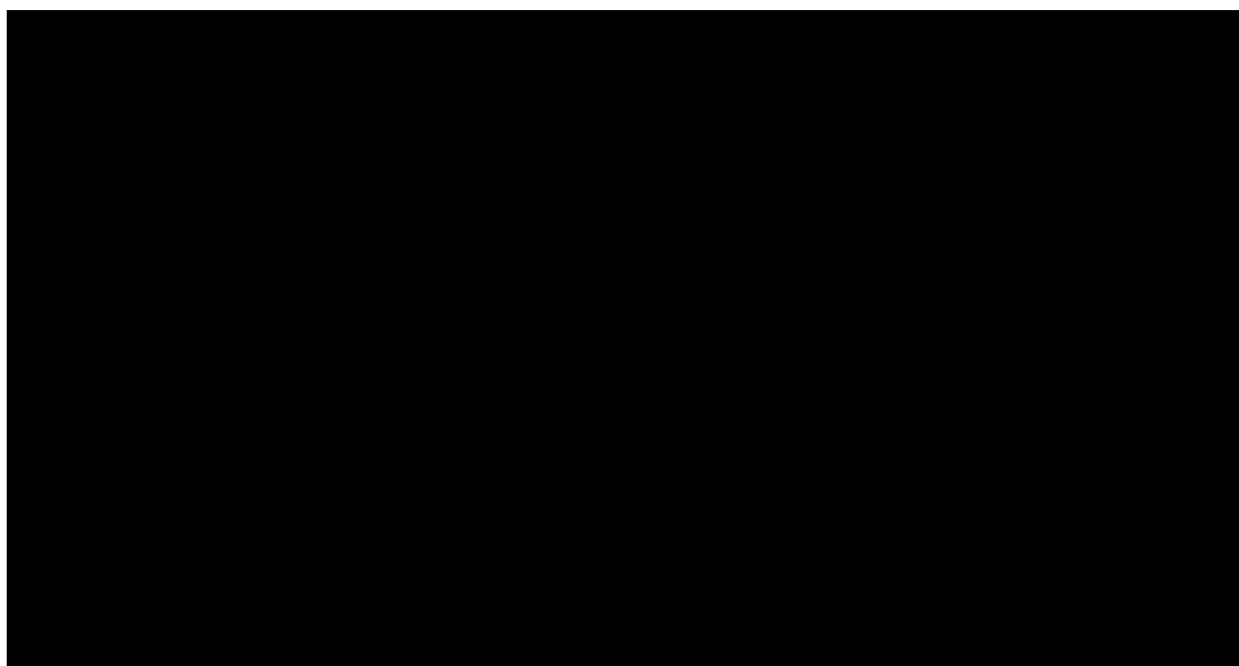
‡These baseline characteristics are limited to the factors that were consistently reported in ADHERE and the comparator study under evaluation.

§ESS is the effective sample size and is shown for the weighted analysis as count (%).

||Estimated using linear regression. A positive score shows improvement in mean grip strength.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ESS: Effective sample size; Ig: Immunoglobulin; INCAT: Inflammatory neuropathy cause and treatment disability score; I-RODS: Inflammatory Rasch-built overall disability scale; MAIC: Matching-adjusted indirect comparison; RCT: Randomised controlled trial.

Figure 12: Relative weights distribution in the ITC on the change from baseline in mean grip strength (non-dominant hand) ADHERE Stage B versus PATH, low-dose Hizentra



Abbreviations: ITC: Indirect treatment comparison.

High-dose Hizentra (PATH)

The change from baseline in MGS in the non-dominant hand up to 25 weeks was comparable between efgartigimod and high-dose Hizentra.

Table 26: Efgartigimod versus high-dose Hizentra for change from baseline in mean grip strength (non-dominant hand) in CIDP patients pre-treated with Ig

	High-dose Hizentra (PATH RCT)	Efgartigimod (ADHERE Stage B)			
		Unweighted ^a		Weighted ^b	
Endpoint timing	Up to 25 weeks	Last visit up to 25 weeks			
Baseline characteristics ^c					
Number/ESS ^d					
Female, %					
Mean age, years					
Mean disease/diagnosis duration, years					
Mean total INCAT score					
Mean I-RODS					
Mean grip strength (dominant hand)					

	High-dose Hizentra (PATH RCT)	Efgartigimod (ADHERE Stage B)	
		Unweighted ^a	Weighted ^b
Anchored MAIC analyses			
Difference in means (95% CI) vs placebo ^e			
Difference in means (95% CI) for efgartigimod vs Hizentra	Reference		
P-value	-		

Notes: All p-values are nominal.

*Based on restricted ADHERE population to align with comparator study.

†Adjusted for listed baseline characteristics.

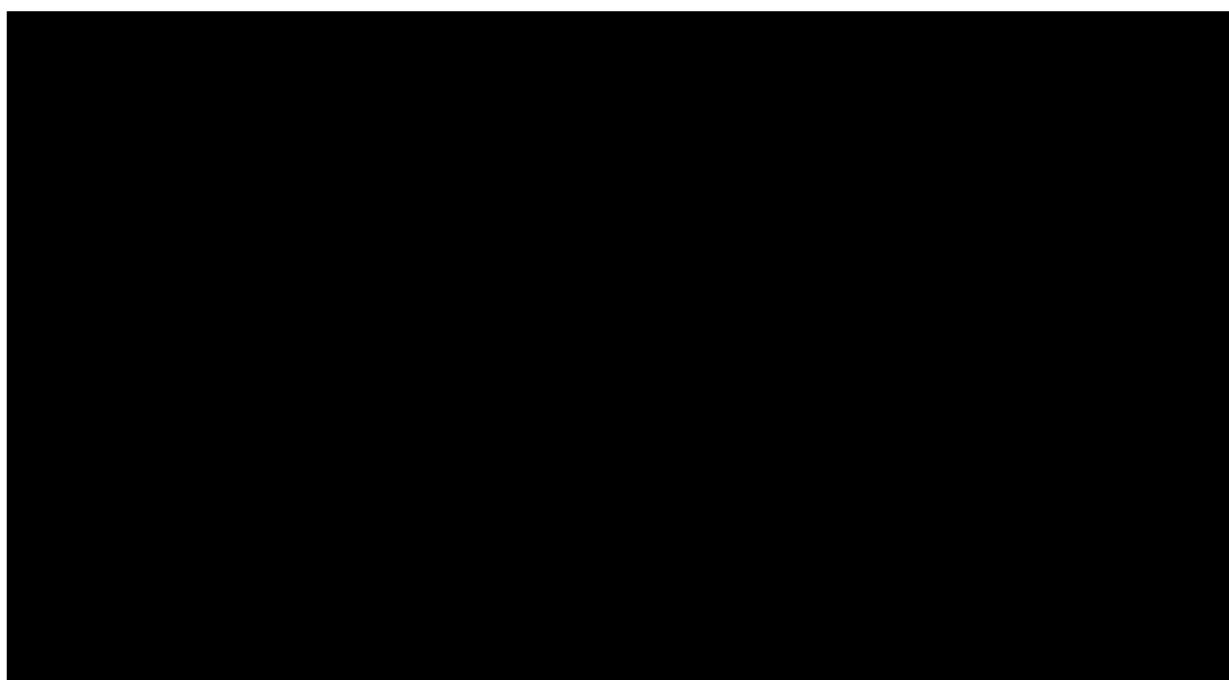
‡These baseline characteristics are limited to the factors that were consistently reported in ADHERE and the comparator study under evaluation.

§ESS is the effective sample size and is shown for the weighted analysis as count (%).

||Estimated using linear regression. A positive score shows improvement in mean grip strength.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ESS: Effective sample size; Ig: Immunoglobulin; INCAT: Inflammatory neuropathy cause and treatment disability score; I-RODS: Inflammatory Rasch-built overall disability scale; MAIC: Matching-adjusted indirect comparison; RCT: Randomised controlled trial.

Figure 13: Relative weights distribution in the ITC on the change from baseline in mean grip strength (non-dominant hand) ADHERE Stage B versus PATH, high-dose Hizentra



Abbreviations: ITC: Indirect treatment comparison.

Gamunex (ICE)

The change from baseline in MGS in the non-dominant hand up to 24 weeks was comparable between efgartigimod and Gamunex.

Table 27: Efgartigimod versus Gamunex for change from baseline in mean grip strength (non-dominant hand) in CIDP patients who responded to IVIg in the First Period

	Gamunex (ICE RCT)	Efgartigimod (ADHERE Stage B)	
		Unweighted*	Weighted†
Endpoint timing	Up to 24 weeks	Last visit up to 24 weeks	
Baseline characteristics§			
Number/ESS§			
Mean aINCAT score			
Anchored MAIC analyses			
Difference in means (95% CI) vs placebo ^{ll}			
Difference in means (95% CI) for efgartigimod vs Gamunex	Reference		
P-value	-		

Notes: All p-values are nominal.

*Based on restricted ADHERE population to align with comparator study.

†Adjusted for listed baseline characteristics.

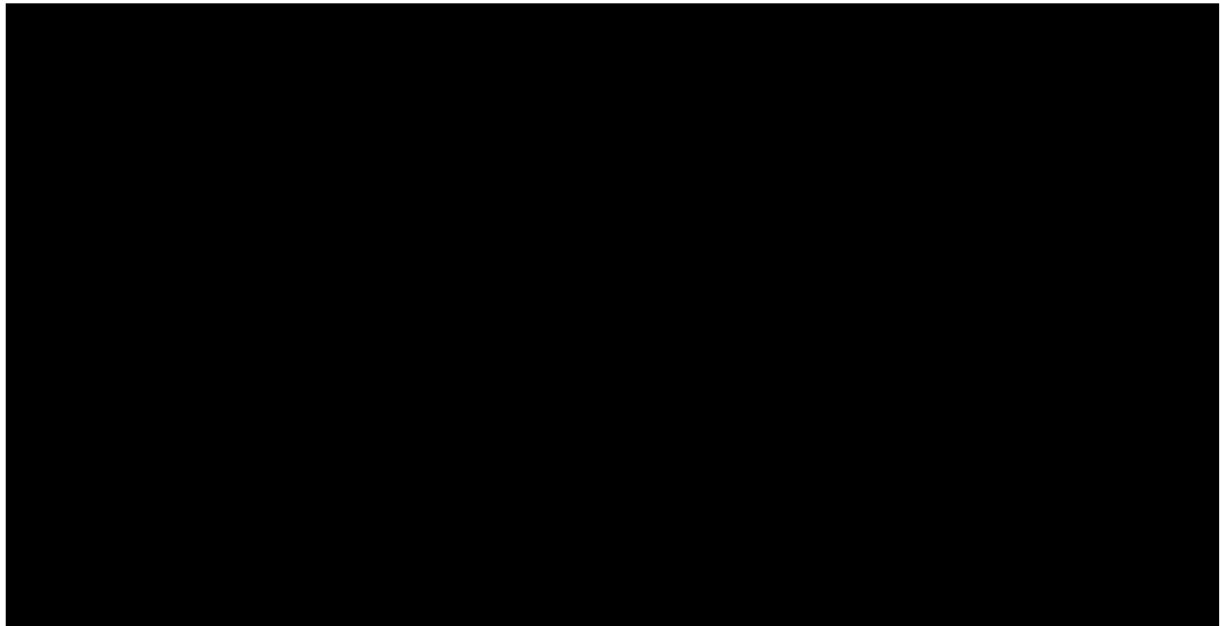
‡These baseline characteristics are limited to the factors that were consistently reported in ADHERE and the comparator study under evaluation.

§ESS is the effective sample size and is shown for the weighted analysis as count (%).

||Estimated using linear regression. A positive score shows improvement in mean grip strength.

Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ESS: Effective sample size; Ig: Immunoglobulin; INCAT: Inflammatory neuropathy cause and treatment disability score; I-RODS: Inflammatory Rasch-built overall disability scale; MAIC: Matching-adjusted indirect comparison; RCT: Randomised controlled trial.

Figure 14: Relative weights distribution in the ITC on the change from baseline in mean grip strength (dominant hand) ADHERE Stage B versus ICE extension part

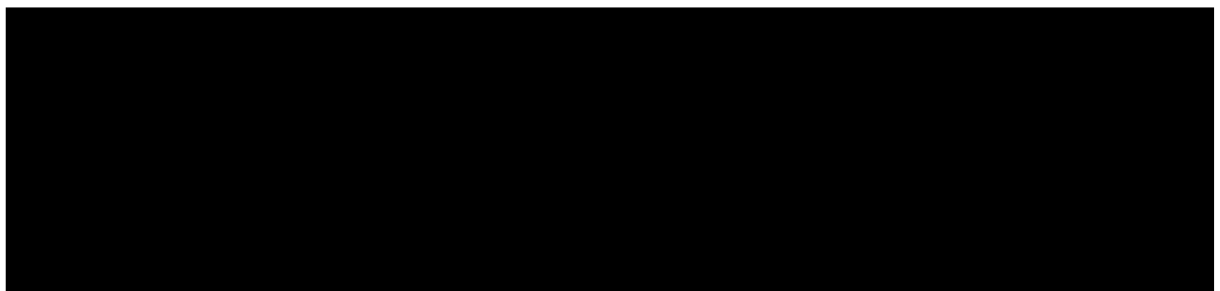


Abbreviations: ITC: Indirect treatment comparison.

Meta-analysis results

Figure 15 combines the MAIC results for the analysed Ig products (Hizentra, Gamunex). The pooled difference in means indicates that efgartigimod was associated with a greater improvement from baseline in MGS of the non-dominant hand than Ig (difference in means [95% CI] = [REDACTED] nominal p = [REDACTED]).

Figure 15: Efgartigimod (ADHERE Stage B) versus Ig (Hizentra [PATH] and Gamunex [ICE]) for change from baseline in mean grip strength (non-dominant hand) in CIDP patients pre-treated with Ig



Abbreviations: CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; Ig: Immunoglobulin.

In summary, within data limitations and acknowledging residual uncertainty, the anchored MAICs consistently show that efgartigimod achieves at least comparable, and in many cases greater, improvements in functional outcomes (I-RODS and MGS) than the evaluated Ig maintenance regimens in Ig-responsive CIDP. Taken

together, these results support the clinical plausibility of efgartigimod as an alternative to current Ig-based maintenance treatment in the target population.

A16. Priority question: The EAG notes that Sections 20.1.1.1.1 and 20.1.1.1.2 of the ITC Technical Report appear to provide a comparison between mean change from baseline in aINCAT between the PATH trial and ADHERE. However, Table 17-1 in the ITC technical report states that PATH is excluded from comparisons because only the median is reported for aINCAT:

- a) Please clarify if Sections 20.1.1.1.1 and 20.1.1.1.2 are comparing mean change from baseline in aINCAT;**
- b) If mean aINCAT scores are available from the PATH trial, please perform an anchored MAIC between ADHERE and PATH. Please provide information on the relative weight distributions (as provided in Appendix 8 of the ITC Technical Report) and the results from the adjusted placebo group of any comparator studies, as requested in question A13.**

(a) In the PATH publication, only median, IQR and min/max for the change in aINCAT are reported, and not the mean value and the SD.²² Estimating mean and SD from the median requires assuming an underlying distribution (typically Normal and symmetric), but this assumption cannot be verified with the available PATH data. If the true distribution of change in aINCAT is skewed, the derived “mean” will systematically differ from the true mean, and the relationship between dispersion measures (i.e. IQR) and the SD will also be distorted. As a result, the reconstructed mean and SD may be biased, particularly for the SD, which is highly sensitive to violations of the Normality assumption; this is why the ITC comparing ADHERE and the PATH study was not included in the base case ITC.

(b) As sensitivity analysis we derived approximate means and SD from the reported median and min/max aINCAT change from baseline using the approach published by Wan et al. (2014)²⁹, and then performed anchored MAICs between ADHERE and PATH. Two separate MAICs were conducted, consistent with the trial reporting, for low-dose Hizentra, and high-dose Hizentra. The results of these MAICs are presented in the Appendix of the ITC Technical Report submitted with the CS. The difference in mean change from baseline in aINCAT between efgartigimod and pooled high-dose and low-dose Hizentra is [REDACTED]

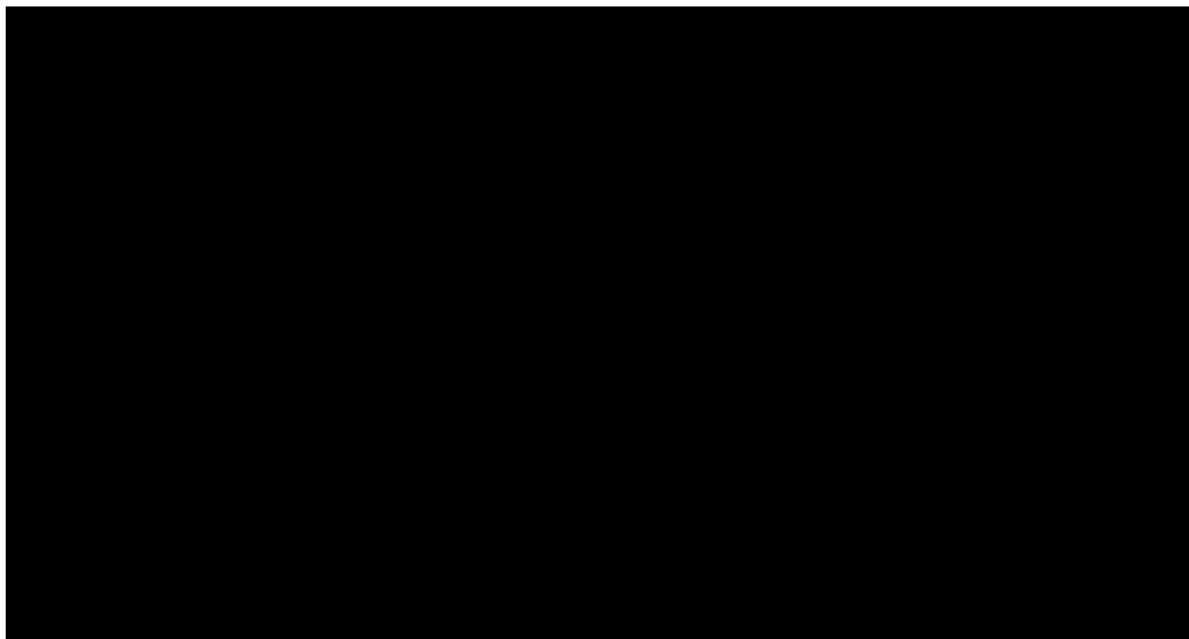
[REDACTED]. As requested, Figure 16 and Figure 17

presents the relative weights distribution for the ITC on aINCAT change from baseline versus PATH low-dose and high-dose Hizentra, respectively.

When pooling the MAIC results across efgartigimod versus Hizentra (low-dose and high-dose) from PATH and Hyqvia from ADVANCE-CIDP 1, the pooled difference in mean change from baseline in aINCAT (efgartigimod versus pooled Ig) was [REDACTED]

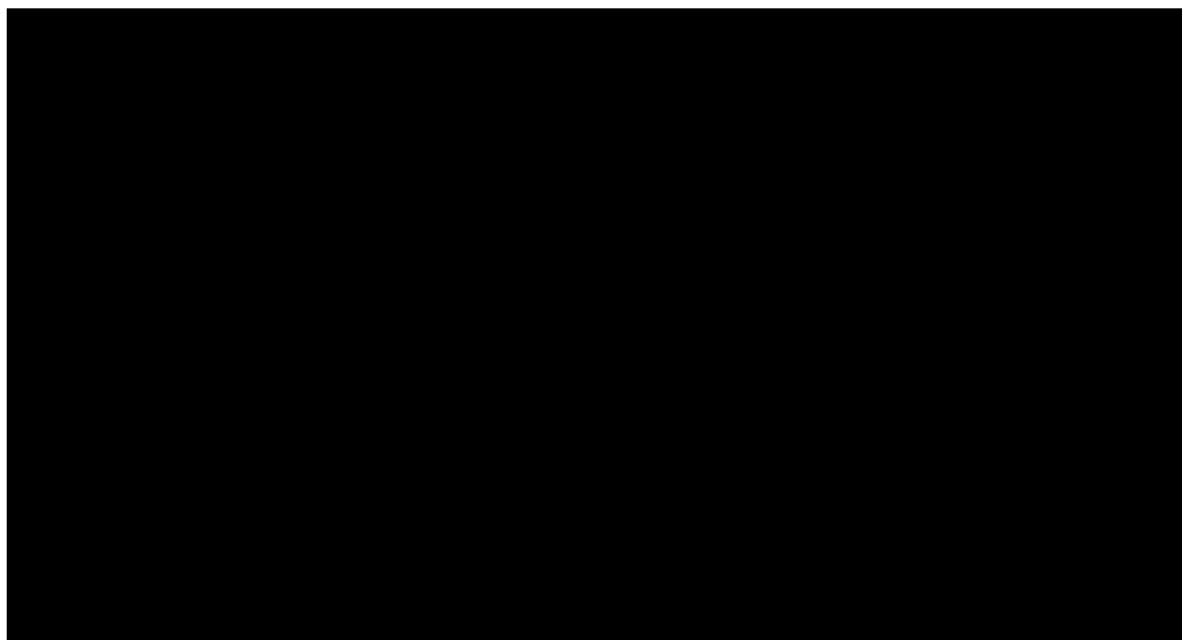
Given the need to approximate mean values from median and min/max values under the assumption of Normality, these PATH-based MAICs were retained as supportive sensitivity analyses rather than being incorporated into the base-case ITC used in the cost-effectiveness model.

Figure 16: Relative weights distribution in the ITC on the change from baseline in aINCAT ADHERE Stage B versus PATH, low-dose Hizentra



Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; ITC: Indirect treatment comparison.

Figure 17: Relative weights distribution in the ITC on the change from baseline in aINCAT ADHERE Stage B versus PATH, high-dose Hizentra



Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; ITC: Indirect treatment comparison.

Table 28 presents the change in aINCAT from baseline in the placebo arm of the PATH study and in the placebo arm of ADHERE (stage B), before and after weighting.

There is some small difference in the aINCAT change from baseline between ADHERE and the PATH and this difference persists after MAIC weighting, however it is not significant. Moreover, the purpose of the indirect comparison is to estimate the relative treatment effect in terms of aINCAT change from baseline versus placebo within each trial. Therefore, differences in absolute placebo responses across trials do not compromise the anchored MAIC. Nonetheless, there are limitations related with the approximation of mean and SD for the PATH study, which suggest the results of these MAICs should be interpreted with caution.

Table 28: Change from baseline in aINCAT in the placebo arm of ADHERE and PATH studies

	Placebo in comparator study	Placebo in ADHERE Stage B	
		Unweighted*	Weighted
Change in aINCAT from baseline, means (SE)			
Comparison vs PATH, low-dose Hizentra	1.3 (0.144) [†]		
Comparison vs high-dose Hizentra	1.3 (0.144) [†]		

* after selection of patients to meet inclusion/exclusion criteria in the PATH study.

† The mean and SE are not reported in the PATH published data. These were therefore calculated based on the sample number, the median and min/max using the approach published by Wan et al. (2014).²⁹

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; SE: Standard error.

A17. Priority question: The sensitivity analyses reported for the ITCs include a comparison against Gamunex from the ICE trial (Section 20.1.1.1.4 of the ITC Technical Report).

- a) Please clarify why the ICE trial was not included in the company's ITC.
- b) Please perform an anchored MAIC between ADHERE and the first period (prior to the crossover period) of the ICE trial. Please provide information on the relative weight distributions (as provided in Appendix 8 of the ITC Technical Report) and the results from the adjusted placebo group of any comparator studies, as requested in question A13.

(a) The ICE trial was not included in the main ITC for the following reasons:

- In ICE, patients entered a double-blind first period, and non-responders crossed over to the alternative treatment after the early assessment (Week 6). By contrast, in ADHERE, patients left Stage A when they achieved ECI, and responders subsequently entered Stage B (randomised withdrawal). As a result, the populations remaining under observation and the reasons for leaving the first treatment period are fundamentally different between the two trials (non-responders in ICE versus responders in ADHERE), making it impossible to compare the outcomes.
- The ICE trial included patients who did not receive treatment with IVIg, corticosteroids, or PLEX in the 3 months prior to study entry. Thus, not aligned with the Ig pre-treated target population.

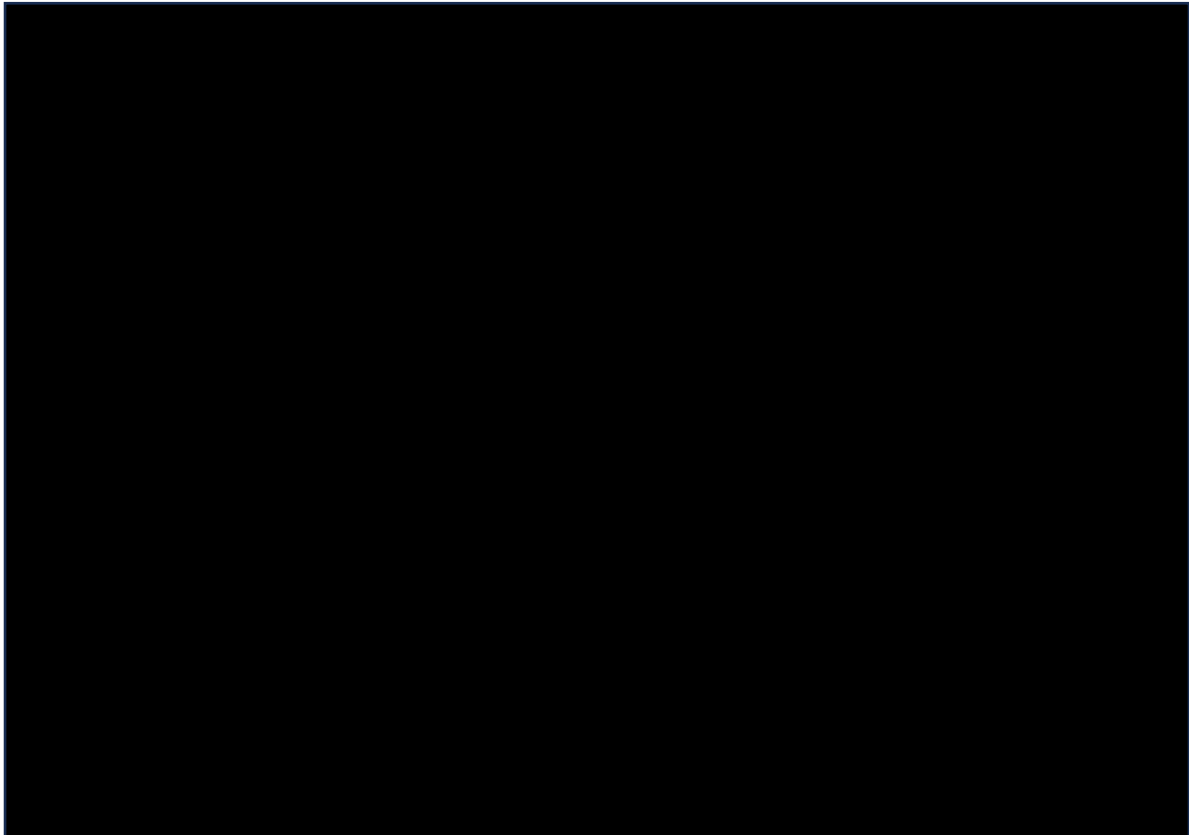
(b) As outlined above in part (a), an anchored MAIC between ADHERE and the first period of ICE is not feasible. Nevertheless, to explore the potential impact of including the ICE study, we conducted a sensitivity analysis in which an ITC was performed between ADHERE Stage B and the extension phase of ICE. The extension phase included IVIg responders from both the first and crossover periods. As noted in your question, the results of this ITC were included in the Appendix of the ITC report provided as part of the CS. This analysis has two important limitations: 1) the population in the trial was treatment-naïve, and for this reason, there was no run-in period analogous to the ADHERE study, and 2) it is not clearly reported whether concomitant medications were permitted, which could influence the observed treatment effect. As requested, Figure 18 presents the relative weights distribution (not included in the ITC report previously submitted).

Under these caveats, when the ICE extension data are included, the ITC results for efgartigimod versus Ig are:

- Efgartigimod versus pooled Hizentra (PATH), Hyqvia (ADVANCE-CIDP 1), and Gamunex (ICE extension part): [REDACTED], nominal [REDACTED].

- Efgartigimod versus pooled Hyqvia (ADVANCE-CIDP 1) and Gamunex (ICE extension part): [REDACTED]

Figure 18: Relative weights distribution in the ITC on the change from baseline in aINCAT ADHERE Stage B versus ICE extension part



Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; ITC: Indirect treatment comparison.

Table 29 presents the change in aINCAT from baseline in the placebo arm of the ICE study and in the placebo arm of ADHERE (stage B), before and after weighting.

There is some small difference in the aINCAT change from baseline between ADHERE and the ICE and this difference increases after MAIC weighting, however it is not significant. Moreover, the purpose of the indirect comparison is to estimate the relative treatment effect in terms of aINCAT change from baseline versus placebo within each trial. Therefore, differences in absolute placebo responses across trials do not compromise the anchored MAIC.

Table 29: Change from baseline in aINCAT in the placebo arm of ADHERE and ICE studies

	Placebo in comparator study	Placebo in ADHERE Stage B	
		Unweighted*	Weighted
Change in aINCAT from baseline, means (SD)			
Comparison vs ICE	0.4 (1.7)		

* after selection of patients to meet inclusion/exclusion criteria in the ICE study.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score; SE: Standard error.

Adverse events

A18. Please provide a breakdown of the SAEs and Grade 3 or higher AEs experienced by patients in ADHERE in:

- a) The efgartigimod arm;
- b) The placebo arm.

(a) Table 30 presents the treatment-emergent adverse events of serious or Grade 3 or higher severity that occurred in Stage B of ADHERE. Results are summarised by MedDRA system organ class and preferred term and are shown separately for participants randomised to the efgartigimod arm. Only treatment-emergent events occurring during Stage B are included.

(b) The corresponding results for participants randomised to the placebo arm are presented in the adjacent columns of Table 30.

Table 30: Treatment-emergent adverse events by MedDRA system organ class and preferred term – serious grade 3 or higher – Stage B of ADHERE (Stage B safety analysis set)

System organ class and preferred term	Efgartigimod (N=111, PYFU=56.7)		Placebo (N=110, PYFU=42.1)	
	n (%)	m (ER)	n (%)	m (ER)
Any TEAE	████	████	████	████
Ear and labyrinth disorders	████	████	████	████
Deafness unilateral	████	████	████	████
Hepatobiliary disorders	████	████	████	████
Cholelithiasis	████	████	████	████
Infections and infestations	████	████	████	████
Appendicitis	████	████	████	████
COVID-19 pneumonia	████	████	████	████
Pneumonia	████	████	████	████
Injury, poisoning and procedural complications	████	████	████	████
Foot fracture	████	████	████	████
Metabolism and nutrition disorders	████	████	████	████
Dehydration	████	████	████	████
Neoplasms benign, malignant and unspecified (including cysts and polyps)	████	████	████	████
Lipoma	████	████	████	████
Prostate cancer	████	████	████	████
Transitional cell carcinoma	████	████	████	████

Source: argenx data on file – analyses for NICE clarification questions.⁸

Coding is based on MedDRA version 25.1 (Nov 2022).

In case a safety follow-up phase follows immediately after Stage B, adverse events during the follow-up phase are also counted as treatment-emergent events and the duration of the follow-up phase is included in the follow-up time (PYFU).

n = number of participants with the event; participants with multiple events within the same system organ class or preferred term are counted only once under those categories; m = number of events. Abbreviations: ER: Event rate per 100 participant years of follow-up ($m \times 100 / \text{PYFU}$); PYFU: Participant years of follow-up (sum of follow-up time of all participants expressed in years); TEAE: Treatment-emergent adverse event.

A19. Please provide a breakdown of the most common SAEs and Grade 3 or higher AEs experienced by patients in ADHERE+. Please provide this information separated by:

- a) Patients who completed Week 48 of the double-blind Stage B of ADHERE and were in the efgartigimod arm;**
- b) Patients who completed Week 48 of the double-blind Stage B of ADHERE and were in the placebo arm;**
- c) Patients who experienced clinical deterioration during Stage B; or**
- d) Patients who discontinued early once sufficient events for the primary endpoint in ADHERE had been reached and the trial had concluded.**

(a) Table 31 provides a breakdown of treatment-emergent adverse events of serious or Grade 3 or higher severity that occurred during ADHERE+ in participants who completed Week 48 of double-blind Stage B and were previously randomised to the efgartigimod arm. Events are summarised by MedDRA system organ class and preferred term. This subgroup includes participants who completed treatment and all visits up to and including the Week 48 visit in Stage B and subsequently entered ADHERE+. Only adverse events occurring during the ADHERE+ open-label extension are included.

(b) Table 31 also presents the corresponding data for participants who completed Week 48 of double-blind Stage B and were previously randomised to the placebo arm. These results are shown in adjacent columns within the same table to allow direct comparison between prior treatment groups.

Table 31: ADHERE+ treatment-emergent adverse events by MedDRA system organ class and preferred term – serious Grade 3 or higher – participants who completed Week 48 of Stage B by prior Stage B treatment arm (ADHERE+ safety analysis set – patients who entered ADHERE Stage B)

System organ class and preferred term	Stage B – Efgartigimod (N=33, PYFU=44.10)		Stage B – Placebo (N=17, PYFU=24.67)		Total (N=50, PYFU=68.77)	
	n (%)	m (ER)	n (%)	m (ER)	n (%)	m (ER)
Any TEAE	████	████	████	████	████	████
Acute respiratory failure	████	████	████	████	████	████
Angina unstable	████	████	████	████	████	████

System organ class and preferred term	Stage B – Efgartigimod (N=33, PYFU=44.10)		Stage B – Placebo (N=17, PYFU=24.67)		Total (N=50, PYFU=68.77)	
	n (%)	m (ER)	n (%)	m (ER)	n (%)	m (ER)
Aortic valve stenosis						
Atrial fibrillation						
Atrial flutter						
Benign prostatic hyperplasia						
Blood loss anaemia						
Cardiac arrest						
Coagulopathy						
Hepatic failure						
Hepatic steatosis						
Hypovolaemic shock						
Inguinal hernia						
Pelvic fracture						
Radius fracture						
Renal failure						
Rib fracture						
Shock						

Source: argenx data on file – analyses for NICE clarification questions.⁸

Adverse events that started during follow-up (if any) are included in this table.

Coding is based on MedDRA version 25.1 (Sep 2022).

n = number of participants with the event; m = number of events.

Abbreviations: ER: Event rate per 100 participant years of follow-up ($m \times 100 / \text{PYFU}$); PYFU: participant years of follow-up (sum of follow-up time of all participants expressed in years, per treatment group); TEAE: Treatment-emergent adverse event.

(c) Table 32 presents the treatment-emergent adverse events of serious or Grade 3 or higher severity reported during ADHERE+ in participants who experienced clinical deterioration during Stage B. Results are summarised by MedDRA system organ class and preferred term.

Table 32: ADHERE+ treatment-emergent adverse events by MedDRA system organ class and preferred term – serious or Grade 3 or higher – participants who experienced clinical deterioration during Stage B (ADHERE+ safety analysis set – patients who entered ADHERE Stage B)

System organ class and preferred term	Stage B – Efgartigimod (N=30, PYFU=41.07)		Stage B – Placebo (N=58, PYFU=80.84)		Total (N=88, PYFU=121.92)	
	n (%)	m (ER)	n (%)	m (ER)	n (%)	m (ER)
Any TEAE						
Chronic inflammatory demyelinating polyradiculoneuropathy						

System organ class and preferred term	Stage B – Efgartigimod (N=30, PYFU=41.07)		Stage B – Placebo (N=58, PYFU=80.84)		Total (N=88, PYFU=121.92)	
	n (%)	m (ER)	n (%)	m (ER)	n (%)	m (ER)
Accident	■	■	■	■	■	■
Acute kidney injury	■	■	■	■	■	■
COVID-19	■	■	■	■	■	■
COVID-19 pneumonia	■	■	■	■	■	■
Cranial nerve disorder	■	■	■	■	■	■
Deafness neurosensory	■	■	■	■	■	■
Hepatic function abnormal	■	■	■	■	■	■
Lymphadenitis	■	■	■	■	■	■
Pneumonia	■	■	■	■	■	■
Rib fracture	■	■	■	■	■	■
Seizure	■	■	■	■	■	■
Sternal fracture	■	■	■	■	■	■
Tracheal stenosis	■	■	■	■	■	■
Traumatic haematoma	■	■	■	■	■	■
Urinary tract infection	■	■	■	■	■	■
Wound infection	■	■	■	■	■	■

Source: argenx data on file – analyses for NICE clarification questions.⁸

Adverse events that started during follow-up (if any) are included in this table.

Coding is based on MedDRA version 25.1 (Sep 2022).

n = number of participants with the event; m = number of events.

Abbreviations: ER: Event rate per 100 participant years of follow-up ($m \times 100 / \text{PYFU}$); PYFU: Participant years of follow-up (sum of follow-up time of all participants expressed in years, per treatment group); TEAE: Treatment-emergent adverse event.

(d) Table 33 presents the treatment-emergent adverse events of serious or Grade 3 or higher severity reported during ADHERE+ in participants who discontinued ADHERE Stage B early at the occurrence of the 88th event. Results are summarised by MedDRA system organ class and preferred term.

Table 33: ADHERE+ treatment-emergent adverse events by MedDRA system organ class and preferred term – serious or grade 3 or higher – participants who discontinued early at the occurrence of the 88th event in Stage B (ADHERE+ safety analysis set – patients who entered ADHERE Stage B)

System organ class and preferred term	Stage B – Efgartigimod (N=35, PYFU=27.10)		Stage B – Placebo (N=23, PYFU=18.75)		Total (N=58, PYFU=45.85)	
	n (%)	m (ER)	n (%)	m (ER)	n (%)	m (ER)
Any TEAE	■	■	■	■	■	■
Breast cancer	■	■	■	■	■	■
Chronic inflammatory demyelinating polyradiculoneuropathy	■	■	■	■	■	■

System organ class and preferred term	Stage B – Efgartigimod (N=35, PYFU=27.10)		Stage B – Placebo (N=23, PYFU=18.75)		Total (N=58, PYFU=45.85)	
	n (%)	m (ER)	n (%)	m (ER)	n (%)	m (ER)
Blood creatine phosphokinase increased	████	████	████	████	████	████
Bronchitis	████	████	████	████	████	████
COVID-19	████	████	████	████	████	████
Connective tissue disorder	████	████	████	████	████	████
Dizziness	████	████	████	████	████	████
Metastases to central nervous system	████	████	████	████	████	████
Metastatic malignant melanoma	████	████	████	████	████	████
Myocardial necrosis marker increased	████	████	████	████	████	████
Type 2 diabetes mellitus	████	████	████	████	████	████

Source: argenx data on file – analyses for NICE clarification questions.⁸

n = number of participants with the event; m = number of events.

Abbreviations: ER: Event rate per 100 participant years of follow-up ($m \times 100 / \text{PYFU}$); PYFU:

Participant years of follow-up (sum of follow-up time of all participants expressed in years, per treatment group); TEAE: Treatment-emergent adverse event.

A20. Priority question: The NICE technical team considers that the company's proposed target populations should be outlined more clearly, and the company should outline how this population would be identified in clinical practice. For example:

- **Define what high burden of Ig treatment is**
- **What is meant by “symptomatic” (i.e what level of symptoms/disease severity)**
- **What is meant by “high doses” of Ig**
 - **Could the company please outline how it feels the current clinical trial evidence for efgartigimod is generalisable to the target populations (given the trial data submitted does not include these populations)**

For the Company Submission, specialist neurologists were consulted to define the treatment pathway in CIDP and the target population for efgartigimod. To further define how these populations may be identified in clinical practice, the Company consulted five different UK CIDP specialist neurologists to develop practical criteria anchored to existing NHS England commissioning policy language. These criteria were co-developed with five geographically representative UK CIDP specialist neurologists in an advisory board specifically convened to define implementable eligibility criteria for efgartigimod in NHS practice. The proposed thresholds are anchored to existing NHS England commissioning policy language, ensuring clinical familiarity.³⁰ Allowing any of the three criteria to qualify reflects real-world clinical practice, where patients may present with different manifestations of unsatisfactory Ig-based management. These presentations are not mutually exclusive, and patients may meet multiple criteria, but requiring combined criteria would inappropriately restrict access to patients who derive genuine clinical benefit.

Within the Ig-maintained population monitored under NHS England commissioning pathways, neurologists would identify eligible patients through standard clinical assessment of treatment burden, functional status, and dosing requirements.

Proposed target population definition

The company proposes efgartigimod for adults with probable or definite CIDP diagnosed according to EAN/PNS guidelines⁵ who are eligible for Ig treatment under the NHS England Clinical Commissioning Policy for the use of therapeutic immunoglobulin (Ig)³⁰ but for whom Ig treatment is unsatisfactory, defined by at least one of:

High burden of Ig treatment:

Patients meeting at least one of the following:

- Requiring hospital-based IVIg treatment more frequently than every four weeks
- Unable to tolerate more than half-maximal intravenous infusion rates due to side effects or contraindications (such that infusion times are substantially prolonged)
- Adverse events from Ig therapy that impact treatment tolerability or quality of life despite management attempts
- A regular Ig infusion or injection schedule that significantly impacts daily life (as jointly determined by the patient and clinician)

OR

Symptomatic despite Ig maintenance

Patients experiencing significant functional impairment limiting daily activities despite ongoing Ig treatment. This is defined by the NHS England CIDP commissioning policy threshold for initiating Ig therapy.³⁰

OR

High Ig dose requirements

Patients receiving Ig doses equivalent to a weekly IV average of ≥ 0.33 g/kg (e.g., doses of ≥ 1 g/kg every 3 weeks or 2 g/kg every 6 weeks). This threshold aligns with the NHS England commissioning policy reference to 2 g/kg every 6 weeks as the threshold for high-dose Ig requiring specialist monitoring.³⁰

Clinical trial evidence

High burden of Ig treatment

Before entering ADHERE, a high proportion of IVIg pre-treated received infusions more frequently than every 4 weeks, meeting the proposed criterion for hospital-based IVIg administered at high frequency. Additionally, the voluntary nature of trial participation itself signals treatment burden. Patients accepted a treatment withdrawal run-in with explicit risk of symptom return, followed by transition to an investigational therapy with uncertain efficacy. This decision inherently selected for patients willing to change treatment despite substantial challenges. In the company-commissioned UK patient survey conducted with INUK, 67% of respondents reported "often" or "always" worrying about symptoms returning or worsening, yet ADHERE participants volunteered despite these well-founded concerns, given CIDP's risk of permanent nerve damage from inadequate treatment.³¹ This self-selection combined with the high treatment frequency data supports that ADHERE enrolled patients experiencing treatment burden consistent with the proposed criterion.

Symptomatic despite Ig maintenance

All ADHERE participants met the "Symptomatic Despite Treatment" criterion by trial design. Entry criteria required INCAT score ≥ 2 , scoring at least two exclusively from leg disability, indicating significant functional impairment such as requiring walking aids (INCAT 2: unilateral support; INCAT 3: bilateral support). All Ig pre-treated patients (51%) were receiving maintenance therapy at screening yet still met this disability threshold, confirming they experienced persistent functional impairment limiting daily activities despite ongoing treatment, exactly as defined in the proposed eligibility criterion.

High Ig dose requirements

Before entering ADHERE, a majority of IVIg pre-treated received Ig doses ≥ 0.33 g/kg weekly equivalent at baseline, meeting the proposed high-dose threshold aligned with NHS England commissioning policy for doses requiring specialist monitoring.

ADHERE's enrolment criteria required a documented CIDP diagnosis but did not mandate treatment failure, ensuring the trial reflected an Ig-responsive,

maintenance-treated cohort rather than refractory outliers. The 66% response rate in open-label Stage A further confirms that ADHERE participants were Ig-responsive patients capable of achieving clinically meaningful improvement with efgartigimod.²

Section B: Clarification on cost-effectiveness data

The company has provided a revised base case reflecting the changes requested by the EAG. Each modification has been implemented cumulatively, as outlined in Table 34.

Table 34: Revised base case following changes requested by the EAG (each change is presented as cumulative on the previous)

EAG question	Change to model base case	Cumulative impact of each subsequent change			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
	Base case submitted in Company Submission	██████	██	██████	██████
B1	Removal of █████ discount on Ig	██████	██	██████	██████
B16	Corrected Probability of returning to active disease	██████	██	██████	██████
B17	All discontinuations in Stage B of ADHERE and AHERE+ to be included in TTE analysis	██████	██	██████	██████
B18	Use of Kaplan-Meier data in TTE analysis for discontinuation	██████	██	██████	██████
B24c	Updated ORs for Adverse Events (Waheed 2019)	██████	██	██████	██████
B34	Removal of age-adjustment for patients occupying the very severe health state	██████	██	██████	██████
B47	Updated the cost of PLEX from £273 to £502.51 in line with NHS National Cost Collection Data (2024/2025)	██████	██	██████	██████
B49	Updated cost of Mycophenolate to £5.99	██████	██	██████	██████
B52b	Updating funded transport to include only one return journey	██████	██	██████	██████
B54	Updating cost of HRG cost WF02A from £126.64 to £171	██████	██	██████	██████
B56a	Updating the outpatient visit cost code to WF01A (£236)	██████	██	██████	██████
B57	Updated cost of mobility aids (WCE03 – WCE06)	██████	██	██████	██████
B60ai	Updated costs of AEs	██████	██	██████	██████
B24b	Updated AEs of Hizentra, based on all N events reported in OLE	██████	██	██████	██████
	Correction of the calculation of the disutility of administration for Flebogamma* = -0.116	██████	██	██████	██████

EAG question	Change to model base case	Cumulative impact of each subsequent change			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
	Revised base case				

*In the Company Submission, the disutility of administration for Flebogamma was hardcoded=0, by mistake. In line with the other IVIg products, the disutility of administration for Flebogamma has been calculated considering the disutility associated with administration route, setting, frequency and infusion time. Since no data for infusion time in CIDP are available for Flebogamma, the minimum time between Gamunex and Privigen has been applied, keeping the choice conservative.

Abbreviations: AE: Adverse event; CIDP: Chronic inflammatory demyelinating polyneuropathy; HRG: Healthcare Resource Group; ICER: Incremental cost-effectiveness ratio; NMB: Net monetary benefit; OLE: Open-label extension; OR: Odds ratio; PLEX: Plasma exchange; QALY: Quality-adjusted life year; TTE: Time-to-event; WTP: Willingness-to-pay.

Table 35: Results of scenario analyses, starting from revised base case

EAG Question	Scenario	Deterministic results				Probabilistic results			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
	Revised base case								
B4	Time horizon = 2 years								
B2	Subgroup 4: only Ig intolerant/refractory								
B5b	Distribution of treatments in the basket obtained from the Centres Chart Review								
B5b	Assuming 25% of cohort in the basket is on corticosteroid and the percentage of the other treatments as obtained from the SEE with the residual redistributed equally among them.								

EAG Question	Scenario	Deterministic results				Probabilistic results			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
B5b	Assuming 25% of cohort in the basket is on corticosteroid and 75% of cohort redistributed equally among them.								
B5b	Assuming 0% of cohort in the basket is on corticosteroid and the percentage of the other treatments as obtained from the SEE with the residual redistributed equally among them.								
B5b	Assuming 0% of cohort in the basket is on corticosteroid and 75% of cohort redistributed equally among them.								
B5c	Cohort in treatment basket receives Ig: 10% of PLEX on Ig								
B5c	Cohort in treatment basket receives Ig: 30% of PLEX on Ig								
B5c	Cohort in treatment basket receives Ig: 60% of PLEX on Ig								

EAG Question	Scenario	Deterministic results				Probabilistic results			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
B5c	Cohort in treatment basket receives Ig: 90% of PLEX on Ig								
B6	Patients are assumed to go back into the same treatment following efgartigimod treatment discontinuation as before starting efgartigimod (i.e. 95% Ig and 5% basket of treatment)								
B6	A majority of patients are assumed to go back into the same treatment following efgartigimod treatment discontinuation as before starting efgartigimod (i.e. 60% Ig and 40% basket of treatment)								
B6	Post-efgartigimod discontinuation, the same distribution as post-Ig discontinuation is applied								
B6	Post-efgartigimod discontinuation, the cohort is distributed based on the paper bound from Structured Expert Elicitation								
B8a	Patient weight informed by UK-real world evidence								

EAG Question	Scenario	Deterministic results				Probabilistic results			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
B9	Patients in comparator arm remain in same aINCAT category as at baseline indefinitely								
B9	The last observed transition matrix (18-24 months) is recycled throughout the entire analysis								
B10	Patients have 100% chance of remaining in 'severe' and 'very severe' health states								
B13	Comparator arm is modelled by recycling the transitions in the first 6 months up to 24 months, then identity matrix is applied								
B13	Comparator arm is modelled by applying identity matrix from 6 months								
B17	Discontinuation of efgartigimod is based on time-to-event analysis of discontinuations due to AEs								
B19	Permanent treatment discontinuation is applied indefinitely over the time horizon of the model for efgartigimod and Ig								

EAG Question	Scenario	Deterministic results				Probabilistic results			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
B20	Discontinuation of Ig in the first treatment cycle is aligned with ADVANCE-CIDP-1								
B20	Discontinuation of Ig in the first treatment cycle is based on ADVANCE-CIDP-1, PATH and ICE								
B21	Patients receiving Ig or a treatment in the comparator barked do not permanently discontinue treatment at any time								
B22c	Grade ≥3 treatment-related AEs occurring in ≥5% efgartigimod patients included								
B24d	AEs based on the inclusion criteria of occurring in ≥5% of patients are included in the model for IVIg and SCIg								
B25c	AEs for PLEX are excluded from the model								
B26b	Corticosteroid AEs: Inclusion of hypertension, endocrine disorders and peripheral oedema only								

EAG Question	Scenario	Deterministic results				Probabilistic results			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
B27	Gastrointestinal disturbances are included in model where they occur in ≥5% of patients (immunosuppressants)	████████	██	████████	████████	████████	██	████████	████████
B28	AEs for efgartigimod, Ig, PLEX, corticosteroids and immunosuppressants are excluded from the model.	████████	██	████████	████████	████████	██	████████	████████
B29	Complications related to IV excluded	████████	██	████████	████████	████████	██	████████	████████
B34	Age-adjustment for patients in 'very severe' health states is included	████████	██	████████	████████	████████	██	████████	████████
B35	Utility Value for very severe health state = 0	████████	██	████████	████████	████████	██	████████	████████
B35	Utility in Severe and Very severe HS are projected from the estimates for Very limited, Mild, and Moderate HS	████████	██	████████	████████	████████	██	████████	████████
B30	Health states utilities based on descriptive analysis of ADHERE data (stage A and B)	████████	██	████████	████████	████████	██	████████	████████
B32	Health states utilities based on ADELPHI study (UK cohort)	████████	██	████████	████████	████████	██	████████	████████

EAG Question	Scenario	Deterministic results				Probabilistic results			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
B38d	AE disutilities based on Sullivan et al, disutility and duration for dizziness, fatigue, influenza, nasopharyngitis and pyrexia are set to 0	████████	██	████████	████████	████████	██	████████	████████
B40b	Duration of infusion based on data in CS	████████	██	████████	████████	████████	██	████████	████████
B41	Disutility of administration based on Jørgensen et al only	████████	██	████████	████████	████████	██	████████	████████
B41	Disutility of administration based on Jørgensen et al and considering only the coefficient for route of administration	████████	██	████████	████████	████████	██	████████	████████
B41	Disutility of administration combining the coefficient for route from Jørgensen et al and infusion duration from Matza et al.	████████	██	████████	████████	████████	██	████████	████████
B41; B43	Disutility of administration is excluded	████████	██	████████	████████	████████	██	████████	████████
B45	IVIg /SCIg split: 76.7% / 23.3%	████████	██	████████	████████	████████	██	████████	████████
B46	All patients receiving efgartigimod are assumed to be on the weekly dosing regimen	████████	██	████████	████████	████████	██	████████	████████

EAG Question	Scenario	Deterministic results				Probabilistic results			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
B51a	Ig is only delivered in an outpatient setting.	████████	██	████████	██████	████████	██	████████	██████
B52ci	Funded transport included for efgartigimod	████████	██	████████	██████	████████	██	████████	██████
B52d	All funded transport excluded	████████	██	████████	██████	████████	██	████████	██████
B53a	Administration cost of SCIg is the same as efgartigimod	████████	██	████████	██████	████████	██	████████	██████
B55b	Standard GP costs with a 10-minute appointment (£45)	████████	██	████████	██████	████████	██	████████	██████
B58a	Proportion requiring a mobility aid based on EAG clinical experts	████████	██	████████	██████	████████	██	████████	██████
B59b	Cost of critical care £1,907 – cost per day of ICU	████████	██	████████	██████	████████	██	████████	██████
B60ci	AE costs sourced from NHS reference costs	████████	██	████████	██████	████████	██	████████	██████
B60e	Implementation of EAGs clinical experts' advice on treatment setting, using NHS reference cost of GP visit as £45 (AEs for back pain and peripheral oedema)	████████	██	████████	██████	████████	██	████████	██████
B61d	Impact on informal care excluded	████████	██	████████	██████	████████	██	████████	██████
B61e	Cost of professional care excluded	████████	██	████████	██████	████████	██	████████	██████

EAG Question	Scenario	Deterministic results				Probabilistic results			
		Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
B62d	Patients have at most one caregiver for any health state, proportion requiring a caregiver informed by UK ADELPHI dataset								
B63	12-week model cycle for the first two years, followed by a 6-month time horizon thereafter								
N/A	Subgroup 1: only patients on Ig maintenance								
N/A	Subgroup 2: only Ig-dependent patients								
N/A	Subgroup 3: only Ig dependent patients on ultra-high dose Ig maintenance								
N/A	ITC vs all comparator studies (ADVANCE-CIDP-1; PATH; ICE)								
N/A	Time of eligibility for treatment dependency test: efgartigimod cohort eligible from simulation start								
N/A	Time of eligibility for treatment dependency test: Ig cohort eligible from Cycle 3 onwards								
N/A	Deterioration upon returning to active disease state								

Abbreviations: AE: Adverse event; aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; CIDP: Chronic inflammatory demyelinating polyneuropathy; CS: Company Submission; GP: General practitioner; HS: Health state; ICER: Incremental cost-effectiveness ratio; ICU: Intensive care unit; Ig: Immunoglobulin; IVIg: Intravenous immunoglobulin; ITC: Indirect treatment comparison; IV: Intravenous; NHS: National Health Service; NMB: Net monetary benefit; PLEX: Plasma exchange; QALY: Quality-adjusted life year; SCIg: Subcutaneous immunoglobulin; SEE: Structured Expert Elicitation; WTP: Willingness-to-pay.

Base case results

B1. Priority question: Only list prices for comparator drugs should be used in the company's base case analysis. The company has assumed a [REDACTED] discount on the list price for Ig products, which has not been supplied by NICE.

Therefore, please remove this discount and supply a new version of Section 3.10 to 3.12 of the company submission, incorporating any changes made as a result of the clarification questions. Please ensure any scenarios requested by the EAG do not include the assumed discount for Ig products.

The base-case analysis was updated by removing the [REDACTED] discount applied to Ig and implementing the changes requested by the EAG, as summarised in Table 34. All results include the confidential PAS of efgartigimod of [REDACTED]. This table reports the cumulative impact of each change on the base-case ICER. In the updated analysis, the incremental cost of efgartigimod versus the comparator is [REDACTED], with an incremental QALY gain of 4.26. Efgartigimod therefore dominates the comparator, and the resulting NMB at a £30,000 per QALY willingness-to-pay threshold (WTP) is [REDACTED]. Full details of the updated base-case and sensitivity analyses are provided in Appendix 2 (structured in line with Sections 3.10–3.12 of the CS). The results of the scenario analyses are presented in Table 35.

B2. Priority question: Please update the model to include an option to conduct a subgroup analysis for patients intolerant/refractory to Ig, and provide results for this analysis.

The model was updated to include the option to run the analysis on a subgroup of patients where 50% of the cohort at baseline is intolerant to Ig and 50% is refractory to Ig.

The ICER in this Ig-intolerant/refractory subgroup analysis is higher than in the base case [REDACTED] per QALY versus dominant result, respectively). This finding is expected for several methodological reasons:

1. Different comparator cost structure: In this scenario, the comparator arm receives the basket of alternative treatments rather than Ig. The differential acquisition costs between efgartigimod and this basket differ substantially from the differential between efgartigimod and Ig, affecting the incremental cost calculation.
2. Absence of Ig cost offsets: A key driver of cost-effectiveness in the base case is the reduction in ongoing Ig costs among efgartigimod responders. In this scenario, there are no Ig costs to offset in the comparator arm, fundamentally changing the economic value proposition.
3. Different administration and monitoring costs: The basket of comparators (PLEX, corticosteroids, immunosuppressants) has different administration patterns, monitoring requirements, and associated healthcare resource utilisation compared to Ig, which affects the overall cost differential.
4. Small and non-representative population: Critically, this scenario does not reflect the real-world epidemiology of CIDP or the expected patient population for efgartigimod.

It is important to note that the inclusion of Ig-intolerant and Ig-refractory patients in the base case (at 2.5% each, totalling 5%) is not favourable from a cost-effectiveness perspective - as this analysis demonstrates, these patients drive a higher ICER. However, the company have included them in the base case because they represent patients with the highest unmet need. These are patients who have no satisfactory alternative to the basket of treatments (PLEX, corticosteroids, immunosuppressants), each of which carries substantial limitations, including invasive procedures (PLEX), significant adverse effect burdens (corticosteroids, immunosuppressants), risk of iatrogenic conditions (corticosteroids), challenges with long-term tolerability, and poor evidence base. The company inclusion of this small but clinically important subgroup reflects our commitment to addressing unmet need across the full spectrum of CIDP patients who could benefit from efgartigimod.

B3. Priority question: Please explain what is driving the large discrepancy between probabilistic and deterministic base case results (in particular, incremental costs).

a) Please present probabilistic results for all scenario analyses, including both the scenario analyses presented in the original CS and those requested by the EAG.

The company acknowledge some discrepancy between deterministic and probabilistic results. On the cost side, this appears to be driven by distribution of the cohort between Ig doses and the time between Ig cycles. The 95% confidence interval for the proportion of the cohort between Ig doses are asymmetric, with the upper bound further from the mean than the lower bound. This allows larger shifts towards higher dosing in the probabilistic analysis, resulting in higher Ig costs compared with the deterministic base case. When these are fixed on the mean estimate, the probabilistic costs are close to deterministic results. In terms of QALYs, the discrepancy between deterministic and probabilistic results is smaller than that observed for costs. The aINCAT change from baseline for efgartigimod versus Ig in the ITC appears to be the main driver of this difference in QALYs. As also shown in the one-way sensitivity analysis (OWSA), a smaller treatment effect (i.e. a smaller difference between efgartigimod and Ig) has a larger impact on worsening the ICER than a correspondingly larger treatment effect has on improving it.

As requested, Table 35 presents probabilistic results for all scenario analyses included in the original submission and those requested by the EAG. Each scenario is conducted as an independent change on the revised base case (Table 34). The revised base case and each scenario conducted includes the confidential PAS for efgartigimod of [REDACTED]. Deterministic results are presented for all scenarios. For each scenario, both deterministic and probabilistic outcomes are reported in terms of:

- Incremental cost
- Incremental QALY
- ICER

- NMB at a cost-effectiveness threshold of £30,000

Time horizon

B4. Please provide a scenario where the time horizon of the model is set to two years. Please update the model so the time horizon is a user-adjustable option.

The time horizon has been added as a user-adjustable input in the *Settings* sheet of the model. The default value is set to 44.9 years, representing a lifetime horizon for a cohort with a mean age of 55.1 years at model entry.

As requested, the company have included a scenario analysis using a 2-year time horizon (see Table 35). This scenario can now be reproduced directly in the model using the time horizon input field.

The company recognise the EAG's interest in assessing sensitivity to long-term extrapolations. While a 2-year horizon limits the model's ability to capture the chronic, lifelong nature of CIDP and the full trajectory of disability progression and treatment patterns, we provide this scenario as requested. The shorter time horizon will show a less favourable ICER, which is expected, given the need for induction treatment and the time required to realise the full clinical and cost benefits of reducing relapse risk and disability progression.

Treatment pathway

B5. Priority question: The EAG considers there are limitations to the company's approach to modelling the 'basket' of alternative treatments as a comparator to patients refractory or intolerant to Ig, or as a subsequent treatment following treatment with Ig.

- a) The proportion of patients receiving each treatment in the basket was informed by the proportion of patients switching to each treatment immediately after discontinuing Ig. Please explain why these values were also considered appropriate to inform the proportion of patients receiving each treatment in the long term.**
 - b) The EAG's clinical experts stated that corticosteroids are generally only for managing patients experiencing intolerable symptoms in the short term. Therefore, the assumption that 77% of patients in the basket are receiving corticosteroids at any given time is unlikely to be reflective of UK clinical practice. Please provide scenarios varying the proportion of patients in the basket receiving corticosteroids, including a scenario in which no patients receive corticosteroids.**
 - c) The EAG's clinical experts stated that PLEX would likely be used to treat patients in the short term, with patients eventually returning to treatment with Ig. Please provide a range of scenarios in which some patients in the treatment basket are treated with Ig.**
- (a)** The company acknowledges that the assumption of stable long-term proportions represents a necessary modelling assumption in the absence of published longitudinal data on treatment patterns in Ig-refractory or intolerant CIDP patients. The basket approach applies average cross-sectional utilisation estimates derived from clinical expert elicitation, rather than modelling individual patient trajectories over time. This methodology was necessitated by the rarity of CIDP and the particularly small subset of Ig-refractory/intolerant patients, the absence of published cohort studies tracking long-term treatment sequences in this specific population, and the heterogeneity of treatment patterns.

The proportions used to populate the basket of treatment after Ig discontinuations were informed by clinician-reported practice patterns from the Structured Expert Elicitation (SEE) with five clinical experts from geographically representative key CIDP specialist centres across England.

In clinical practice, patients may cycle between several immunomodulatory treatments over time, and the specific sequence can vary substantially across individuals. However, clinicians participating in the SEE reported that the overall distribution of use across the basket (e.g., corticosteroids, PLEX, immunosuppressants) remains broadly stable at the population level. That is, while individual patients may move from one option to another, the aggregate proportions observed immediately following Ig discontinuation reflect the average pattern of long-term treatment utilisation in this patient group.

Applying this distribution in the long term is consistent with the expert-elicited view of real-world practice and provides a reasonable approximation of the expected mix of comparator treatments over time in patients who cannot continue on Ig (refractory or intolerant to Ig and the cohort who discontinues over the time horizon of the analysis).

The base case, therefore, likely overstates corticosteroid use and understates use of more resource-intensive alternatives like PLEX, potentially conservative to efgartigimod's cost-effectiveness case.

(b) To address the EAG request, we ran scenario analyses varying the proportion of patients in the basket of treatment receiving corticosteroids after discontinuing Ig treatment. The following scenarios were tested:

- **Scenario 1:** Distribution of treatments in the basket obtained from the Centres Chart Review
- **Scenario 2:** Assuming 25% of cohort in the basket is on corticosteroids and the percentage of the other treatments as obtained from the SEE with the residual redistributed equally among them.
- **Scenario 3:** Assuming 25% of cohort in the basket is on corticosteroids and 75% of cohort redistributed equally among them.

- **Scenario 4:** Assuming 0% of cohort in the basket is on corticosteroids and the percentage of the other treatments as obtained from the SEE with the residual redistributed equally among them.
- **Scenario 5:** Assuming 0% of cohort in the basket is on corticosteroids and 100% of cohort redistributed equally among them.

Table 36: Distribution of the cohort in the basket of treatment after Ig discontinuation

	Base case (from SEE)	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
PLEX	22.9%	19.05%	48.9%	37.5%	61.4%	50.0%
Corticosteroid	77.0%	52.38%	25.0%	25.0%	0.0%	0.0%
Immunosuppressants	0.13%	28.57%	26.1%	37.5%	38.6%	50.0%

Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange; SEE: Structured expert elicitation.

The NMB resulting from these explored scenarios ranges between [REDACTED] and [REDACTED], thus not materially different from the revised base case with NMB [REDACTED] (Table 35). The base case distribution reflects expert consensus from five UK geographically representative neurology centres specialising in CIDP treatment, gathered through a structured elicitation process. However, we recognise clinical practice may vary, and the scenarios presented allow exploration of alternative assumptions aligned with different clinical perspectives.

c) As requested, we implemented the possibility of patients receiving Ig treatment as part of the treatment basket. The proportion of the cohort on Ig has been added in the “Treatment basket after Ig discontinuation” section of the *Cost* sheet as user-modifiable input. A dropdown selector was added in the *Settings* sheet which allows the user to run the model considering the following scenarios:

- 10% of cohort on PLEX returns to Ig
- 30% of cohort on PLEX returns to Ig
- 60% of cohort on PLEX returns to Ig
- 90% of cohort PLEX returns to Ig

To avoid overcomplexity in the engine, the proportion returning to Ig has been implemented as an adjustment to the discontinuation rate of Ig, in both the comparator engine and the efgartigimod responders and non-responders engine.

The results of these scenario analyses go from a NMB of [REDACTED] when 10% of PLEX is assigned to Ig, to a NMB of [REDACTED] when 90% of PLEX is assigned to Ig. As expected, the ICER decreases in favour of efgartigimod. This is because Ig is a more expensive treatment than PLEX, and any change to the use or cost of Ig has a greater impact on the comparator arm than on the efgartigimod arm. In the efgartigimod arm, Ig is only administered to patients who discontinue efgartigimod (due to lack of response or unplanned discontinuations), whereas in the comparator arm, Ig is the principal treatment option (with approximately 95% of patients receiving Ig at baseline).

B6. Please provide scenarios in which people are assumed to go back onto the same treatment following efgartigimod treatment discontinuation as before starting efgartigimod.

The impact of these scenarios were already included in the Company Submission (CS Table 93; Scenario 14). These scenarios can be run using a drop-down selector in the *Settings* sheet of the model. In one analysis, patients who discontinue efgartigimod are assumed to return to the same treatment they were receiving prior to initiating efgartigimod. This corresponds to the baseline treatment distribution used in the comparator arm. Under this distribution, 95% of the cohort return to Ig, while the remaining 5% (representing those who are refractory or intolerant to Ig) return to the basket of alternative treatments (PLEX, corticosteroids, and immunosuppressants). Another scenario was explored where a majority of the cohort discontinuing efgartigimod goes back to the treatment as before starting efgartigimod, i.e. 60%. The remaining 40% are assigned to the basket of treatment.

For completeness and ease of reference, we have included this scenario in Table 35 of this response document. Starting from the revised base case, assuming all cohort goes back to the basket of treatment results into an ICER of [REDACTED] per QALY. When 60% of the cohort is assumed to go back to Ig, the ICER is [REDACTED] per QALY.

Clinician input through the company structure expert elicitation (SEE)¹³ indicates that patients are not always immediately returned to prior Ig therapy after stopping

efgartigimod, especially when Ig was previously discontinued due to clinical need. Instead, other treatment options may be explored first, so a range of alternatives was modelled, with this scenario analysis provided for transparency.

Two additional scenarios were conducted on the distribution of treatment after efgartigimod discontinuation:

- The same distribution of treatment as after Ig discontinuation: 22.9% PLEX, 77% corticosteroid and 0.1% immunosuppressants. As expected, this favourably impacts the ICER since the cost of corticosteroid is much lower than Ig. The ICER remains dominant
- The distribution of treatments obtained considering the upper bound of the distribution post efgartigimod obtained from the SEE (48% Ig, 10.9% PLEX, 37.6% corticosteroid and 3.5% immunosuppressants). The ICER increases compared with the revised base case, but remains below the £30K threshold (██████ per QALY)

Patient population

B7. Priority question: Please provide further details of how the distribution of patients between health states at baseline was derived. In particular:

- a) Please justify why it is appropriate to use the distribution at Stage A baseline in the ADHERE trial for the baseline distribution for patients in the Ig-refractory cohort.**
- b) The EAG notes that the company chose to use the distribution at Stage B baseline in the ADHERE trial to inform the distribution between health states for efgartigimod responders; however, in the model, this was applied at a time point of 6 months, whereas Stage A in the ADHERE trial lasted for a maximum of 12 weeks. Please clarify whether any adjustments were made to account for the discrepancy in these timepoints, and if not, comment on the potential bias that may result from assuming that these timepoints align.**

c) For all population subgroups, please clarify whether the distribution at baseline is informed by data from the whole ADHERE trial population, or the subgroup of patients who were pre-treated with Ig.

(a) The use of the Stage A baseline distribution from ADHERE to inform the baseline health state distribution for the Ig-refractory/intolerant cohort is appropriate because patients entering Stage A of ADHERE had discontinued Ig.

Stage A enrolled patients who had stopped Ig and were actively deteriorating. By requiring active deterioration off treatment, Stage A baseline captures the disease severity distribution at the point of inadequate control and thus the functional state when Ig alternatives are required. Therefore, the Stage A health state distribution is appropriate for modelling the Ig-refractory/intolerant cohort baseline severity.

(b) No adjustment was made to account for the difference between the ADHERE Stage A duration (up to 12 weeks) and the 6-month timepoint at which the Stage B baseline distribution is applied in the model. This approach was taken to avoid making assumptions about the trajectory of functional improvement beyond what is directly observed in the trial data.

We note that this decision is conservative. By applying the Stage B baseline distribution only at 6 months, rather than at 3 months, the model effectively extends the time the cohort remains in worse health states before transitioning to the improved distribution observed among responders in Stage B. As a result, any health gains attributable to efgartigimod may be underestimated, biasing the model against the intervention.

Following the EAG's request in question B63, we conducted a scenario analysis using a 3-month cycle length for the first 24 months and 6-month cycles thereafter. The method for the implementation and limitations of using 3-month rather than 6-month cycles are fully described in our response to question B63. In this scenario, discounted QALYs for efgartigimod increase compared with the 6-month-cycle base case (█████ versus 5.91 QALYs), indicating that shortening the cycle length captures additional health gains for patients. At the same time, total costs in the efgartigimod

arm decrease in the 3-month-cycle scenario compared with the 6-month-cycle base case ([REDACTED] versus [REDACTED]).

(c) All baseline distribution and transition probabilities in the model are based on the subgroup of Ig pre-treated patients in the ADHERE trial.

B8. Priority question: The EAG does not agree with the company's assertion that the use of patient weight informed by the ADHERE trial, which is lower than the expected weight in a UK patient population, is conservative, since weight-based dosing is used for both the intervention and comparator treatments.

a) Please provide a scenario analysis in which patient weight is informed by UK real-world evidence.

b) Please consider updating the model to use a distribution of patient weights rather than only the mean weight.

(a) The EAG states that weight-based dosing is used for both the intervention and the comparator. However, it should be noted that subcutaneous efgartigimod is administered as a fixed 1,000 mg dose (vial) per administration; therefore, efgartigimod drug costs are unaffected by patient body weight. Based on UK Health Survey for England (HSE) data (2021),³² the mean adult weight in the UK, reweighted to reflect the gender distribution in ADHERE (38.8% female), is 79.9 kg (71.8 kg for females and 85.1 kg for males). This is slightly lower than the mean weight observed in ADHERE (80.6 kg). A scenario using the UK HSE-derived mean weight has been implemented, and the results are presented in Table 35. However, as expected this small change in average weight does not impact the results.

(b) Ig dosing is continuous and based on weight, without discrete dosing bands. Moreover, we could not identify any weight-based thresholds and associated distribution in the UK population statistics data. Therefore, we believe that using the mean weight is appropriate.

Treatment efficacy

B9. Priority question: In order to maintain consistency with the assumption that patients on long-term maintenance treatment experience no change in aINCAT score, please provide a scenario analysis in which patients in the comparator arm remain in the same aINCAT category as at baseline indefinitely (i.e., the only movement between health states is between the ‘active disease’ and ‘remission’ health states).

The company would like to note that from 24 months onwards (i.e. beyond the ADHERE+ observation period) the identity matrix (the cohort remains in same aINCAT health state) was applied to both the efgartigimod and the comparator arms. This was chosen as a conservative assumption, given the absence of efgartigimod data beyond 24 months and to make the extrapolation of efficacy symmetric in both the intervention and the comparator arm. A scenario analysis was included in the Company Submission in which the last observed transition matrix (18–24 months) was instead recycled for the remainder of the time horizon. Under this scenario, incremental QALYs increase slightly from [REDACTED], and the ICER becomes more favourable (starting from the revised base case, the resulting NMB is [REDACTED]).

From a clinical perspective, the company consider that assuming that Ig patients on maintenance treatment experience no change in aINCAT score does not reflect the natural history of Ig-treated CIDP and risks confusing stable Ig dosing with absence of disease activity. In clinical practice, patients who are “stable on Ig” are generally on a stable IVIg or SCIg regimen, but not necessarily free of ongoing inflammatory activity or axonal loss. Expert advice obtained from Dr. Stephen Keddle, a neurologist expert in CIDP and working in a specialised centre in England (Royal London NHS Trust), highlighted that even apparent “responders” may continue to accumulate axonal damage over time despite maintenance Ig, with axonal loss being the main determinant of irreversible disability. Quoting his feedback: *“If you do neurophysiology on those patients over time, you’ll see that they’re accumulating axonal damage. And axonal damage is a marker of irreversible neuro-disability. So, you may have sorted out the demyelination to a degree, but they are very likely to continue picking up axonal loss.”*

Rajabally and Narasimhan evaluated 31 patients with clinically stabilised CIDP and showed that significant axonal loss persisted, predominantly in the lower limbs, and that about 50% of demyelinating abnormalities were found in regions that were clinically asymptomatic.³³ Electrophysiological markers (e.g. CMAP amplitudes) correlated with weakness and functional scores, indicating that axonal damage continues to accrue and is closely linked to disability, even in patients considered clinically “stable”.

The recent UK study by Koay et al. provides quantitative evidence on how many patients on maintenance IVIg can genuinely be considered clinically stable.³⁴ In their cohort, 125 individuals with CIDP were on maintenance IVIg. Only 45 of 125 patients (36%) met strict criteria for clinical stability over ≥ 12 months whilst on a static IVIg dosing regimen, based on minimal change in validated CIDP outcome measures (MRC-SS, I-RODS, grip strength, 10-m walk). This is already captured in the model as it informs the probability of being in remission at six months after having undergone planned withdrawal of treatment.

Finally, all five neurologists who participated in the qualitative validation of the CIDP care pathway, as well as the additional five neurologists involved in the structured expert elicitation and further validation of the pathway, agreed that Ig dosing aims at reaching the minimum effective dose for each individual patient, balancing disease burden against treatment and administration burden. They also highlighted that this minimum effective dose can be as high as 2 g/kg with frequent administration in some patients. At such doses, patients may still experience gradual disease worsening over time, which can in turn prompt further adjustments to Ig dose or frequency (when still possible, considering the burden of treatment).

Thus, a more clinically plausible representation of the comparator arm is that some patients remain stable or improve, while others accumulate disability over time despite stable Ig dosing, with transitions between aINCAT categories reflecting relapses, progression and, for some, remission. This pattern is reflected in the transition probabilities used in the Company Submission (please see Section 3.3.3 in the CS).

While the company disagrees with this assumption for the clinical reasons outlined above, the company provides the requested scenario analysis for completeness. In this scenario, patients in the Ig (and basket of treatment) comparator arm are constrained to remain in their baseline aINCAT health state for the entire model time horizon, with movement allowed only between 'active disease' and 'remission' at that same aINCAT level.

The numerical results of this scenario are presented Table 35. As expected, the incremental QALYs are lower than in basecase analysis (█████ versus 4.26, respectively) since the cohort in the comparator arm does not have any worsening in aINCAT, even when this is observed for a proportion of cohort in the efgartigimod arm. Similarly, the incremental costs are higher, thus resulting into an ICER of █████/QALY. We consider this a structural sensitivity analysis that is informative but likely optimistic for long-term disability outcomes in the comparator arm, given the evidence summarised above that many Ig-treated patients either fluctuate or worsen over time and that only a subset can be considered truly stable.

B10. Priority question: Please clarify whether patients in the placebo arm of ADHERE were included in the dataset used to derive transition probabilities for patients receiving efgartigimod. If so, please explain if any adjustments were made to account for the time on placebo between ADHERE Stage A and ADHERE+.

Only patients in the efgartigimod arm were included in the dataset used to derive transition probabilities. Patients in the placebo arm of Stage B of the ADHERE trial were not included in these analyses and therefore did not contribute to the estimation of transition probabilities from ADHERE and ADHERE+ used in the model. As a result, no adjustment was required to account for the time spent on placebo between ADHERE Stage A and ADHERE+.

B11. Priority question: The EAG notes that there are very limited ‘shift count’ data to inform the transition probabilities out of the ‘very severe’ and ‘severe’ health state for patients receiving efgartigimod ([REDACTED] [REDACTED]). Please provide a scenario analysis in

which patients have a 100% chance of remaining in these health states for all cycles, for both the intervention and comparator.

The company agrees that there are very limited observations informing transitions out of the Very Severe and Severe health states for patients receiving efgartigimod. This reflects the fact that by Stage B of ADHERE, most patients had already improved to better health states, resulting in sparse shift-count data in the most severe categories.

In response to the EAG's request, the company has implemented a scenario in which patients in the Very Severe and Severe health states have a 100% probability of remaining in those states for all cycles. This assumption is applied equally to the intervention and comparator transition matrices. The scenario can be selected directly from the *Settings* sheet, and the results are presented in Table 35.

As expected, this scenario has only a minimal effect on the model results. Efgartigimod remains dominant and the resulting NMB is [REDACTED]. Given the very small number of patients in these states and the limited movement observed in the trial data, constraining transitions out of these health states to 0% does not materially alter the overall cohort trajectories or the model results.

B12. Priority question: Please provide details of how many data points were missing in the dataset used for the analysis to derive transition probabilities for patients receiving efgartigimod, and comment on whether the method used to impute missing data may have led to bias in the subsequent analysis.

The number of patients with missing aINCAT data in the dataset used to derive transition probabilities for patients receiving efgartigimod is summarised in Table 37 and Table 38. The initial analysis population comprised 49 Ig pre-treated patients from ADHERE, with follow-up extended to 96 weeks (2 years) using data from ADHERE and ADHERE+ to construct the shift tables for transition probabilities. Shift tables were constructed by comparing, for each patient, the aINCAT score at the visit defining the start of the period of interest with the aINCAT score at the visit defining the end of that same period. Thus, inclusion in a given shift table required that a patient had at least two aINCAT assessments within the target period. For example,

for the 0-24 weeks period, the starting aINCAT score was taken from the baseline ADHERE Stage B visit, and the follow-up score was taken from the recorded visit at Week 24. For patients who have a recorded visit at the beginning of the target period but no recorded visit at the target date at the end of the period, the last available observation within the correspondent period was used. For example, if a patient has no recorded visit at Week 24 but a record at Week 22, the latter is used in the analysis. Thus, a last-observation-carried-forward (LOCF) approach was conducted within each target period when calculating the shift-tables to derive the transition probabilities. Relying solely on complete cases (i.e. including only patients with no missing aINCAT assessments over the relevant interval) would have reduced the sample size informing each shift-table and risked selection bias, as patients with complete follow-up may differ systematically from those with intermittent missing data (e.g. in terms of disease severity, tolerability, or adherence). We recognise that LOCF has limitations: it assumes that a patient's disability remains unchanged beyond the last observed score. However, any bias introduced by LOCF would be expected to impact both improvement and worsening in aINCAT transitions, rather than systematically favouring efgartigimod.

By contrast, when scores were not recorded at any visit after the baseline visit for a target period, patients were excluded from the estimation of the shift-table. The number of patients with missing data at any follow-up visit within the target period and therefore excluded from the analysis are reported in Table 37 and Table 38 for 6-months and 3-months model cycle length, respectively. The data loss observed with 12-week cycles directly informed the company response to question B63, where the EAG requested 12-week model cycles. As demonstrated here, 12-week cycles would result in transition probabilities informed by as few as 10 patients in later periods, which would substantially reduce the reliability and precision of these critical model inputs.

Table 37: Number of patients from ADHERE and ADHERE+ excluded in the determination of transition probabilities at each six-month cycle

Target period in ADHERE and ADHERE +	Patients with missing data excluded from the estimation of shift-tables
Week 0-24	0
Week 24-48	5
Week 48-72	17
Week 72-96	28

Table 38: Number of patients from ADHERE and ADHERE+ excluded in the determination of transition probabilities at each 3-month cycle

Target period in ADHERE and ADHERE +	Patients with missing data excluded from the estimation of shift-tables
Week 0-12	0
Week 12-24	8
Week 24-36	20
Week 36-48	24
Week 48-60	30
Week 60-72	37
Week 72-84	38
Week 84-96	39

B13. Please justify why the difference in treatment effect between efgartigimod and Ig was assumed to persist for two years in the company's base case, although the input was derived from data collected over a considerably shorter time period in ADHERE and ADVANCE-CIDP-1.

The transition probabilities for the efgartigimod arm are applied over a 24-month period. To ensure a consistent comparison, it would not be appropriate to assume that no transitions occur in the Ig arm during this period. Please see response to question B9. For this reason, the result from the ITC was projected over 24 months. This results in a representation of the transitions which considers some patients remain stable or improve, while others worsen over time. Nevertheless, the company acknowledges there is some uncertainty related to transitions applied beyond 6 months which is the period over which data used in the ITC are observed.

However, the assumption that the difference in treatment effect persists over two years is supported by emerging longer-term evidence for efgartigimod. In ADHERE, participants who continued on weekly dosing maintained clinical response into ADHERE+,²⁰ with some domains showing continued improvement over time. A substudy also demonstrated maintenance of response on every-other-week dosing, indicating durability beyond the initial blinded period.³⁵ These findings are biologically consistent with the mechanism of action discussed in the clarification response to question A8; FcRn blockade provides continuous reduction of pathogenic IgG as long as treatment is maintained. Taken together, this supports the use of a 2-year projection in the base case, while recognising the residual uncertainty, which has been addressed through scenario analyses:

1. Apply the ITC results to estimate the transitions in the comparator arm for the first 6 months. Thereafter, recycle the transition probabilities over these 6-months repeatedly for each next cycle up to 24 months. This scenario results into an ICER of [REDACTED]/QALY.
2. Apply the ITC results to estimate the transitions in the comparator arm for the first 6 months. Thereafter, assume the cohort remains stable except from moving to remission part of the model and relapsing to active states. The resulting ICER is [REDACTED]/QALY. This scenario was modelled for transparency; however we believe it suffers from limitations associated with introducing disease stability in initial model cycles and not being reflective of disease progression as discussed in the response to question B9.

B14. The EAG notes that the company's approach to deriving transition probabilities for comparator treatments implicitly assumes that the difference in change from baseline in aINCAT score for comparator treatments compared to efgartigimod is the same across all health states. Please justify this assumption.

The ADHERE Stage B data do not suggest a meaningful interaction between baseline aINCAT category (health state) and the magnitude of change in aINCAT with efgartigimod maintenance treatment. As shown in Table 5 of the response to

A6b, the mean change from Stage B baseline at the last Stage B assessment in the efgartigimod arm is very similar for patients starting in the Very Limited, Mild, and Moderate impairment health states, with values ranging from 0.0 to 0.1 points. Patients starting in the Severe health state show a slightly higher mean change (1.0 point). This pattern indicates that, across most of the aINCAT range relevant to the model, the absolute change from baseline is largely independent of baseline health state. There is therefore no empirical evidence from ADHERE of a strong baseline-severity-by-treatment interaction that would justify imposing different relative treatment effects by health state in the model.

Furthermore, the MAIC framework used to estimate the comparative efficacy provides overall treatment effects but does not provide health state-specific estimates; attempting to model different treatment effects by health state would require unverifiable assumptions. Furthermore, the MAIC framework used to estimate the comparative efficacy provides overall treatment effects but does not provide health state-specific estimates; attempting to model different treatment effects by health state would require unverifiable assumptions.

Remission and relapse

B15. Please justify the ‘cross-sectional estimate’ assumption informing the proportion of patients eligible to undergo treatment withdrawal trials (i.e., the assumption that the proportion of patients eligible to undergo withdrawal is constant over time).

This is consistent with the way the parameter was elicited. The proportion of patients eligible and willing to undergo planned withdrawal among patients on a stable maintenance dose was obtained from the SEE. Clinical experts were explicitly asked to provide this proportion without fixing it to a specific time point in the treatment journey, but instead to reflect their typical experience with patients on maintenance Ig treatment. Thus, by design, the SEE yields a time-agnostic, cross-sectional estimate: *“Among patients with active CIDP receiving maintenance treatment with Ig at a stable dose (i.e. no variation in dosing), what proportion do you estimate would*

be both clinically eligible and personally willing to undergo a planned dependency test?”

Moreover, assuming that in each cycle a fixed proportion of the cohort on maintenance treatment is considered eligible for a planned withdrawal is consistent with the way eligibility for cessation trials is defined and implemented in Koay et al.³⁴ In that study, patients on maintenance IVIg were offered the possibility to withdraw treatment if they had clinical stability for at least 12 months on a stable IVIg regimen. Eligibility, therefore, depends on current clinical status over the preceding year, not on absolute disease duration or total time on Ig. Koay et al. do not report any systematic change in this proportion over the study period, and eligibility is operationalised as an annual, cross-sectional assessment.

In routine practice, as described by Koay et al., the pool of patients on maintenance Ig is in approximate “steady state”: new patients start treatment, some relapse early and discontinue, and a subset becomes long-term stable.³⁴ At any review point, the proportion who meet the stability criteria is determined by current disease activity, not by how long the cohort has been treated.

B16. The per-cycle probability of returning to active disease after entering remission has been calculated incorrectly (the 12-month probability has been divided by two, rather than adjusting by assuming an exponentially distributed time to relapse). Please correct this error in the model and report the effect on the results.

The company acknowledges the error, which has been corrected in the updated version of the model. The 12-month probability of relapsing has now been estimated using the formula: $1 - (1 - \text{probability at 12 months})^{0.5}$. The cycle probability of relapse to active disease from remission changes from 10.31% (estimate with error in CS) to 10.91%. This correction is included in the revised base case analysis and the contribution to the updated base case results is included in Table 34.

Treatment discontinuation

B17. Priority question: The EAG considers that all discontinuations in Stage B of ADHERE and ADHERE+ should have been included in the time-to-event analysis for treatment discontinuation for efgartigimod. Please update the time-to-event analysis to include all discontinuations.

The company updated the time-to-event analysis to include all discontinuations observed in ADHERE and ADHERE+. When all discontinuations are incorporated, 76.3% of patients remain on treatment at the last ADHERE+ timepoint (40 months), compared with 84.1% when only discontinuations due to AEs are included. The corresponding Kaplan–Meier (KM) data and parametric extrapolations have been added to the *ToT_efgartigimod* sheet of the model. A selector has also been added to the *Settings* sheet, enabling the user to run the analysis using either (i) only AE–related discontinuations or (ii) all discontinuations.

In line with the EAG's request, the company updated the base case using time-to-event data, including all discontinuations. The cumulative impact of this change in the base case is reported in Table 34.

The company also included a scenario analysis presenting the results with the time-to-event analysis, including only discontinuations related to AEs, as in the original CS. In this scenario efgartigimod remains dominant versus the comparator arm and the resulting NMB is [REDACTED]. The company considers this scenario relevant since discontinuations observed in the trial (e.g., related to trial design, protocol-driven assessments) are unlikely to occur at the same frequency in routine clinical practice. AE–related discontinuations, by contrast, reflect a clinical mechanism that is expected to translate more reliably to real-world use.

B18. Priority question: Since the model base case only considers discontinuation of efgartigimod up to 18 months, the EAG considers that it is inappropriate to use extrapolated data to inform treatment discontinuation. Please update the analysis to use Kaplan-Meier data from the time-to-event analysis directly.

The company have updated the base case analysis so that the probability of unplanned discontinuation in the efgartigimod arm is now informed directly by the KM data. This allows unplanned discontinuation rates to be derived without relying solely on parametric extrapolation.

The cumulative discontinuation estimates remain closely aligned. By month 18, the proportion of patients discontinuing is ████████ using the exponential function and ████████ using the KM data. These differences are minimal and do not materially affect model outcomes.

The per-cycle probabilities derived from the KM data and from the exponential parametric function are reported in Table 39. The contribution of this change to the updated base case results is included in Table 34.

Table 39: Cycle probability of unplanned discontinuation in the efgartigimod arm based on ADHERE and ADHERE+ time-to-event analysis of discontinuations due to adverse events

	6-month cycle length		3-month cycle length	
	Cycle probability based on Kaplan-Maier data	Cycle probability based on Exponential	Cycle probability based on Kaplan-Maier data	Cycle probability based on Exponential
Month 3	██████	██████	██████	██████
Month 6			██████	██████
Month 9	██████	██████	██████	██████
Month 12			██████	██████
Month 15	██████	██████	██████	██████
Month 18			██████	██████

B19. Priority question: Please provide a scenario analysis in which permanent treatment discontinuation is applied indefinitely over the time horizon of the model for efgartigimod and Ig.

As requested, we have added a scenario analysis in which both the efgartigimod and Ig cohorts are assigned a probability of unplanned discontinuation throughout the entire time horizon of the analysis. For the efgartigimod cohort, the probability of discontinuation over time is derived from the exponential parametric function fitted to the time-to-event data from ADHERE and ADHERE+. As reported in the CS, the exponential function provided the best overall fit to the observed KM data and is therefore used to generate cycle-level discontinuation probabilities for this scenario. For the Ig cohort, the cycle probability of unplanned discontinuation is based on data from the open-label extension study of Hizentra reported by van Schaik et al.,³⁶ specifically, the discontinuation rate observed between 6 and 18 months. This cycle probability is then recycled from Month 6 onwards for the duration of the model time horizon.

This scenario can be selected by the user in the *Settings* sheet of the model. The results of this scenario analysis show a dominant result in favour of efgartigimod (NMB = [REDACTED]). However, we do not consider this scenario to be clinically realistic, as clinical experts indicated that unplanned discontinuations mainly occur in the initial treatment period and that patients rarely discontinue treatment thereafter.

B20. Priority question: Please justify why the ICE and PATH studies were considered appropriate for informing discontinuation from Ig, but not ADVANCE-CIDP-1, which informs the clinical inputs in the model. Please provide a scenario analysis in which discontinuation of Ig in the first treatment cycle is aligned with ADVANCE-CIDP-1.

Clinicians advised that, while efficacy is broadly comparable across Ig products, safety profiles may differ between products. Because unplanned discontinuations are typically driven by tolerability and safety (rather than efficacy), the probability of unplanned Ig discontinuation in the model was informed by studies using Ig products that are reflective of current Ig use in CIDP clinical practice in England and are

therefore included as comparators in the model. The same approach was taken for the sourcing of AEs.

Moreover, the safety profile observed in ADVANCE-CIDP-1 differs from that seen with standard IVIg and SCIg products, largely due to the unique formulation and administration method of facilitated SCIg (fSCIg). fSCIg combines immunoglobulin with recombinant human hyaluronidase, enabling larger infusion volumes and less frequent dosing compared to conventional SCIg. However, this approach can introduce distinct tolerability challenges, such as a higher incidence of local infusion-site reactions and potential systemic effects related to the enzyme or higher local Ig concentrations. These factors likely contributed to the higher discontinuation rate observed in ADVANCE-CIDP-1, which does not reflect the experience with the Ig products most commonly used in England. By basing discontinuation and adverse event rates on ICE and PATH, the model more accurately captures the safety and tolerability profile relevant to current UK clinical practice, ensuring that the analysis remains representative and robust.

For this reason, the ICE and PATH studies were preferred to inform Ig discontinuation, rather than ADVANCE-CIDP-1.

In ADVANCE-CIDP-1, among 48 patients receiving Ig, 10 discontinued treatment over 24 weeks: three due to adverse events, three due to physician decision, four due to patient withdrawal.

This corresponds to an observed discontinuation rate of 20.8% (10/48) over 24 weeks. When converted to a 6-month (model cycle) probability, this yields a 6-month discontinuation probability of 22.4%.

To address the EAG's request, we implemented two additional scenario analyses:

- ADVANCE-CIDP-1–based early discontinuation: Ig discontinuation in the first 6-month cycle is set equal to the ADVANCE-CIDP-1-derived probability (22.4%). Since a higher discontinuation is applied to the Ig cohort, this results in lower total cost in the comparator arm than in efgartigimod arm and

therefore a positive incremental cost of [REDACTED]. The resulting ICER for this scenario is [REDACTED] per QALY.

- Pooled Ig discontinuation across studies: Ig discontinuation in the first -6-month cycle is based on the pooled (average) discontinuation probability from ICE, PATH, and ADVANCE-CIDP-1, resulting in a 6-month discontinuation probability of 11.2%. In this scenario efgartigimod remains dominant with a NMB of [REDACTED]

B21. Priority question: In order to align with the assumption that patients on stable maintenance treatment do not discontinue treatment in the long-term, please provide a scenario analysis in which patients receiving Ig or a treatment in the comparator basket do not permanently discontinue treatment at any time.

We implemented this scenario by setting the probability of unplanned discontinuations in the Ig arm equal 0 at any model cycle. This scenario can be run by the user using the selector added in the *Settings* sheet of the model. This scenario results into a dominant ICER for efgartigimod versus the comparator and with a NMB of [REDACTED]. Given that the cohort has already been treated with Ig before entering the simulation, we consider this scenario potentially reflective of current practice. However, to maintain consistency with the efgartigimod arm, unplanned discontinuations were included for the Ig cohort in the base-case analysis.

Adverse events

B22. Priority question: In the model, the company has included common adverse events (AEs) for efgartigimod occurring in ≥5% of patients from stage B of ADHERE. Typically, for economic models submitted to NICE, AEs are commonly defined as Grade ≥3 treatment-related AEs as these are associated with substantial treatment costs and impacts on health-related quality of life (HRQoL).

- a) Please provide Tables 14.3.1.11 and 14.3.1.12 of the ARGX-113-1802 CSR (grade ≥ 3 AEs in Stage A and B by MedDRA SOC and PT).
- b) Please justify the use of common AEs instead of Grade ≥ 3 treatment-related AEs for inclusion in the model.
- c) Based on the data requested in part a), please provide a scenario using Grade ≥ 3 treatment-related AEs occurring in $\geq 5\%$ efgartigimod patients in the model.

(a) The company provides Table 14.3.1.11 and 14.3.1.12 of the ARGX-113-1802 CSR below (Table 40 and Table 41).

Table 40: Grade 3 or more treatment-emergent adverse events by MedDRA system organ class and preferred term - Stage A

System organ class and preferred term	Efgartigimod (N=322, PYFU=46.9)	
	n (%)	m (ER)
Any grade 3 or more treatment-emergent adverse event	████	████
Cardiac disorders	████	████
Cardiac arrest	████	████
General disorders and administration site conditions	████	████
Fatigue	████	████
Hepatobiliary disorders	████	████
Hepatic function abnormal	████	████
Infections and infestations	████	████
Clostridium difficile colitis	████	████
COVID-19	████	████
COVID-19 pneumonia	████	████
Suspected COVID-19	████	████
Metabolism and nutrition disorders	████	████
Hypernatremia	████	████
Hypertriglyceridemia	████	████
Musculoskeletal and connective tissue disorders	████	████
Muscular weakness	████	████
Nervous system disorders	████	████
Chronic inflammatory demyelinating polyradiculoneuropathy	████	████
Quadriparesis	████	████
Renal and urinary disorders	████	████
Calculus urinary	████	████
Vascular disorders	████	████

System organ class and preferred term	Efgartigimod (N=322, PYFU=46.9)	
	n (%)	m (ER)
Hypertension	████	████

Source: argenx data on file - tables, figures and listings table 14.3.1.11

Coding is based on MedDRA version 25.1 (Sep 2022).

n = number of participants with the event; m = number of events.

Abbreviations: ER: Event rate per 100 participant years of follow-up ($m \times 100 / \text{PYFU}$); PYFU: participant years of follow-up (sum of follow-up time of all participants expressed in years, per treatment group); TEAE: Treatment-emergent adverse event.

Table 41: Grade 3 or more treatment-emergent adverse events by MedDRA system organ class and preferred term - Stage B

System organ class and preferred term	Efgartigimod (N=111, PYFU=56.7)		Placebo (N=110, PYFU=42.1)	
	n (%)	m (ER)	n (%)	m (ER)
Any grade 3 or more TEAE	████	████	████	████
Blood and lymphatic system disorders	████	████	████	████
Anaemia	████	████	████	████
Ear and labyrinth disorders	████	████	████	████
Deafness unilateral	████	████	████	████
Hepatobiliary disorders	████	████	████	████
Cholelithiasis	████	████	████	████
Infections and infestations	████	████	████	████
Appendicitis	████	████	████	████
COVID-19 pneumonia	████	████	████	████
Pneumonia	████	████	████	████
Wound infection	████	████	████	████
Injury, poisoning and procedural complications	████	████	████	████
Foot fracture	████	████	████	████
Metabolism and nutrition disorders	████	████	████	████
Dehydration	████	████	████	████
Neoplasms benign, malignant and unspecified (including cysts and polyps)	████	████	████	████
Lipoma	████	████	████	████
Prostate cancer	████	████	████	████
Transitional cell carcinoma	████	████	████	████
Nervous system disorders	████	████	████	████
CIDP	████	████	████	████
Vascular disorders	████	████	████	████
Hypertension	████	████	████	████

Source: argenx data on file - tables, figures and listings table 14.3.1.12

Coding is based on MedDRA version 25.1 (Sep 2022).

n = number of participants with the event; m = number of events.

Abbreviations: CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; ER: Event rate per 100 participant years of follow-up ($m \times 100 / \text{PYFU}$); PYFU: participant years of follow-up (sum of follow-up time of all participants expressed in years, per treatment group); TEAE: Treatment-emergent adverse event.

(b) We used common AEs rather than Grade ≥ 3 treatment-related AEs because the comparator trials do not report Grade ≥ 3 treatment-related AEs consistently. As a result, applying only Grade ≥ 3 treatment-related AEs for efgartigimod while having no equivalent data for Ig would have introduced an imbalance and potentially underestimated AE burden in the comparator arm. Using common AEs therefore represents a conservative and more comparable approach across treatment arms, given available published data.

(c) As presented in the table in point (a) above, there were no Grade ≥ 3 treatment-related AEs occurring in $\geq 5\%$ efgartigimod patients in ADHERE trial. Thus, a scenario analysis was conducted where the probability of AEs in the efgartigimod arm of the model was set equal 0%. The results of this scenario analysis are presented in Table 35, the impact on the ICER is minimal (in favour of efgartigimod).

B23. Table 37 of the CSR was reported as the source of AEs for efgartigimod in the model. However, this table also included data for COVID-19, which was reported to have occurred in [REDACTED] of efgartigimod patients. Please explain why COVID-19 was excluded from efgartigimod AEs in the model?

COVID-19 was excluded from the efgartigimod AE inputs. Inclusion of COVID-19 would introduce bias by inflating the AE burden for efgartigimod relative to comparators, whose trials were conducted in different time periods with substantially lower or negligible COVID-19 prevalence. As COVID-19 is no longer circulating at pandemic levels, its exclusion ensures that the model reflects treatment-attributable risks relevant to current clinical practice and provides a generalisable estimate of AE burden consistent with NICE standards.

B24. Priority question: Adverse events for IVIg and SCIg are based on multiple sources with various definitions for inclusion. The EAG has investigated the sources used for IVIg and SCIg and has identified several issues that warrant clarification and further analysis.

- **AEs for Privigen (IVIg) are obtained from the PATH study (Mielke *et al.* 2019). The model references the ADVANCE study (Bril *et al.* 2023) as a**

source, but this does not appear to be used. The data from the PATH study were used in the model for all the most common AEs, with no severity defined. However, applying the threshold of occurring in $\geq 5\%$ of patients as per the inclusion criteria for efgartigimod, the only AEs that are applicable are headache (16.4%) and nasopharyngitis (5.8%). The company has assumed the AEs associated with Privigen would be the same for Flebogamma DIF, but has not justified this assumption.

- AEs for Hizentra (SCIg) are obtained from the PATH extension study (van Schaik *et al.* 2019) and are reported for all AEs occurring in $\geq 2\%$ of patients (overall population). The EAG is unclear how the company selected AEs from the study to be included in the model. Applying the threshold of occurring in $\geq 5\%$ of patients as per the inclusion criteria for efgartigimod, the only AEs that are applicable are local reactions (22.0%) and nasopharyngitis (13.4%).
- AEs for Gamunex (IVIg) are obtained from the ICE study (Hughes *et al.* 2008) and are reported for all AEs occurring in $\geq 5\%$ of patients, irrespective of causality.

The odds ratios (ORs) obtained from the Waheed *et al.* 2019 study estimate the odds of experiencing an AE based on IVIg dose, but no definition of severity of AE was provided. Additionally, the ORs reported in the paper do not match what has been included in the model. Additionally, of the AEs reported, headache was the only one that occurred in more than 5% of patients.

- a) Please justify why AEs for Privigen have been assumed for Flebogamma DIF.
- b) Please clarify how AEs were selected for inclusion for Hizentra.
- c) The ORs reported in Table 55 do not match the ORs in Table 3 of Waheed *et al.* 2019. Please check and correct the model as necessary.
- d) Please conduct a scenario where AEs based on the inclusion criteria of occurring in $\geq 5\%$ of patients are included in the model for IVIg and SCIg.

(a) Adverse events for Privigen were assumed for Flebogamma because no published or trial-based AE data were available for Flebogamma in the CIDP population. Both products are IVIg formulations with comparable composition and administration characteristics. In the absence of product-specific data, it was considered reasonable and consistent with modelling practice to use Privigen AE data as a proxy for Flebogamma.

(b) The rate of AEs for Hizentra was obtained based on the number of events reported in the OLE of the PATH study published by van Schaik et al. (2019).³⁶ This was chosen over the double-blind trial, as it has a longer follow-up, i.e. 48 Weeks. To calculate the AE rate, the number of events (overall) per each AE reported in Table 5 of the publication was divided by the estimated per person follow-up ($N=82 \times \text{follow-up in model cycles}=2$). The AE rate was then transformed into a probability per cycle using the formula $1-EXP(-rate)$. We noticed some of the AEs reported in the publication were missed. We updated the numbers and added a clarification note on the respective events in Table 5 of the PATH OLE publication. The revised base case includes the corrected inclusion of the AEs for Hizentra as reported in Table 42. This change only minimally impacts the ICER and the contribution to the revised base case is reported in Table 34.

Table 42: Adverse events for Hizentra from the PATH OLE

Adverse event	N events, CS	N events, updated	Source
Back Pain and muscle spasms	3	6	Table 5, Overall, N event: back pain (3) and Muscle spasm (3)
Dizziness or Falls	0	8	Table 5, Overall, N event: Dizziness (5) and Falls (3)
Fatigue	4	4	Table 5, Overall, N event: Fatigue (4)
Headache or Sciatica	5	8	Table 5, Overall, N event: Headache (4) and Sciatica (4)
Infusion/injection site reaction	40	40	Table 5, Overall, N event: Local reactions (40)
Nasopharyngitis and Urinary Tract Infection	13	15	Table 5, Overall, N event: Nasopharyngitis (13) and Urinary Tract Infection (2)
Nausea	2	2	Table 5, Overall, N event: Nausea (2)

Gastrointestinal disturbances	0	5	Table 5, Overall, N event: Diarrhoea (2) and Vomiting (3)

Abbreviations: OLE: Open-label extension.

- (c) The company confirm there was an error in the calculation. This has been corrected in the revised base case model and the contribution of this correction to the base case results is presented in Table 34.
- (d) The company have added a scenario only including AEs occurring in $\geq 5\%$ of patients. This only minimally impact the results as shown in Table 34.

B25. Priority question: The EAG investigated the Dorst *et al.* 2020 study informing AEs for PLEX. The paper reported that no severe AEs were recorded for PLEX and that, “adverse events were uncomplicated and did not necessitate any specific therapy”.

- a) Please clarify why allergic skin reactions were assumed to be infusion/injection site reactions in the model.
- b) Given the paper reported that AEs did not require specific treatment, please justify the inclusion of these for PLEX in the model.
- c) Please provide a scenario where AEs for PLEX are excluded from the model.

(a) Injection site reactions (ISRs) are AEs that occur in response to a drug or its excipient administered subcutaneously. They typically present as localised pain, pruritus, or erythema. ISRs may arise either from irritative reactions driven by the proinflammatory properties of the drug or from allergic responses to the drug itself (Kim et al., 2023).³⁷

Allergic skin reactions are hypersensitivity events that manifest on the skin, such as rash, urticaria, or eczema. According to the updated World Allergy Organisation (WAO) grading classification system, allergic manifestations can be systemic but may also remain localised, restricted to the injection site (for example, localised urticaria or rash at the site of drug administration). Examples of local allergic reactions include “warmth and/or pruritus at the injection site following subcutaneous

immunotherapy or vaccine administration” and “skin reactions at the site of allergen application during epicutaneous immunotherapy” (Turner et al., 2024).³⁸

Both allergic skin reactions (e.g., rash, urticaria) and ISRs (e.g., erythema, swelling, pruritus) involve the skin or subcutaneous tissue, making them clinically visible and comparable from the perspective of patient-reported outcomes. They share key features: cutaneous involvement, immune-mediated inflammation, overlapping symptomatology, and temporal association with drug administration. These parallels support the use of allergic skin reactions as a pragmatic proxy for ISRs.

Further evidence of the shared immune-driven mechanisms comes from the Medical Dictionary for Regulatory Activities (MedDRA),³⁹ the standardised terminology system for coding adverse events. Within MedDRA, the ISR category explicitly includes “injection site hypersensitivity” as a subclass (Medical Dictionary for Regulatory Activities Terminology (MedDRA) - Injection site reactions - Class...), while the broader “hypersensitivity” category encompasses “allergic reactions” as a subclass (Medical Dictionary for Regulatory Activities Terminology (MedDRA) - Allergic conditions NEC - Class...). This overlap highlights hypersensitivity as a mechanistic link between allergic skin reactions and ISRs, reinforcing their clinical comparability.

(b) Whilst Dorst et al.,⁴⁰ reported that AEs were uncomplicated and did not require specific therapy, they were still documented as occurring events. From an HTA perspective, inclusion of these AEs ensures transparency and consistency in capturing all reported safety signals, even if their clinical impact is minimal. Cost inputs for these AEs were derived from NHS reference costs (2024/25 pay award prices) to maintain alignment with the UK payer perspective, rather than the German setting of the original study.⁴¹ Whilst the rates of AEs were obtained from Dorst et al.,⁴⁰ the costs associated with these AEs are taken from the 24/25 pay award prices associated with the AEs. Since the Dorst paper is set in Germany, it is appropriate to include the costs for the AEs to remain in line with the NHS perspective.

(c) We have added a scenario to exclude PLEX adverse events from the model. This change only minimally impacts the results as shown in Table 34.

B26. Priority question: The EAG investigated the Nobile-Orazio *et al.* 2012 study informing AEs for IV methylprednisolone. The paper did not report AEs by severity and most AEs occurred in one patient.

a) Please justify why depression, increased anxiety, agitation, delirium and visual hallucination have been grouped under the category of "psychiatric disorders" with an associated unit cost of £627.

i) The duration of psychiatric disorders (95 days) is based on the value for depression from TA706. Please justify why the duration of psychiatric disorders based on depression is appropriate.

b) In the model, applying the threshold of occurring in $\geq 5\%$ of patients as per the inclusion criteria for efgartigimod, the only AEs that are applicable for corticosteroids are hypertension (14.29%), endocrine disorders (9.52%) and peripheral oedema (9.52%). All other AEs, when not grouped, do not meet the threshold. As such, please provide a scenario where AEs based on the inclusion criteria of occurring in $\geq 5\%$ of patients are included in the model.

(a) Depression, increased anxiety, agitation, delirium, and visual hallucinations were grouped under the category of psychiatric disorders as these AEs share overlapping symptomatology, underlying neuropsychiatric mechanisms, and similar management pathways. This grouping reflects a pragmatic method to capture resource use for psychiatric complications without overestimating costs.

TA706 is an appropriate reference due to the similar symptoms experienced by CIDP and relapsing-remitting multiple sclerosis. The associated unit cost was the average of the most appropriate cost-codes.

i) The value of 95.03 days for the duration of depression AE has come from the weighted average of the AE in TA706. In the absence of data for all psychiatric disorders within CIDP, we have used depression as a proxy for all psychiatric disorders due to its chronic nature and

treatment. As we grouped these AEs, taking a single utility value based on a proxy was appropriate and avoided double-counting.

- (b) We have added a scenario where hypertension (14.29%), endocrine disorders (9.52%) and peripheral oedema (9.52%) only are included as AEs in the model for corticosteroids. The impact on the base case results is seen in Table 34.

B27. Priority question: The EAG investigated the Narayanaswami *et al.* 2024 study informing AEs for mycophenolate mofetil. The paper reported that one out of nine AEs reported for mycophenolate mofetil was Grade 3 (no detail given on which AE), with the rest reported as Grade 1 and 2. In the model, applying the threshold of occurring in $\geq 5\%$ of patients as per the inclusion criteria for efgartigimod, the only AE that is applicable for immunosuppressants is gastrointestinal disturbances (14.89%). As such, please provide a scenario where gastrointestinal disturbances, based on the inclusion criteria of occurring in $\geq 5\%$ of patients, are included in the model for immunosuppressants.

We have conducted a scenario analysis where only AEs with an incidence of $\geq 5\%$ are included in the model for immunosuppressants. Based on Narayanaswami *et al.* (2024),⁴² gastrointestinal disturbance (14.89%) is the only AE that meets this threshold. The impact of this analysis is seen in Table 35Table 34.

B28. Priority Question: Based on the issues identified in questions B21 - B26, the EAG considers there is not sufficient evidence to suggest that AEs for efgartigimod, Ig, PLEX, corticosteroids and immunosuppressants are severe in nature and would require substantial costs to treat nor would they have a clinically meaningful impact on HRQoL. The EAG also considers the company has not sufficiently justified the inclusion of AEs in the model and no consideration or discussion was given to the differences in populations, treatment regimens, inclusion criteria and study designs, which creates a high level of uncertainty in the cost-effectiveness results. As such, please provide a

scenario where AEs for efgartigimod, Ig, PLEX, corticosteroids and immunosuppressants are excluded from the model.

Recognising the high burden of CIDP treatment experienced by some patients, the company maintains that AEs experienced by patients with CIDP may require substantial costs to treat and could have a clinically meaningful impact on HRQoL. Treatment with efgartigimod is associated with a relatively low incidence of serious adverse events (AEs) with 21 (6.5%) patients in ADHERE Stage A reporting any serious treatment-emergent AE.² Short- and long-term treatment with PLEX and corticosteroids is documented to cause serious AEs and reductions in HRQoL.^{43,44} These harms are mainly related to catheter- and procedure-associated complications such as hypotension and infections, with vascular events during PLEX and the long-term AEs associated with corticosteroids contributing to treatment burden and reduced HRQoL in people living with CIDP.^{43,44}

Patient interaction and testimony also tell us that treatment with IVIg can affect the day-to-day life of a patient substantially, with severe weakness, tiredness and limited ability to function reported.³¹ In addition, the repeated administration of IVIg over time becomes problematic, with the insertion of the cannula bringing discomfort and challenges when the number of available vein sites reduces. Survey data confirm this, with 33.3% of IVIg users reporting dissatisfaction with treatment, citing “unpleasant side effects” as a reason.³¹

Whilst the company considers that the NHS perspective should contain all costs and benefits pertaining to the NHS, including AEs, we acknowledge the EAG’s concerns. To address this, we have added a scenario analysis that excludes all AEs for efgartigimod, Ig, PLEX, corticosteroids and immunosuppressants. As expected, because treatments in the comparator arm are associated with more AEs than efgartigimod, both incremental costs and incremental QALYs are less favourable to efgartigimod than when AEs are included. Nonetheless, the resulting ICER remains dominant in favour of efgartigimod, with a net monetary benefit of [REDACTED]

B29. Priority question: Rates of complications related to IV access are based on a US budget impact model comparing IVIg to SCIg, and data informing the model are based on numerous sources, many of which are over 20 years old. The EAG considers that the NHS adopts robust sterile techniques to deliver IV treatment and understands from its clinical experts that healthcare professionals delivering IVIg and PLEX are well-trained and experienced. As such, please supply evidence related to NHS practice of complications related to IV access for patients receiving IV treatment for CIDP.

a) Please supply a scenario that excludes complications related to IV access.

Real-world evidence from UK patients and clinical experts demonstrates that complications related to IV access remain a significant and under-recognised burden in CIDP care. Nurses report that IV access difficulties are common, especially in patients on long-term IVIg.⁴⁵ Infusions often need to be split or slowed, increasing the number of cannulations and the risk of access-related complications, while some patients require multiple attempts or specialist input for cannulation, further increasing distress and resource use.⁴⁵ In appendix L of the Company Submission, patient testimonials are presented where one patient reported: *“I now only have one vein site on one arm that can be accessed for IVIg; when this becomes problematic also, I do not know what I will do. It has become so painful to insert the cannula now.”* This statement highlights that, even with best practice, repeated IV access leads to vein depletion, pain, and procedural anxiety. As requested, we ran a scenario analysis excluding complications related to IV access. The results of this scenario are presented in Table 35.

Utility values

B30. Priority question: There is a lack of detail in the CS around the EQ-5D-5L index data collected in ADHERE used in the economic model.

- a) Please provide details on how EQ-5D-5L was measured in the trial (for example, timepoints of measurement, number of responses at each time point, length of follow up, etc.) along with the mean EQ-5D values (cross-walked to the 3L using UK value set) at each timepoint.
- b) Please perform a descriptive analysis of the EQ-5D utility data for each health state in the model and provide the number of responses informing each health state utility value.

(a) EuroQol Five Dimensions, Five Levels (EQ-5D-5L) assessment in ADHERE was done at Baseline of Stage A and every week thereafter up to Week 12 in Stage A. Then it was done at Baseline of Stage B and every 4 weeks thereafter up to Week 48 in Stage B. Table 43 presents the time point of EQ-5D-5L measurement in ADHERE, along with the number of responses and descriptive statistics for each time point. EQ-5D-5L scores were transformed into utility values using crosswalk-walk from five levels (5L) to 3L published by Hernandez et al.⁴⁶ Overall, at Baseline Stage A ADHERE, the utility was 0.378 (SD: 0.283). The utility at Week 48 of Stage B had improved to 0.708 (0.171). The average length of follow-up was 153 days and 172 days when considering the last visit at Stage A+B and last visit at Stage B, respectively.

Table 43: Descriptive analysis of the EQ-5D utility data for each time point of measurement in ADHERE (Stage A and B)

Variable	N	Mean (SD)	Q1 Median Q3	Min Max
Stage A - Baseline	315	0.378 (0.283)	0.183 0.470 0.602	-0.378 0.891
Stage A - Week 1	7	0.229 (0.530)	-0.393 0.263 0.744	-0.453 0.893
Stage A - Week 2	15	0.234 (0.369)	-0.064 0.287 0.597	-0.316 0.731
Stage A - Week 3	7	0.276 (0.203)	0.157 0.217 0.505	-0.041 0.515
Stage A - Week 4	103	0.627 (0.263)	0.555 0.649 0.744	-0.250 0.989

Variable	N	Mean (SD)	Q1 Median Q3	Min Max
Stage A - Week 5	30	0.453 (0.328)	0.321 0.603 0.666	-0.276 0.893
Stage A - Week 6	14	0.466 (0.353)	0.165 0.569 0.691	-0.155 0.987
Stage A - Week 7	18	0.567 (0.256)	0.382 0.637 0.745	-0.119 0.987
Stage A - Week 8	6	0.417 (0.174)	0.247 0.401 0.611	0.216 0.627
Stage A - Week 9	19	0.449 (0.277)	0.255 0.545 0.666	-0.151 0.864
Stage A - Week 10	13	0.574 (0.206)	0.543 0.612 0.681	0.138 0.823
Stage A - Week 11	16	0.568 (0.292)	0.444 0.649 0.751	-0.166 0.933
Stage A - Week 12	16	0.515 (0.228)	0.376 0.530 0.682	-0.043 0.860
Stage A - Week 13	17	0.590 (0.213)	0.597 0.638 0.679	-0.145 0.771
Stage B - Baseline	195	0.611 (0.232)	0.545 0.640 0.736	-0.250 0.989
Stage B - Week 4	46	0.381 (0.348)	0.148 0.459 0.598	-0.415 0.987
Stage B - Week 8	34	0.543 (0.257)	0.500 0.597 0.676	-0.166 0.987
Stage B - Week 12	137	0.606 (0.262)	0.537 0.641 0.733	-0.343 0.988
Stage B - Week 16	15	0.596 (0.272)	0.483 0.642 0.754	-0.054 0.988
Stage B - Week 20	13	0.574 (0.257)	0.500 0.663 0.791	0.137 0.868
Stage B - Week 24	90	0.645 (0.225)	0.572 0.667 0.764	-0.187 0.988
Stage B - Week 28	11	0.580 (0.388)	0.442 0.680 0.797	-0.459 0.987
Stage B - Week 32	6	0.712 (0.107)	0.674 0.748 0.762	0.517 0.823
Stage B - Week 36	67	0.650 (0.229)	0.573 0.670 0.758	-0.207 0.988
Stage B - Week 40	4	0.633 (0.266)	0.454 0.600 0.813	0.347 0.987
Stage B - Week 48	51	0.708 (0.171)	0.622 0.707 0.806	0.173 0.987
EQ-5D follow-up time (Days) Stage A+B - Last visit Stage A+B	320	152.7 (131.9)	50.0 92.5 250.5	1.0 443.0
EQ-5D follow-up time (Days) Stage B patients only - Last visit Stage B	282	172.2 (128.6)	65.0 124.5 276.0	21.0 443.0

Abbreviations: EQ-5D: EuroQol 5 Dimensions; Min: Minimum; Max: Maximum; Q1: First quartile; Q3: Third quartile; SD: Standard deviation.

(b) Table 44 presents the descriptive statistics of the utility value by health state, calculated based on pooled ADHERE Stage A+B and using the crosswalk value set from 5L to 3L published by Hernandez et al.⁴⁶ As it can be observed, the utility

values obtained from a descriptive analysis are broadly similar to those obtained when applying a mixed model for repeated measure (used in the base case analysis). The mean utility by health state reported in Table 44 was used to run a scenario analysis, showing minimal impact on the model results - the discounted incremental QALYs when using descriptive statistics are [REDACTED] instead of 4.26 when applying the mixed model to estimate the health state utilities (Table 35).

Table 44: Descriptive analysis of the EQ-5D data from ADHERE Stage A+B by health state, UK utility value set with cross-walk from 5L to 3L published by Hernandez et al.

Health state	N	Mean (SD)	Q1 Median Q3	Min Max
Very limited impairment (aINCAT 0-1)	96	0.868 (0.130)	0.795 0.891 0.986	0.288 0.989
Mild impairment (aINCAT 2-3)	432	0.631 (0.185)	0.562 0.648 0.736	-0.270 0.988
Moderate impairment (aINCAT 4-6)	437	0.447 (0.240)	0.293 0.511 0.622	-0.316 0.988
Severe impairment (aINCAT 7-8)	82	0.083 (0.270)	-0.145 0.069 0.248	-0.453 0.665
Very Severe impairment (aINCAT 9-10)	19	-0.240 (0.096)	-0.304 -0.225 -0.151	-0.459 -0.119

Abbreviations: 3L: 3 levels; 5L: 5 levels; EQ-5D: EuroQol 5 Dimensions; Min: Minimum; Max: Maximum; Q1: First quartile; Q3: Third quartile; SD: Standard deviation.

B31. Priority question: There is a lack of detail in the CS on the mixed model used to generate the health state utility values included in the model. Please provide an explanation of the methods for the mixed model specification, including covariates considered for the analysis, handling of missing data, model fit statistics and results.

A linear mixed-effects model was fitted to ADHERE data to estimate health state utility values. The analysis was conducted using the lme4 package in R. The objective was to estimate EQ-5D-5L utility values associated with each aINCAT-based health state category while appropriately accounting for repeated measurements within patients.

The dependent variable was the EQ-5D-5L utility score. The only fixed-effect covariate included in the model was aINCAT cluster, a categorical variable representing disease-severity levels based on aINCAT health states. This aligns with

the purpose of the model, which was to obtain utilities that vary only by health state and not by other patient characteristics.

To account for within-patient correlation arising from repeated measures, a random intercept was included for patient identifier (USUBJID). This allows each patient to have an individual baseline utility level while estimating the effect of INCAT severity on utility.

The model can be expressed as:

$$Utility = aINCAT\_clust + random\ intercept\ for\ USUBJID.$$

A complete-case approach was used. Missing EQ-5D measurements were infrequent and not systematically associated with aINCAT severity, and therefore their exclusion was considered unlikely to introduce bias. Because EQ-5D values cannot be reliably imputed without strong assumptions, complete-case analysis was judged the most appropriate approach.

Model fit was evaluated using standard diagnostics, including Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), marginal and conditional R², and visual inspection of residuals and random-effects distributions. Diagnostics did not indicate any violations of model assumptions. The random-intercept structure adequately captured intra-patient correlation.

B32. Please clarify if utility values derived from ADHERE were validated with UK clinical experts and if so, please provide their feedback.

Utility values derived from the ADHERE study were presented to clinical experts in two individual interviews aimed at validating the health state definition. The primary aim was to validate the health state definitions and ensure the estimated impact on health-related quality of life (HRQoL) by aINCAT health state was clinically plausible. Overall, clinical experts confirmed that they would expect a large difference between lower and higher aINCAT scores, with disability in higher aINCAT scores being comparable to worse Expanded Disability Status Scale (EDSS) in multiple sclerosis (MS). In addition, EQ-5D data from the Adelphi study conducted by argenx⁴⁷ are broadly aligned with those observed in the ADHERE study. The utilities in this study

were derived by applying the same crosswalk value set used for the analysis on the ADHERE data (i.e. Hernandez et al.⁴⁶). A scenario analysis was implemented, using utilities derived from a descriptive analysis of the Adelphi study EQ-5D data instead of the mixed model on ADHERE data. The incremental discounted QALYs in this scenario are [REDACTED] compared with 4.26 in the base case analysis (Table 35).

Table 45: Descriptive analysis of the EQ-5D data from the Adelphi study by health state, UK utility value set with cross-walk from 5L to 3L published by Hernandez et al.

Health state	N	Mean	SD
Very limited impairment (aINCAT 0-1)	[REDACTED]	[REDACTED]	[REDACTED]
Mild impairment (aINCAT 2-3)	[REDACTED]	[REDACTED]	[REDACTED]
Moderate impairment (aINCAT 4-6)	[REDACTED]	[REDACTED]	[REDACTED]
Severe impairment (aINCAT 7-8)	[REDACTED]	[REDACTED]	[REDACTED]
Very Severe impairment (aINCAT 9-10)	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: 3L: 3 levels; 5L: 5 levels; EQ-5D: EuroQol 5 Dimensions; SD: Standard deviation.

B33. The EAG is concerned that the EQ-5D-5L to EQ-5D-3L crosswalk algorithm has led to overly low health state utility values for the severe and very severe impairment health states. Please provide the mean value and range of EQ-5D-5L observations from the ADHERE trial, corresponding to each health state in the model.

Table 46 presents the number of observations and descriptive statistics of the EQ-5D-5L observations from pooled ADHERE Stages A and B.

Table 46: Mean value and range of EQ-5D-5L observations from the ADHERE trial, Stage A and B, by model health states.

Variable	Very limited impairment (aINCAT 0-1)	Mild impairment (aINCAT 2-3)	Moderate impairment (aINCAT 4-6)	Severe impairment (aINCAT 7-8)	Very Severe impairment (aINCAT 9-10)
Original EQ-5D-5L score – Mobility					
N	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Q1 Median Q3	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Min Max	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Variable	Very limited impairment (aINCAT 0-1)	Mild impairment (aINCAT 2-3)	Moderate impairment (aINCAT 4-6)	Severe impairment (aINCAT 7-8)	Very Severe impairment (aINCAT 9-10)
Original EQ-5D-5L score - Self-care					
N					
Mean (SD)					
Q1 Median Q3					
Min Max					
Original EQ-5D-5L score – Usual Activities					
N					
Mean (SD)					
Q1 Median Q3					
Min Max					
Original EQ-5D-5L score - Pain-Discomfort					
N					
Mean (SD)					
Q1 Median Q3					
Min Max					
Original EQ-5D-5L score - Anxiety-Depression					
N					
Mean (SD)					
Q1 Median Q3					
Min Max					

Abbreviations: EQ-5D-5L: EuroQol 5 Dimensions, 5 Levels; Min: Minimum; Max: Maximum; Q1: First quartile; Q3: Third quartile; SD: Standard deviation.

B34. The EAG has noted that age-adjustment has been applied to patients occupying the very severe impairment health state. Please explain, with supporting evidence, why it is appropriate to assume age-related decline for patients who consider their health state is worse than death?

- a) Please explain why the inverse of the standard age-adjustment multiplier has been applied to negative health state utility values.
- b) Please provide a scenario that removes the age-adjustment for patients in the very severe impairment health state.

(a) Age-adjustment was included in any health state, including the very severe impairment state, to ensure symmetrical impact in each health state across the entire disease spectrum. Moreover, as per the Hernandez et al. value set,⁴⁶ the minimum attainable utility value is lower than the value in the Very Severe health state.

(b) As requested, we have updated to the model and added the option to remove the age-adjustment from the patients within the Very Severe health state utility calculation over the model time horizon of the analysis. The results of this scenario are presented in Table 35.

B35. Please provide a scenario where the utility value for the very severe health state is set to 0.

A scenario analysis was conducted with the utility value in the Very Severe health state equal to 0, rather than the negative value used in the base case. The resulting impact on the model results is minimal, because there are only a few patients in the Very Severe health state over the time horizon of the analysis, in both the intervention and the comparator arms. The incremental QALYs in this scenario are [REDACTED] compared with 4.26 in the base case. As also presented in the CS, an alternative scenario was explored where the utilities in Severe and Very Severe were projected based on the utilities in the other health states. Based on this approach, the incremental QALYs are [REDACTED]. Efgartigimod remains dominant over the comparator in both scenarios.

B36. The utility values presented in Table 31 of the CS do not match those presented in Table 53 of the CS (which are the values used in the model). Please explain the difference between the two sets of utility values.

The company acknowledges that the utility values in Table 31 of the Company Submission did not match those in CS Table 53 – the values used in the cost-effectiveness model. The correct values are those reported in the cost-effectiveness model, and the updated table is provided below.

Table 47: Updated version of CS Table 31

Health state	Mean (SE)
Very limited impairment	
Mild impairment	
Moderate impairment	
Severe impairment	
Very severe impairment	

Source: ADHERE data.

Abbreviations: SE: Standard error.

B37. In the QALY calculations in the main model engines, a value of -0.52882 has been used as a maximum limit. Please clarify what this value relates to.

The value of -0.52882 represents the lowest possible health state utility based on the Hernandez et al. published EQ-5D-5L value sets for England.⁴⁶

B38. Priority question: In the model, the company has extracted disutility values for most AEs from a single source (Sullivan *et al.* 2011). The study by Sullivan *et al.* is a well-established source of utility values used in several NICE TAs. AE disutility values from TA706 are derived from multiple sources, including NICE TAs for ocrelizumab (TA533) and cladribine (TA616), but the company has presented no discussion around the appropriateness of these values based on the primary source from the related TAs. The EAG considers that it is best practice that utility values be based on a single source. Additionally, in TA706, duration and disutility of dizziness, fatigue, influenza, nasopharyngitis and pyrexia were assumed to be zero. However, the company has included the impact of these AEs, citing TA706 as the source.

- a) Please explain if AE disutilities and durations included in the company's base case analyses were validated by clinical experts, and if so, please provide their feedback.
- b) Please discuss why TA706 was selected as the most appropriate source of disutility values and durations for AEs, giving consideration to the approach that the AEs were included as a one-off impact in the first

cycle of the model and how that relates to the current approach used for this topic.

- c) Please provide a scenario using AE disutilities based on Sullivan *et al.* already included in the model (tab “HRQoL_data”, cells, F75:F97) and setting the duration and disutility for dizziness, fatigue, influenza, nasopharyngitis and pyrexia to zero.**

(a) The disutility values and durations applied for adverse events were not validated directly with clinical experts. The company instead would like to refer to primary research conducted with patients and caregivers to inform the expected impact of treatment-related complications on quality of life.^{31,48}

As outlined in B28, one-third (33.3%) of IVIg users who were dissatisfied with treatment reported unpleasant side effects as a contributing factor.³¹ Patients described headaches, fatigue and infusion reactions as highly disruptive to day-to-day activities, with testimonies illustrating the extent of this burden (Appendix L of the CS). Caregivers also reported substantial consequences, with 81% experiencing physical health problems and 66.7% mental health problems attributable to managing AEs.⁴⁸

As clarified in B29, the company addressed uncertainties around IV access-related complications by providing UK-specific real-world evidence and conducting a scenario analysis that excluded these events. The company therefore considers that the patient and caregiver survey provides an appropriate basis for inclusion of AE-related disutilities in the base case.

(b) The company have used multiple sources for disutilities as neither TA706⁴⁹ nor Sullivan *et al.* (2011)⁵⁰ provided values for all included AEs in the model. Additionally, there is no specific NICE guidance on best practice with respect to including disutilities in economic evaluations⁵¹ and therefore the decision to use multiple sources was made to ensure comprehensive coverage and clinical relevance. NICE TA706 was selected as the most appropriate source for disutility values and durations due to the similar nature of the disease, and provides precedent for handling AEs disutilities in neurological conditions where transient AEs are common.⁴⁹ TA533 and TA616 are both for MS,^{52,53} and as such may be more

clinically relevant than Sullivan et al. (2011)⁵⁰ for this context, as MS shares clinical features with CIDP. Disutilities were an average of Sullivan et al. and NICE TA706, and duration was from TA706.^{49,50} Taken together, the company considers that this approach provides the most appropriate and comprehensive basis for applying AE disutilities in the model given the evidence available and the lack of specific NICE direction on preferred methodology.

(c) A scenario analysis was conducted to include the possibility to set the durations for dizziness, fatigue, influenza, nasopharyngitis and pyrexia to zero, and Sullivan et al. (2011) was used as the only source for AE disutilities.⁵⁰ The results of this scenario analysis are presented in Table 35. The company would like to highlight that the inclusion of AE disutilities in the model is strongly supported by published sources and robust primary evidence gathered from UK patients and caregivers, which demonstrates the significant HRQoL impact of treatment-related AEs in CIDP.

B39. Priority question: The EAG considers that there is a lack of detail around the data used to estimate disutilities for complications related to IV access.

- a) **Please explain where the durations for complications related to IV access are derived from.**
- b) **Please justify why a disutility lasting 7 days for a permanent peripherally inserted central catheter is appropriate to apply every 6 months?**
- c) **Please justify why TA804 (teduglutide for short bowel syndrome) was considered appropriate as a source of disutilities related to IV access for patients with CIDP, giving consideration to differences in treatment for short-bowel syndrome and CIDP?**
 - i) **Please explain, with supporting evidence, if complications related to IV access would be similar for patients with CIDP and patients with short-bowel syndrome.**
- d) **Please explain if disutilities for complications related to IV access and the durations included in the company's base case analyses were validated by clinical experts, and if so, please provide their feedback.**

(a) As referenced in the model (HRQoL_data sheet), the duration for disutility related to venous access have been sourced from NICE TA352 and Sullivan et al.^{50,54} These sources provide established estimates for the duration of impact associated with IV access complications, which were applied in the absence of CIDP-specific data.

(b) and (c): TA804 used disutilities for infections from TA352.^{54,55} The company acknowledges the error in referencing TA804 directly for IV access disutilities. As the disutilities and durations are associated with the treatment as opposed to the disease, we have assumed that these hold in this population. In TA804, this same rationale was accepted by the committee, even considering the target population of the treatment included children aged one year and above.

(d) The disutilities for complications related to IV access and the associated durations were not validated by clinical experts. The company sponsored patient and caregiver survey conducted with INUK did not quantify disutility related to IV administration and therefore could not be used for validation. However, the patient survey found that IVIg users reported concerns with treatment frequency, inconvenience of hospital attendance and perceived lack of symptom control.³¹

B40. Priority question: In Section 3.4.8 of the CS, it is reported that the duration for infusion is 3.9 hours for Privigen and 3.3 hours for Gamunex. However, in the model, the duration for infusion is 5.89 hours for Privigen and 5.01 hours for Gamunex (tab “HRQoL”, cells D47:D48).

a) Please clarify where the data in the CS are derived from.

b) Please provide a scenario where the duration of infusion is based on the data provided in the CS.

(a) The values reported in the model are accurate and should be viewed as the correct values (please disregard the values reported in the CS).

(b) We have added a scenario where the duration of infusion is based on the data in the CS. The impact of this scenario on base case results is minimal and it can be seen in Table 35.

B41. Priority question: Please provide details of the linear regression used to estimate the incremental disutility associated with IV administration.

Disutility associated with route, location and setting of administration based on Jørgensen et al.

The vignette study by Jørgensen et al. (2017)⁵⁶ was identified as the most relevant source for disutility related to treatment administration since it reports the disutility values by route of administration (IV infusion or SC injection), the place where the treatments were provided (home or hospital) and the administration frequency (i.e. interval of weeks between treatment). An important aspect of this study is that the impact on HRQoL from treatment administration type was not specific to any condition but was based on comparisons between different schemes of administration without reference to a disease or medication name. The time-trade-off (TTO) method was used to measure utilities in the study, and data were collected through an internet-based survey provided to a representative sample of the general population in the UK (1,645 respondents in the final sample), including only people aged 18 years or more. Based on participants' TTO results, a utility value was assigned to each description representing a distinct drug administration scenario.

A linear regression model was fitted to the data reported in Jørgensen et al.⁵⁶ (Table 48), using R. The dependent variable was the utility value. The independent variables were: (i) route of administration (IV versus SC), (ii) treatment setting (hospital versus home), and (iii) frequency of administration (in weeks). The reference category (intercept) was SC injection at home every 12 weeks, which corresponds to the regimen with the highest reported utility.

The model was specified as follows:

$$Utility = ADMIN\_ROUTE + SETTING + FRQ$$

The results of the regression analysis are presented in Table 49.

Table 48: Data from Jørgensen et al. 2017

ADMIN_ROUTE	SETTING	FRQ (weeks)	UTILITY
SC	home	12	0.879

ADMIN_ROUTE	SETTING	FRQ (weeks)	UTILITY
SC	home	8	0.878
SC	hospital	12	0.873
SC	home	2	0.861
SC	home	1	0.861
SC	hospital	8	0.86
IV	hospital	8	0.849
IV	hospital	4	0.836

Source: Jørgensen et al. (2017)⁵⁶

Abbreviations: FRQ: Frequency; IV: Intravenous; SC: Subcutaneous.

Table 49: Results of the linear regression run on the data from Jørgensen et al. 2017 to estimate the disutility of IV administration in the cost-effectiveness model

Variable	estimate	std.error	statistic	p-value
(Intercept)	0.879	0.005	164.762	0.000
ADMIN_ROUTE IV	-0.022	0.007	-3.136	0.035
SETTING hospital	-0.011	0.007	-1.549	0.196
FRQ	-0.006	0.002	-2.385	0.076

Abbreviations: FRQ: Frequency; IV: Intravenous; std.error: Standard error.

Source: Jørgensen et al. (2017)⁵⁶

Disutility associated with infusion time based on Matza et al.

Because the study by Jørgensen et al. did not report the impact of infusion duration on patient HRQoL, a separate linear regression analysis was conducted using the data reported in Matza et al. (2013)⁵⁷ This additional analysis was used to quantify the disutility specifically associated with the length of an infusion session.

A linear regression model was fitted in R, with utility as the dependent variable and two independent variables: (i) administration route (IV versus SC) and (ii) infusion duration (in hours).

The model specification was:

$$Utility = ADMIN\_ROUTE + DURATION$$

The results of this regression were then used to estimate the incremental disutility associated with longer infusion times.

Table 50: Data from Matza et al. 2013

ADMIN_ROUTE	DURATION	UTILITY
SC	0	0.39
IV	0.5	0.38
IV	2	0.36

Source: Matza et al. (2013)⁵⁷

Abbreviations: IV: Intravenous; SC: Subcutaneous.

Estimation of the total disutility of administration in the cost-effectiveness analysis

The disutilities associated with treatment setting, route and frequency of administration, and infusion duration were estimated by combining the regression results from Jørgensen et al.⁵⁶ and Matza et al.⁵⁷ A key limitation of this approach is that, because the coefficients are derived from two different studies, there is a risk of double counting aspects of administration burden.

To address this uncertainty, we explored three alternative scenario analyses:

1. Jørgensen only: administration disutilities were based solely on the regression results from Jørgensen et al.
2. Route only (Jørgensen): only the administration route coefficient from Jørgensen et al. was included, reflecting that this was the only statistically significant administration-related coefficient.
3. Route (Jørgensen) + infusion time (Matza): the administration route coefficient from Jørgensen et al. was combined with the infusion time coefficient from Matza et al.

The resulting administration-related disutilities for each treatment included in the analysis are presented in Table 51. Please note that, to be conservative, no disutility was applied for SCIg. The results from these scenarios are presented in Table 35. Across the four scenarios, incremental QALYs for efgartigimod versus the comparator range from [REDACTED], depending on whether no administration-related disutility is applied or whether administration disutility is estimated using Jørgensen et al. for route, setting and frequency of administration.

Table 51: Administration-related disutility

	Administration related disutility			
	Base case	Scenario 1: Jørgensen only	Scenario 2: Route only (Jørgensen)	Scenario 3: Route (Jørgensen) + infusion time (Matza)
Efgartigimod	0.000	0.000	0.000	0.000
Privigen - maintenance	-0.124	-0.069	-0.022	-0.077
Gamunex - maintenance	-0.116	-0.069	-0.022	-0.069
Flebogamma - maintenance	-0.116	-0.069	-0.022	-0.069
Hizentra - maintenance	0.000	0.000	0.000	0.000
Average (weighted) for Ig	-0.114	-0.065	-0.021	-0.070
PLEX	-0.218	-0.168	-0.022	-0.073

Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange.

B42. Priority question: Disutility associated with PLEX administration is included in the model but is not described in the CS. Please describe the assumptions, with supporting evidence, for the inclusion of a disutility associated with PLEX administration (tab “HRQoL”, cell D61).

a) Please justify why an average of the Privigen and Gamunex infusion duration was used to inform the duration for PLEX treatment.

The disutility associated with PLEX administration was calculated considering the IV administration, the hospital setting, the frequency of administrations multiplied by the number of exchanges per cycle, and the duration of each exchange. Because PLEX is administered intravenously and requires hospital attendance, we assumed that the administrative and setting-related components of disutility would be comparable to those associated with IVIg infusions. In the absence of robust published evidence on the exact duration of PLEX sessions in the UK setting, the model uses the average infusion duration of Privigen and Gamunex as a proxy for the number of hours a patient spends receiving a supervised IV hospital-based procedure. We believe this provides a reasonable approximation of the time burden experienced by patients during PLEX, given the similar setting of delivery.

B43. Priority question: The EAG's clinical experts explained that patients who are stable on Ig become used to their treatment, such that it has a limited impact on their HRQoL. In particular, they explained that patients feel happier knowing their doses and treatment regimen are being managed by a professional and the hospital setting provides reassurance that if anything happens, they are in the right place for care. As such, the EAG considers that the inclusion of disutilities associated with IV administration have not been sufficiently justified. Additionally, the paper by Matza *et al.* 2013 reports on utility data for patients with bone metastases from over 20 years ago and may not be reflective of the lived experience of CIDP patients today. As such, please provide a scenario that excludes disutilities associated with IVIg administrations.

The company recognises the EAG's clinical expert view that some patients stable on long-term IVIg may perceive limited impact of hospital-based administration on their quality of life and appreciate specialist oversight. However, it is important to note that patient experience is heterogeneous, and the burden of hospital-based infusions remains well-documented across chronic conditions. Extensive evidence shows that many patients and caregivers find repeated hospital infusions burdensome due to travel, waiting times, and disruption to daily life.³¹ A systematic review across diseases found 84% of patients preferred home-based or subcutaneous treatment.⁵⁸ Excluding disutilities could therefore underestimate the real-world impact of IV administration on patients and caregivers, particularly given the strong preference for home-based care demonstrated in these data.

It is also important to reiterate that IVIg for CIDP typically requires infusions lasting several hours over multiple consecutive days, repeated every few weeks. This repeated and prolonged administration amplifies the cumulative impact on patients' quality of life, making infusion-related disutilities particularly relevant in modelling. The company-commissioned UK CIDP patient surveys support this,³¹ showing various situations where patients would benefit from home or community administration. This aligns with current NHS policy that aims to shift suitable care closer to patients' homes to improve experience and system efficiency.^{59,60} While it may be appropriate for some patients to remain hospital-based, consistent with the

NHS England Immunoglobulin Commissioning Policy (which notes that a very small minority of CIDP patients may require higher dose Ig and close monitoring in specialist centres), many could experience meaningful improvements in quality of life if treatment were delivered closer to home. argenx will provide a fully funded home care service at launch where required, to support this transition from hospital to community setting for eligible patients, aligning to NHS priorities.

The paper by Matza et al.⁵⁷ reports the disutility associated with IV infusions of different durations and is used to derive the disutility associated with a longer administration time. The company considers this an appropriate source in the absence of CIDP-specific data but has provided a scenario analysis excluding the IV disutilities. This balanced approach acknowledges patient heterogeneity, real-world burden, and policy direction while exploring the model sensitivity to disutilities associated with IV administration in scenario analyses. The results of this scenario analysis are presented in Table 35. Efgartigimod remains dominant, with incremental QALYs versus the comparator decreasing from 4.26 in the base-case analysis to [REDACTED] under this scenario.

Drug acquisition costs

B44. In Section 3.11.3.8, the company has described a scenario where the induction costs of efgartigimod are zero, simulating a scenario where the induction cost is sponsored by the company for all patients. Please clarify if the intention is to submit to NICE this proposed reimbursement of efgartigimod in combination with the patient access scheme (PAS) discount already included in the submission?

A simple Patient Access Scheme (PAS) has been submitted for the current submission for efgartigimod; a complex PAS is not included at this time.

B45. Based on data from the Immunoglobulin Database Annual Report 2023/24, the split between IVIg and SCIg use is 76.7% for IVIg and 23.3% for SCIg. In the model, it is assumed that 94.9% is IVIg and 5.13% is SCIg, with the data obtained from the company's UK chart review study. Please provide a

scenario reflecting the split of IVIg (76.7%) and SCIg (23.3%) based on the Immunoglobulin Database Annual Report 2023/24.

As requested, we have added a scenario based on the Immunoglobulin Database Annual Report 2023/24.⁶¹ However, the company would like to note the limitation of the source due to reporting overall Ig use and not use specifically related to CIDP. CS Section 1.3.5.2 outlines why the uptake of SCIg in the UK remains limited.

The report specifies a larger number of IVIg and SCIg brands than in our model. Therefore, in the scenario analyses the company have used the proportions of the brands that are used in the model and reweighted to 100%. This means that the split of IVIg and SCIg is 76.6% and 23.3% respectively, split as by brand as presented in Table 52. The results of this scenario analysis are presented in Table 35 and show the results are not largely different from base case, with a dominant ICER and a NMB of £[REDACTED]

Table 52: Distribution of Ig brands based on the Immunoglobulin Database Annual Report 2023/24

Brand	Percentage of each Ig product
Privigen	64.63%
Gamunex - C	7.97%
Hizentra	23.00%
Flebogamma DIF	4.11%

Abbreviations: Ig: Immunoglobulin.

B46. Please provide a scenario analysis in which all patients receiving efgartigimod are assumed to be on the weekly dosing regimen.

We added an option in the model to run the analysis assuming that the entire efgartigimod cohort receives weekly dosing. As expected, placing all patients on weekly dosing increases total costs in the intervention arm. Under this scenario, incremental costs versus the comparator are [REDACTED], and the ICER is £[REDACTED] per QALY.

However, as shown in the ADHERE+ substudy, there is evidence that treatment benefit can be maintained with bi-weekly dosing in a subset of patients. Assuming

weekly dosing for the entire cohort therefore departs from the available evidence and is unlikely to reflect expected use in clinical practice.

B47. Priority question: The EAG could not verify the cost of PLEX (NHS reference costs, HRG code SA44A, £273) in the model. Please clarify if the source referenced for the cost used is correct and amend as necessary.

We have reviewed the costing source and confirm that the most recent NHS Reference Cost (2024/2025) lists the cost for “Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over” (HRG code SA44A) as £502.51 per exchange.

Accordingly, the model has been updated to use this cost. This change was included in the revised base case analysis, and the contribution of this change to the updated base case is reported in Table 34.

B48. Priority question: In the Company Submission, the number of PLEX administrations is assumed to be 24 based on recommendations in the EFNS/PNS guideline. However, the recommendation in the guideline for plasma exchange (PICO 10) states that, “the initial treatment may start with 5 exchanges over 2 weeks; thereafter, the plasma exchange interval should be individually adapted”. The EAG’s clinical experts advised that PLEX is not a long-term treatment and would not be given indefinitely. As such, please clarify the assumptions used to estimate that 24 exchanges would be administered every 6-months with no stopping rule.

The company acknowledge that PLEX is rarely used for long-term maintenance due to its invasive nature and associated risks.^{17,62} The estimate of 24 PLEX exchanges per 6-month cycle should be interpreted within the context of the “basket” approach, which represents the average use of alternative treatments in clinical practice rather than a treatment pathway for any single patient. As described previously in response to question B5a, the basket distribution reflects a steady-state pattern of real-world use reported by CIDP experts in England. Within this aggregated mix, some patients receive short courses of PLEX, some receive intermittent PLEX, and many do not receive PLEX at all over a given period.

The EFNS/PNS guideline recommends an initial course of approximately five exchanges over 2 weeks, with subsequent treatment intervals tailored to the individual. However, real-world clinical practice involves substantial variation in how often PLEX is repeated, whether additional cycles are given, and how many exchanges are included in each series. Because of this heterogeneity, experts participating in the SEE provided estimates that reflect the average expected utilisation of PLEX in the target CIDP population, rather than the protocol for a single episode of treatment.

B49. The cost of mycophenolate mofetil is now £5.99 based on the BNF. Please update the model accordingly.

The cost of mycophenolate mofetil has been updated from £5.81 to £5.99 as requested, based on latest price published on the BNF.⁶³ This change was included in the revised base case and the contribution to the updated base case results is presented in Table 34.

Drug administration costs

B50. Priority question: Please clarify the source of the assumption that 8% of efgartigimod maintenance administrations and SCIg administrations take place in a hospital setting.

The ADHERE+ schedule highlights that patients mostly administered efgartigimod in a home setting, with administration taking place in a hospital setting once every 3 months (1 administration /12 administrations = 8%).

B51. Priority question: Based on the SEE process, the company has assumed that 3.1% of Ig patients would be admitted to hospital overnight for treatment. Please justify the assumption that patients on IVIg and SCIg would be admitted to hospital overnight.

a) Please provide a scenario where Ig is only delivered in an outpatient setting.

The SEE indicated that a small proportion of patients receiving Ig may require overnight admission for monitoring, typically aimed at monitoring side effects or infusion-related reactions.¹³ This estimate of 3.1% of patients being admitted to hospital is applied to both IVIg and SCIg, however only to the cohort which receives administration in hospital setting. For SCIg, clinicians in the SEE reported that approximately 8% of patients require some form of hospital attendance (e.g., nurse-led supervision or management of complications). Within this 8%, 3.1% are admitted to the hospital for administration, corresponding to approximately 0.25% of all SCIg-treated patients.

As requested, we have included a scenario in which Ig (both IVIg and SCIg) is assumed to be delivered exclusively in an outpatient setting, with zero overnight admissions. Costs associated with hospital stay for the proportion of the cohort receiving Ig represent an important burden for the NHS. Removing these costs therefore reduces total costs in the comparator arm and results in a higher ICER (£7,043 per QALY) compared with the base-case analysis. However, we consider this scenario to be inconsistent with clinical practice, as clinical experts indicated that a proportion of patients require an overnight hospital stay, or use hospital hotels where this option is available.

B52. Priority question: The cost for funded transport to hospital (£42.88) for 16% of Ig patients is included in the model but not described in the CS.

- a) Please describe the approach in the model and the basis for the assumptions, including supportive evidence.**
- b) The EAG considers the cost of funded transport to be potentially overestimated in the model. For patients who are assumed to be admitted to hospital for treatment, please explain why the cost is multiplied by the number of days the patient is in hospital (Tab “Cost”, cell D163? The EAG considers that if the cost of transport is included in the model, it would just be the cost of one return journey.**
- c) Please explain why funded transport to hospital has not been included for the 8% of patients receiving efgartigimod in hospital.**

i) Please provide a scenario where funded transport is included for patients receiving efgartigimod in hospital.

d) Please provide a scenario where the cost of funded transport to hospital is excluded from the model.

(a) The assumption that 16% of Ig patients require funded transport to hospital is based on clinician inputs from the SEE.¹³ Experts indicated that a minority of patients, typically those with mobility limitations or lack of support, require NHS-funded transport for Ig administration. This proportion therefore reflects the clinical practice across five specialised and geographically representative CIDP centres in England. It should be noted that clinical experts explained that for patients who travel long distances, funded transport is often used as an alternative to an overnight hospital stay or a hospital-hotel stay when these options are not available. The estimate that 16% of patients require funded transport therefore aligns with the relatively small proportion of patients who remain in hospital overnight for administration (3.1%) in the model.

The cost of £42.88 per funded trip reflects NHS reference costs for patient transport services. Ig administration commonly occurs over multiple consecutive days; therefore, for patients receiving multi-day hospital-based Ig infusions, funded transport was applied per visit to reflect the need for repeated travel on each treatment day.

(b) We acknowledge the EAG's comment regarding potential overestimation. In response, the model has been amended so that for patients who are admitted overnight, the transport cost is applied once per admission, representing a single return journey, rather than being multiplied by the number of inpatient days. This adjustment avoids overstating transport costs for inpatient admissions. This change is included in the revised base case and the contribution of this change to base case results is presented in Table 34.

(c) Funded transport was not included for patients receiving efgartigimod because infusion occurs on a single day and the duration of the infusion is short, suggesting that patients would be less impacted by a shorter treatment and would

therefore potentially require less support to attend. As requested, we have added a scenario in which 16% of efgartigimod patients receiving treatment in outpatient hospital setting are also assumed to require funded transport for their infusion visit. This scenario can be selected in the *Settings* sheet of the model, and results are reported in Table 35.

(d) A scenario excluding funded transport costs entirely (for both Ig and efgartigimod) has also been implemented, as requested. This option be selected in the *Settings* sheet of the model and the results of this scenario analysis are presented in Table 35.

B53. Priority question: Please explain why the hospital administration cost of SCIg is not the same as the administration cost for efgartigimod presented in Table 67 of the CS.

a) **Please provide a scenario where the administration cost of SCIg is the same as efgartigimod.**

Both Ig and efgartigimod administration incur a cost of £126.64 (Multiprofessional Non-Admitted Face-to-Face Attendance – WF02A). Due to the length of time required for administration of all Ig, inpatient costs incur an additional cost related to the length of time they spend in hospital. This additional cost is £849.96, in accordance with PSSRU NHS reference costs for non-elective inpatient stays (short stays). As requested by the EAG, we have added a scenario where SCIg administration costs are set equal to efgartigimod administration costs. Based on the dosing schedule from Hizentra, we have assumed a weekly dosing schedule, and therefore set the SCIg costs equal to the weekly dosing maintenance costs for efgartigimod. The impact of this scenario analysis is presented in Table 35.

B54. The cost for hospital administration based on HRG code WF02A from the NHS reference costs (Table 67) is £171 and not £126.64 as reported in the CS. Please update the model with the latest cost.

As requested, we updated the cost for hospital administration based on HRG code WF02A from the NHS reference costs (£171). This change was included in the

revised base case, and the contribution to the updated base case results is presented in Table 34.

Health state unit costs and resource use

B55. Typically for economic models submitted to NICE, the cost of GP time, sourced from PSSRU, is assumed to be the GP cost of surgery consultation lasting 10 minutes (£45), unless there is a strong justification along with evidence for why the duration of the consultation is longer than standard.

- a) Please justify the assumption, along with evidence, for the assumption of a one-hour GP visit, resulting in a cost of £268 in the model?**
- b) Please provide a scenario that uses the GP cost of surgery consultation lasting 10 minutes (£45) from PSSRU.**

(a) The assumption of a 1-hour GP consultation was chosen to reflect the complexity of managing patients with CIDP compared with the general population going to the GP. The British Medical Association (BMA) recognise that 10-minute GP appointments are generally too short for patients with complex conditions and state that an aging population with increasing medical complexity and multimorbidity requires longer patient contacts.⁶⁴ We would therefore expect that these consultations are substantially longer than a standard 10-minute appointment.

(b) As requested, a scenario using the standard PSSRU cost for a 10-minute GP surgery consultation (£45) has been added. This scenario can be selected in the *Settings* sheet of the model, and results are provided in Table 35.

(c) B56. Please explain why the cost of a neuropsychology test (HRG code, AA32Z, outpatient procedure, £439) has been assumed for the cost of a neurology outpatient visit?

- a) The EAG considers that more appropriate cost codes from the NHS reference costs would be Outpatient care, WF01B - Non-Admitted Face-to-Face Attendance (£325), First and WF01A - Non-Admitted Face-to-Face Attendance, Follow-up (£236). Please discuss why the company's**

base case assumption is more appropriate than the HRG cost codes suggested by the EAG.

b) Please provide a scenario where the HRG cost code WF01B (£325) is used for the first visit and then the HRG cost code WF01A (£236) is used for all subsequent visits in the model.

(a) We acknowledge the EAG's suggestion to use the HRG codes WF01B (first non-admitted face-to-face attendance) and WF01A (follow-up attendance) for neurology outpatient visit. However, applying these codes in the model involves adding additional complexity since we cannot track when the first visit occurred so the decision to use a single tariff was selected for simplicity. As a result, distinguishing reliably between first and follow-up visits for the purpose of costing is difficult. To avoid unnecessary complexity, and given the small impact of the neurology outpatient visit costs on overall model results, we updated the model to use the lower of the two outpatient tariffs (first or follow-up visit) proposed by the EAG. Accordingly, a cost of £236 (HRG WF01A, follow-up non-admitted face-to-face attendance) was applied for the neurology outpatient visit in the revised base case analysis. The impact of this change on the updated base case results is presented in Table 34.

B57. The cost of mobility aids obtained from NHS reference costs (WCE03 and WCE04) is out of date. Please update the model with the latest costs, which are £689 for WCE03 and £1,548 for WCE04.

We updated the cost of mobility aids based on the latest data published from NHS reference costs. The cost for WCE03 was set to the latest NHS reference costs equal to £689, replacing the previous cost of £903 (WCE05). The cost for WCE04 was set to the latest NHS reference costs equal to £1,548, replacing the previous cost of £1,778 (WCE06). These updates were included in the revised base case and the contribution to the updated base case results is presented in Table 34.

B58. Please explain why the proportions requiring a manual and motorised wheelchair for the severe impairment (INCAT 7-8) are informed by the INCAT 7-10 when data are available for INCAT 7-8?

The EAG's clinical experts advised that the proportion of patients with very severe impairment requiring a motorised wheelchair would be higher than the proportion included in the model. As such, based on data supplied in the company's ADELPHI study, please provide a scenario implementing the proportions requiring mobility aid as outlined in the Table below.

Table 53: Proportions of patients requiring manual and motorised wheelchairs across different levels of disease severity

Health state	Proportion requiring a manual wheelchair	Proportion requiring a motorised wheelchair
Very limited impairment (INCAT 0-1)		
Mild impairment (INCAT 2-3)		
Moderate impairment (INCAT 4-6)		
Severe impairment (INCAT 7-8)		
Very severe impairment (INCAT 9-10)		

Abbreviations: INCAT: Inflammatory Neuropathy Cause and Treatment score.

The Adelphi study report includes the proportions requiring a manual and motorised wheelchair for the Severe health state (INCAT 7-8) and then for INCAT 7-10 grouped together.⁴⁷ Thus, there are no data specifically for the Very Severe health state. For this reason, we applied the proportion reported for INCAT 7-10 for any health state above an aINCAT of 7, namely Severe and Very Severe health states.

The approach used in the company cost-effectiveness model represents a conservative assumption grounded in the available data. Nonetheless, the company acknowledges the EAG feedback that the proportion of wheelchair use among individuals in the most severe health state may be higher than estimated, according to the INCAT disability scale. As requested, we included the possibility of running a scenario considering the data presented in the table above. The results of this scenario analysis are included in Table 35.

B59. In the CS, the company states that the cost per day of ICU is based on service codes CCU01-CCU91 (Adults) from the NHS reference costs. However, there are several currency codes related to the number of organs supported and department.

a) Please explain why codes CCU05 (Neurosciences adult PATIENTS predominate, XC01Z-XC07Z) or CCU01 (Neurosciences adult PATIENTS predominate, XC01Z - XC07Z) were not considered to be the only appropriate codes for the costs?

b) PSSRU estimates the unit cost of critical care to be £1,907 (Table 6.1.1). In the same table, the cost of non-elective inpatient stays (short stays) aligns with the unit cost included in the model (£792). As such, to keep the hospitalisations costs aligned, please provide a scenario using the PSSRU cost of critical care (£1,907) for the cost per day of ICU in the model.

(a) The cost per day of ICU was based on service codes CCU01-CCU91 (Adults) from the NHS reference costs instead of either CCU05 or CCU01 due to the unpredictable nature of the hospitalisations requiring ICU in patients with CIDP. ICU admission in CIDP patients arises from rare but well-documented disease-related complications during acute exacerbations and treatment-related adverse events. Disease exacerbations may necessitate intensive care due to: respiratory failure from phrenic nerve involvement requiring mechanical ventilation,^{65–68} aspiration pneumonia from bulbar weakness;⁶⁹ severe autonomic dysfunction with cardiovascular instability.⁷⁰ Treatment complications include IVIg-related events (thrombosis, acute renal failure), plasma exchange complications (hypotension, sepsis, line infections), and immunosuppression-related severe infections, as outlined in the CS. This heterogeneity, from single-organ to multi-organ support, justifies using broad NHS critical care codes (CCU01-CCU91) rather than neurosciences-specific codes alone.

(b) A scenario analysis was conducted using the PSSRU cost of critical care (£1,907) for the cost per day of ICU in the model. The results of this analysis are included in Table 35.

Adverse event costs

B60. Priority question: The EAG has attempted to validate the costs used to inform AEs in the model against the referenced source, the NHS Payment

Scheme 2025/26. The EAG identified that all of the costs listed in Table 81 and 82 of the CS are slightly misaligned to the "Combined day case /ordinary elective spell (£)" costs from the NHS Payment Scheme.

(a) Please clarify when the AE costs were extracted for the model, as the EAG notes the Payment Scheme page was updated on the 26th of June 2025, which may be responsible for the misalignment.

i) Please update the costs in the model with the latest costs from the source. To increase transparency in the model, ensure that the unit costs are not hardcoded and that the data and calculations feeding into the final unit costs are included in the model.

b) The EAG is unclear how the unit costs for HRG codes cost infections (WH07), sleep disorders (AA43) and endocrine disorders (KA08, corrected from KA80 in Table 81) are estimated, Table 82 of the CS states that it is an average of the codes. Please clarify how the unit cost for these codes has been calculated, for instance, if a weighted average has been calculated?

c) Please clarify why costs from the NHS payment scheme were preferred over NHS reference costs.

i) Please provide a scenario where AE costs are sourced from NHS reference costs. To increase transparency in the model, ensure that the unit costs are not hardcoded and that the data and calculations feeding into the final unit costs are included in the model.

d) Please explain why the "Combined day case /ordinary elective spell" costs were assumed in the model.

e) The EAG's clinical experts considered that most of the AEs captured in the model would be mild. They advised that back pain and peripheral oedema would be treated in an outpatient setting and all other AEs

would be managed in primary care (with one GP visit). Please provide a scenario implementing the EAG's clinical experts' advice on treatment setting, using NHS reference costs for outpatient costs and PSSRU for a GP visit cost (£45).

(a) The adverse event (AE) costs included in the model were extracted in April 2025, prior to the NHS Payment Scheme update published on 26 June 2025. This timing explains the slight misalignment identified by the EAG when validating against the most recent version of the Payment Scheme.

(b) The following codes were used:

- for infection: WH07A, WH07B, WH07C, WH07D, WH07E, WH07F and WH07G;
- for sleep disorder: AA43A and AA43B
- for endocrine disorders: KA08A, KA08B and KA08C

For AEs grouped under infections, sleep disorders, and endocrine disorders the cost for the AE was determined as simple average of the “Combined day case /ordinary elective spell” unit costs for each code considered; The same simple average was used for the costs presented in Table 82 of the CS.

(c) The NHS payment scheme (NHSPS) costs were preferred over reference costs because of the structured and transparent approach to pricing healthcare services. The NHSPS includes rules for various payment mechanisms, ensuring that costs are set based on agreed pay awards and that providers contribute to the scheme to cover legal and compensatory costs of clinical negligence.

- i. In response to the EAG's request, we have updated the model so that all unit costs, including those for adverse events, are calculated from their original NHSPS or NHS Reference Cost inputs within the costing worksheets. No unit costs are now hard coded: the underlying source data, any mappings or groupings, and the calculations leading to final unit costs are explicitly included and can be traced in the model. We have also added a scenario in which adverse event costs are sourced from NHS Reference Costs instead of the NHSPS, while all other assumptions are

kept consistent with the updated base case. The results of this scenario are presented in Table 35.

(d) “Combined day case/ordinary elective spell” costs were preferred over the non-elective ones in light of the more likely mild nature of the AEs experienced by patients. This approach reflects the most likely clinical pathway for CIDP patients experiencing these AEs, where treatment is planned and delivered without the urgency associated with non-elective care.

(e) To reflect the EAG’s recommendation that most AEs are mild and managed outside of inpatient care, a scenario analysis was run using the NHS reference costs for:

- NHS reference outpatient costs for back pain and peripheral oedema
- All other AEs were considered as managed in primary care and are applied the cost for a single GP visit cost reported in the PSSRU (£45 for a 10-minute consultation).⁷¹

The results of this scenario analysis are presented in Table 35.

Caregiver burden

B61. Priority question: The EAG considers that the company’s approach to the inclusion of caregiver burden is not appropriate. The cost of a professional home care worker is included in the model, yet HRQoL impact for informal carers is also included. The EAG considers that either the burden of informal caregivers or the burden on professional caregivers should be included in the economic model, but not both.

(a) Please justify the assumption of including the professional carer costs in the model, especially since the company’s survey of caregivers supporting patients living with CIDP in the UK suggests that 0% of patients would receive formal care from a professional healthcare provider, and the UK Adelphi dataset only notes a single patient with a professional caregiver.

(b) Please explain how the model inputs in Table 77 of the CS relating to the proportion of patients requiring professional caregiving and the hours of professional caregiving per week were derived, as these do not seem to appear in the source given.

(c) Please provide supporting evidence that 45 hours of professional care would be funded by the NHS.

(d) Please provide a scenario where only the cost of professional care is included in the model and HRQoL impact on informal carers is excluded.

(e) Please provide a scenario where only HRQoL impact on informal carers is included and the cost of professional care is excluded.

(a) In the company-sponsored patient survey, 19% (n=12/63) of patients reported receiving formal care (either 'formal care' or 'both formal and informal care').³¹ The company-sponsored caregiver survey reported 9.5% (n=2/21) of caregivers provided formal care (either 'formal care' or 'both formal and informal care').⁴⁸ Whilst the proportion of caregivers providing formal care was reportedly lower in the company-sponsored caregiver survey, it is considered that this is a reflection of the survey recruitment methodology, which did not specifically target formal caregivers. Therefore, the assumption to include professional caregiver costs is based on the broader Adelphi CIDP dataset, which reports a non-negligible proportion of patients receiving formal care. While the UK-specific survey reported 0% and the UK Adelphi subset noted only one patient with a professional caregiver, the broader dataset suggests that formal care is clinically plausible for patients with severe disability. These data formed the basis for the percentage included in the model.

(b) An additional analysis was conducted on Adelphi data including patients from UK, France, Germany, Italy, Spain, US and Japan. This increased the sample to n=804 patients. Only patients who previously received Ig were included to match the population in the model. After stratifying by health states, we estimated the proportion of patients requiring professional caregiving and the average number of caregivers in Table 54.

Table 54: Proportion of patients requiring professional caregiving and average number of caregiving hours per week from the Adelphi study (global)

Health state	Patients requiring professional caregiving	Average number of hours per week
Very limited impairment (INCAT 0-1)	████	████
Mild impairment (INCAT 2-3)	████	████
Moderate impairment (INCAT 4-6)	████	████
Severe impairment (INCAT 7-8)	████	████
Very severe impairment (INCAT 9-10)	████	████

*Assumed as 8-9 aINCAT as no data were reported in 9-10 aINCAT.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score.

(c) The assumption of 45 hours per week for a proportion of the severe and very severe impairment reflects the level of dependency observed in the Adelphi dataset and aligns with NHS Continuing Healthcare packages for individuals with significant motor disability. People with CIDP often experience substantial motor impairment and associated difficulties with activities of daily living. In the UK context, such needs are typically met within the publicly funded health and care system. For individuals whose care needs are primarily health-related, the NHS Continuing Healthcare (CHC) framework provides a fully funded package of care arranged and paid for by the NHS, including support at home with personal care and other daily activities where required.⁷²

Under this framework, care is commissioned on the basis of assessed need rather than a fixed cap on hours, and substantial packages of domiciliary support (several hours per day) are routinely provided for people with severe, long-term neurological conditions. While the exact number of hours is determined individually, a package corresponding to 45 hours of professional care falls within the range of support that may expected for someone with significant motor disability and dependence due to CIDP. Please note that 45 hours are applied only in Severe and Very Severe health states for 80% of the cohort.

(d) and (e) As requested, we have added the possibility to include or exclude the professional care costs and the HRQoL impact on informal carers. These can be selected in the *Settings* sheet of the model. A scenario analysis excluding the impact of informal carers on HRQoL, and a separate scenario excluding the costs of

professional care, were conducted. When caregiver disutility is excluded, incremental QALYs decrease from 4.26 in the base-case analysis to ■■■■, while the ICER remains dominant.

When the costs of professional caregiving are excluded, incremental costs become positive, as this mainly affects patients in worse health states, where a larger proportion of the cohort is in the comparator arm than in the efgartigimod arm. Under this scenario, the resulting ICER is £19,873 per QALY gained.

However, to ensure the analysis is consistent with the NICE reference case and the NHS and PSS perspective, we consider it important to include both the impact on HRQoL of informal carers and the costs of professional caregivers. This is particularly relevant in CIDP, where patients in worse health states experience important motor impairment, leading to substantial dependency on others for basic activities of daily living. Ignoring these elements would therefore underestimate both the burden of disease and the benefits of effective treatment.

B62. Priority question: Please give further details on how caregiver disutilities were calculated:

- a) Please explain how the disutilities in HST9/Gani *et al.* 2008 were mapped to the health states reported in Table 65 of the CS.**
- b) Please clarify whether the disutilities, or the approach used to derive them, were discussed and validated with clinicians or caregivers.**
- c) Please explain how the number of caregivers for each health state was derived.**
- d) Please provide a scenario analysis in which patients have at most one caregiver for any health state, with the proportion requiring a caregiver informed by the UK Adelphi dataset.**

(a) Caregiver disutilities reported in Gani et al. (2008)⁷³ for MS patients were mapped to CIDP health states based on comparable levels of motor functional

impairment. The mapping aligned EDSS categories with aINCAT-based health states as follows:

- EDSS 0–3.0 to aINCAT 0–1 (Very limited impairment)
- EDSS 3.5–7.0 to aINCAT 2–6 (Mild to Moderate impairment)
- EDSS 7.5–9.5 to aINCAT 7–10 (Severe to Very Severe impairment)

This mapping was validated by clinical experts (see point b) and illustrated in Figure 1 of the CS.

(b) The appropriateness of mapping caregiver need in MS from EDSS to aINCAT-based health states was first explored during a qualitative workshop involving five clinical experts from five separate and geographically representative specialised CIDP centres across England and was subsequently validated with one additional clinician. Taken together, the clinical feedback supports the proposed mapping between EDSS and aINCAT categories and the use of MS-derived caregiving patterns as a reasonable analogue for CIDP.

During this process, clinicians were asked two questions designed to validate how caregiver requirements and the consequent impact on their quality of life could be aligned with patterns observed in MS. The questions and summary of response are reported below.

Question 1:

Data from the ADHERE trial suggest that patients with an aINCAT score of 9–10 have EQ-5D utility values below zero, indicating a very poor quality of life—worse than the health state typically associated with death (utility score of 0).

Since in other NICE submissions patients with MS and an Expanded Disability Status Scale (EDSS) score of 7 or higher had a negative EQ-5D, we are considering drawing a parallel with the quality of life experienced by these MS patients. Our understanding is that the limitations in activities of daily living for CIDP patients with an aINCAT score of 9–10 are broadly comparable to those experienced by MS patients at EDSS of 7 or higher, and that their associated quality of life scores may also be similar.

Figure 19: Comparison of limitations in daily living assessed using EDSS in multiple sclerosis versus INCAT in CIDP

EDSS (multiple sclerosis)	INCAT (CIDP)
0.0 Normal neurological examination 1.0–1.5 No disability, minimal signs in one functional system (FS) 2.0–2.5 Minimal disability in one or two FS 3.0–3.5 Moderate disability in one FS or mild disability in three or four FS; still fully ambulatory. 4.0–4.5 Significant disability, still able to walk without aid or rest for about 500 meters. 5.0–5.5 Disability impairs full daily activities; able to walk 200 meters without aid or rest. 6.0–6.5 Requires walking aid (e.g., cane, crutch) to walk 100 meters (6.0) or 20 meters (6.5). 7.0–7.5 Unable to walk beyond ~5 meters, essentially restricted to a wheelchair. 8.0–8.5 Essentially restricted to bed or chair; maintains self-care with effort. 9.0–9.5 Helpless bed patient; able to communicate and eat (9.0) or unable to do so effectively (9.5) 10.0 Death due to MS	 0 No upper limb problems 1 Symptoms, in one or both arms, not affecting the ability to perform ADLs 2 Symptoms, in one arm or both arms, affecting but not preventing any ADLs ¹ 3 Symptoms, in one arm or both arms, preventing one or two ADLs 4 Symptoms, in one arm or both arms, preventing three or all ADLs 5 Inability to use either arm for any purposeful movement  0 Walking not affected 1 Walking affected, but walks independently outdoors 2 Usually uses unilateral support to walk outdoors 3 Usually uses bilateral support to walk outdoors 4 Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps with help 5 Restricted to wheelchair, unable to stand and walk a few steps with help

Abbreviations: ADL: Activities of daily living; CIDP: Chronic inflammatory demyelinating polyneuropathy; EDSS: Expanded Disability Status Scale; FS: Functional system; INCAT: Inflammatory Neuropathy Cause and Treatment.

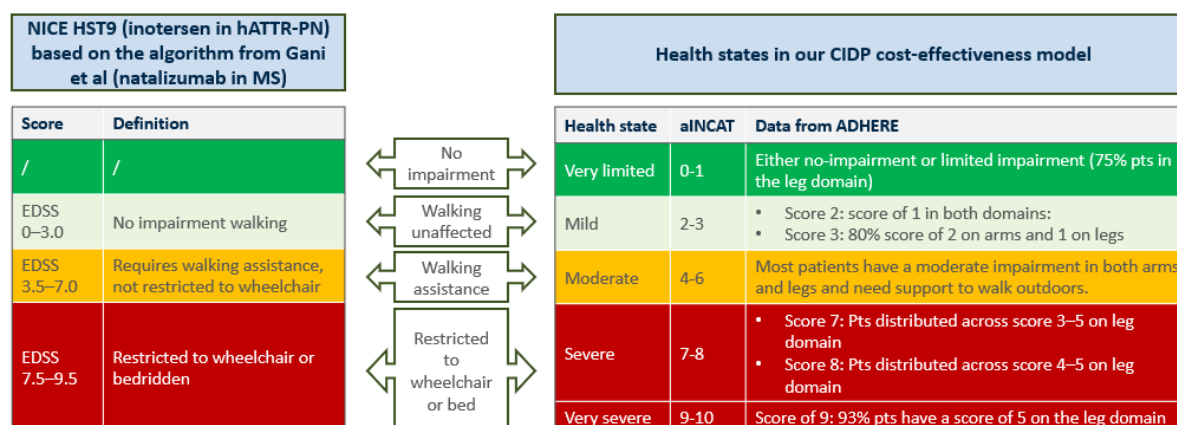
Do you think it is reasonable to assume that the level of functional limitation in daily living experienced by MS patients with an EDSS score of 7 or higher is comparable to that of CIDP patients with an aINCAT score of 9–10? (Yes, No, Unsure)

Synthesis of response: All six clinicians agreed we can assume that CIDP patients with INCAT score of 9-10 have a comparable functional disability to MS patients with EDSS 9-10.

Question 2:

The second question relates to estimating the quality of life impact on carers of CIDP patients. In a previous NICE submission (unrelated to MS), the economic model used carer disutility values derived from studies in MS, with data stratified by EDSS scores.

Figure 20: Mapping between health states in Gani et al. and health states in the model in the CS



Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; CIDP: Chronic inflammatory demyelinating polyneuropathy; CS: Company Submission; EDSS: Expanded Disability Status Scale; hATTR-PN: Hereditary transthyretin amyloidosis with polyneuropathy; MS: Multiple sclerosis; NICE: National Institute for Health and Care Excellence; Pts: Patients.

Do you think it is reasonable to assume that the time and effort required to care for a CIDP patient, across varying levels of INCAT scores, is broadly comparable to that required for MS patients at equivalent EDSS levels?

Synthesis of response: All six clinicians agreed that motor disability observed in CIDP is broadly comparable to that seen in patients with MS. As a result, they considered it reasonable that the motor-related components of caregiver involvement, and related impact on their quality of life, would also be similar across the two conditions. Regarding the overall time and effort required from caregivers, three of the six clinicians fully agreed that caregiving needs for CIDP and MS patients at the proposed mapping of aINCAT and EDSS category are broadly comparable. Two clinicians noted that MS patients may experience additional symptoms, such as bladder and bowel dysfunction, that may lead to different caregiver involvement than what required in CIDP. One clinician agreed that the motor impairment is similar between the two conditions but was unsure about the caregiver involvement.

(c) The number of caregivers was derived for each health state from Gani et al, and HST9.^{73,74} One caregiver was applied for all health states except for the Severe and Very Severe health states, where two caregivers are considered.

(d) The company has included a scenario analysis in which the cohort in each health state is applied one caregiver and the proportion requiring a caregiver is informed by the UK Adelphi dataset (Table 55). The results of this scenario analysis are included in Table 35.

Table 55: Proportion requiring a caregiver from the UK Adelphi dataset

Health state	% of patients who need a caregiver
Very limited impairment (aINCAT 0-1)	2.8%
Mild Impairment (aINCAT 2-3)	14.8%
Moderate Impairment (aINCAT 4-6)	51.8%
Severe Impairment (aINCAT 7-8)	70%
Very severe impairment (aINCAT 9-10)	100%

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment score.

Model implementation

B63. Priority question: The EAG considers that the company's use of a six month cycle length in the model is inappropriate, as this is insufficiently granular to capture changes in patients' disease severity as a new treatment regimen is established, and also leads to misalignment with timepoints in trial data used to inform transition probabilities, response probability, baseline health state occupancy, and approach to modelling q2w dosing. Please update the model to use a 12-week model cycle for the first two years, in order to better align with available trial data. If desired, a six-month cycle may still be used thereafter, for the remainder of the time horizon.

The Company acknowledges the EAG's concern that a 6-month cycle length may be considered insufficiently granular to capture early changes in disease severity and to align with all trial timepoints. However, the Company considers a 6-month cycle to be the most appropriate and robust choice for the base case analysis for the reasons discussed below:

- Transition probabilities: As mentioned in Section 3.3.3.1.1 of the Company Submission and discussed as part of the response to question B12, the transition probabilities between aINCAT-based health states were derived using paired observations for each patient over a 24-week window (baseline

and the last available observation within the same window). This requires at least two assessment visits within that window; if no second visit occurs, the period must be excluded to avoid inappropriate last-observation-carried-forward from baseline. With 24-week windows, most patients have ≥ 2 visits, leading to relatively complete data and robust transition matrices (N=49, 44, 32 and 21 informing the four sets of transition matrices from baseline to Week 96, in order).

When the window is restricted to 12 weeks, a large proportion of patients no longer have two visits within the same 12-week period (e.g. a visit at baseline and then at a point later than Week 12). The observations for these patients cannot be validly imputed and therefore have to be excluded, which substantially increases missing data and reduces the amount of information informing transition probabilities. With 12-week windows, the number of patients informing the eight sets of transition matrices from baseline to Week 96 (2 years) is N=49, 41, 29, 25, 19, 12, 11, 10. As it can be observed, these are much lower than the number of patients informing the transition matrices when a 24-week window is applied (i.e. in the period 24-48 Weeks N=44 in 24-week window and N=32 and 21 in a 12-week window). Thus, transitions are informed by a very small sample for each of the health states. The number of missing data are reported in Table 37 and Table 38, as part of the response to B12.

In addition, over shorter intervals, the observed data show more “no change” observations between health states, i.e. fewer transitions, which is consistent with clinical expert opinion that clinically meaningful change often requires longer than 12 weeks to be observed. Clinical experts suggested that assessment is done every 6 months in maintenance treatment. As a result, the 12-week transition matrices are less data-rich and, in our view, less reliable than those derived using 6-month intervals.

- Response probability: The response probability does not change whether a 3-month or a 6-month cycle length is considered. This is estimated based on the proportion of patients meeting the response endpoint at the end of Stage A of

ADHERE out of the total patients at baseline of Stage A. The responders and non-responders are modelled in separate engines from the beginning of the simulation, and the non-responders are applied the cost of induction of efgartigimod but efficacy is modelled following the same transitions as in the comparator arm (since this cohort is assumed to go back to treatment before efgartigimod after the 12-week induction period).

- Baseline health state occupancy: At the start of the simulation (cycle 0), the cohort is distributed based on the distribution at baseline run-in of ADHERE and baseline Stage A of ADHERE for the Ig-refractory cohort. The 6-month or 3-month cycle length does not impact this distribution. In the pivotal trial, the primary assessment of response to efgartigimod occurs at 12 weeks (end of induction). In the base case model, by using a 6-month cycle, we effectively apply the improvement observed at 3 months only at the end of the first 6-month cycle. In other words, patients are assumed to remain in worse health states for an additional 3 months compared with the trial evidence. This timing assumption is conservative with respect to efgartigimod's benefit, as it delays the accrual of quality-of-life improvements.
- Approach to modelling q2w dosing: As described in Section 3.5.1.3 of the CS, to become eligible for q2w, patients in the ADHERE+ substudy had to be on the q1w schedule for at least 24 weeks, of which the last 12 with a stable disease severity as measured on the aINCAT scale. The data from the ADHERE+ substudy report the proportion eligible for the q2w schedule (82.53%) and the proportion, among them, who remained on q2w schedule for at least 24 weeks (28.9%) remained on q2w schedule for at least 24 Weeks.³⁵ These data are used to estimate the proportion of the cohort switching to q2w after 6 months (approximately 24 weeks) of q1w (23.85%). Thus, choosing a 3-month or 6-month cycle length does not change the implementation of q2w dosing. In either modelling approach, 23.85% of the cohort is assigned to q2w after 6 months.
- Approach to modelling remission and relapse: As discussed in the clarification meeting with the EAG, using a 12-week cycle length creates practical

challenges for modelling remission-relapse without introducing a large number of tunnel states. To keep the model tractable under this alternative structure, remission transitions would only be applied from year 2 onwards. This means that the 12-week-cycle scenario does not allow remission to be modelled from the start of treatment in the same way as the base case analysis. When a 12-week cycle is used throughout and remission is allowed from model initiation, the incremental QALYs for efgartigimod increase slightly because the improvement is captured earlier. Thus, from a health-benefit perspective, the shorter cycle length is actually more favourable to efgartigimod.

- Assessment of disease progression in clinical practice: Clinical experts indicated that, outside the trial context and beyond the initial induction period, patients are typically reviewed, and their disease status formally reassessed on a roughly 6-monthly basis. A 6-month cycle therefore, aligns more closely with how CIDP is managed in routine care and the timeframe over which changes in disability is expected to be observed in maintenance treatment.

For the reasons highlighted above, we retained the 6-month cycle length as the base case analysis. Nevertheless, in response to the EAG's request, we have implemented a scenario analysis which considers a 12-week model cycle for the first 2 years, followed by 6-month cycles thereafter. The results of this scenario analysis are included in Table 35 and show only a modest impact on the ICER, confirming that results are not highly sensitive to cycle length. Incremental QALYs for efgartigimod versus the comparator increased compared with the base case (4.35 versus [REDACTED]), mainly because the benefit observed at Week 12 in Stage A of ADHERE is now applied at 3 months rather than 6 months in the model. As noted above, using 3-month transitions reduces movement of the cohort between health states (including from better to worse states). This leads to a more favourable health state distribution, which is, however, an artefact of the shorter cycle length being insufficient to capture meaningful changes during maintenance treatment. This effect is even more pronounced in the comparator arm. This impacts both QALYs and costs. On the cost side, remission is applied only from Year 2 onwards, which also affects total costs. Under this scenario, incremental costs are [REDACTED], so the ICER remains dominant and the NMB is [REDACTED]. Overall, applying a 3-month cycle length

for the first 2 years does not meaningfully change the results compared with using 6-month cycles from the start of the simulation.

A description of the implementation of 3-month model cycle length for the first 2 years is described hereunder.

Remission/relapse

As mentioned above in this response, the probability of remission was set 0% for the first 2 years in both arm. Therefore, the 3-month transition probabilities only include the transitions between aINCAT health states in active disease part.

Transition probabilities

- Efgartigimod arm: The observed aINCAT health states distribution at baseline of ADHERE Stage B is used to inform the distribution of the efgartigimod responders cohort at month 3 of the analysis. For the next eight 3-month cycles (24 months), the cohort transitions between health states based on the 3-month transition probabilities estimated from pooled ADHERE Stage B and ADHERE+. The pooling of the data from ADHERE and ADHERE+ was done as for the estimation of the 6-month transition probabilities (see Section 3.3.3.1.1 in the CS).

Starting from the baseline of Stage B, the number of patients shifting from each health state to the other eight distinct periods of 12 Weeks (for a total of 96 Weeks, ~24 months) is recorded. This provides eight sets of TPs: from baseline to Week 12, from Week 12 to Week 24, and so forth until Week 96 (approximately 24 months). Beyond 24 months, 6-month time horizon is used and the identity matrix is applied, with the cohort only allowed to shift from active disease to remission and vice versa.

Table 56 reports the 3-month cycle TPs used in the cohort that is on maintenance treatment with efgartigimod for the first 2 years in the analysis.

Table 56: Transition probabilities per 3-month cycle, efgartigimod maintenance from ADHERE Stage B and ADHERE+

		Active disease				
		Very Limited	Mild	Moderate	Severe	Very severe
Baseline to week 12	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					
Week 12 to week 24	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					
Week 24 to week 36	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					
Week 36 to week 48	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					
Week 48 to week 60	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					
Week 60 to week 72	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					
Week 72 to week 84	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					
Week 84 to week 96	Very Limited					
	Mild					
	Moderate					
	Severe					

		Active disease				
		Very Limited	Mild	Moderate	Severe	Very severe
	Very Severe	████	████	████	████	████

- Comparator arm: As in the Company Submission, the results of the ITC between efgartigimod and Ig were used to derive TPs for the comparator arm, starting from the shift counts observed in the efgartigimod arm of ADHERE and ADHERE+ for 12-weeks periods from baseline to Week 96 (approximately 24 months). Table 57 reports the 3-month cycle TPs used in the cohort that is on Ig maintenance treatment for the first 2 years in the analysis.

Table 57: Transition probabilities per 3-months cycle, Ig maintenance

		Active disease				
		Very Limited	Mild	Moderate	Severe	Very severe
Baseline to week 12	Very Limited	████	████	████	████	████
	Mild	████	████	████	████	████
	Moderate	████	████	████	████	████
	Severe	████	████	████	████	████
	Very Severe	████	████	████	████	████
Week 12 to week 24	Very Limited	████	████	████	████	████
	Mild	████	████	████	████	████
	Moderate	████	████	████	████	████
	Severe	████	████	████	████	████
	Very Severe	████	████	████	████	████
Week 24 to week 36	Very Limited	████	████	████	████	████
	Mild	████	████	████	████	████
	Moderate	████	████	████	████	████
	Severe	████	████	████	████	████
	Very Severe	████	████	████	████	████
Week 36 to week 48	Very Limited	████	████	████	████	████
	Mild	████	████	████	████	████
	Moderate	████	████	████	████	████
	Severe	████	████	████	████	████
	Very Severe	████	████	████	████	████
Week 48 to week 60	Very Limited	████	████	████	████	████
	Mild	████	████	████	████	████
	Moderate	████	████	████	████	████
	Severe	████	████	████	████	████

		Active disease				
		Very Limited	Mild	Moderate	Severe	Very severe
Week 60 to week 72	Very Severe					
	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					
Week 72 to week 84	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					
Week 84 to week 96	Very Limited					
	Mild					
	Moderate					
	Severe					
	Very Severe					

Unplanned discontinuations

- Efgartigimod: The same time-to-event analysis of ADHERE and ADHERE+ data used in the 6-month model cycle length is used, with the difference that probabilities from the KM directly (or extrapolated using the Exponential function) are calculated for 3-month period. These probabilities are reported as part of the response to question B18. Beyond 18 months, no unplanned discontinuations are assumed as in the CS.
- Ig: The 24-week probabilities estimated from the literature are transformed into 12-week probabilities based on the formula $1-(1-p)^{0.5}$. The probability of unplanned discontinuation from week 24 to 48 is transformed in 3-months probability and then applied for cycle 3 up to cycle 6 (18 months). Beyond 18 months no unplanned discontinuations are assumed as in CS. When Ig is modelled as part of the sequence after efgartigimod discontinuations, three tunnel states are used to model the different probability of discontinuation in first 24 weeks and the next periods. To avoid having to add additional tunnel states, we assumed no discontinuations apply already after three cycles,

which in the 3-month cycle length approach corresponds to 9 months. This is conservative since it implies more patients remain on treatment with Ig after efgartigimod and Ig is associated with higher costs than PLEX, corticosteroids and immunosuppressants.

Health benefits and costs

- Discounting (costs and benefits) was adjusted to consider 3-month cycle length for the first 2 years in the analysis;
- LYs, QALYs and incidence of events were adjusted in the engine to consider the 3-month cycle length for the first 24 months;
- An index taking the value of 0.5 was applied to all cycle costs to ensure they are adjusted from 6 to 3 months for the first 2 years in the analysis. This adjustment was made in the engine directly to avoid having to build two subset of data in the user sheets and then link these to the engine for the first 2 years of the analysis;
- One-off costs were not impacted.

B64. Priority question: Please update the model so that the proportion of patients in each subgroup (i.e. stable on Ig at baseline, refractory to Ig, and intolerant to Ig) is user-adjustable and can be varied in sensitivity and scenario analyses.

In response to the above request, the proportions of patients in the refractory-to-Ig and the intolerant-to-Ig subgroup were included in the *Settings* sheet, as user-adjustable inputs. These two values were also included in OWSA and probabilistic sensitivity analysis (PSA). The proportion of the cohort on Ig at baseline is dynamically calculated in the engine as 1 minus the proportion in each of the other two subgroups and therefore was not included as explicit input in the *Settings* sheet.

B65. Priority question: Please update the probabilistic analysis and OWSA to vary population baseline characteristics.

In the CS, age, weight and % females were included in the OWSA. As requested, in the revised model we have now included them in PSA also. However, please note that population characteristics are part of first-order uncertainty and as such are not typically included in PSA.

B66. The EAG notes that the model includes the functionality to apply mortality HRs to each health state, although by assumption, these are all set to 1. Please update the implementation of the probabilistic analysis and OWSA to exclude these parameters.

The company has amended the model as requested, with the mortality HR parameters removed from the probabilistic and deterministic sensitivity analyses. When OWSA and PSA run, the model continues to use HR = 1 for each of the health states in the base case and scenarios.

B67. Please update the implementation of the probabilistic analysis to use a beta distribution for all health state utility values and utility decrements instead of a Normal distribution.

A Normal distribution was included in the probabilistic analysis in the Company Submission for utility and disutilities which are negative, since the Beta is restricted in range of values 0-1. Nevertheless, a Beta can be applied as alternative after adjusting for the negative values. This was implemented as requested in the updated version of the model. All probabilistic analysis presented for the revised base case and any of the scenarios is based on Beta distribution for all utility and disutility values.

B68. Priority question: Please update the probabilistic analysis to vary the transition probabilities using a Dirichlet distribution.

A distribution was added to vary the transition probabilities in the updated model. This was done on the shift counts from the ADHERE trial in the Transition probabilities sheet of the model. The shift counts are used to estimate the transitions

for efgartigimod and also the transitions for Ig based on the ITC results. All probabilistic analysis presented for the revised base case and any of the scenarios is now including the transition probabilities in PSA.

B69. Priority question: Please update the implementation of the probabilistic analysis to include a user-adjustable random seed, to ensure probabilistic results can be reproduced.

The probabilistic analysis has been updated to include a user-adjustable random seed. An input field now allows users to specify the seed value, ensuring that PSA results can be exactly replicated when the same seed is used. The model runs 1,000 seeds of random values and these are those used to run the PSA for the revised base case and for any of the scenario analysis conducted. The model also includes the option to use random values (not based on seeds) for the PSA, this can be selected from the dropdown in the PSA seed sheet. Please note that if a new calculation of random seeds is done by clicking on the bottom in the PSA seed sheet, then the PSA results provided in this document will not match the newly conducted analysis.

Section C: Textual clarification and additional points

C1. Priority question: Only UK chart review study protocol has been provided as part of the submission. Please provide the results of the study.

The company acknowledges the request for the full report of the UK chart review study. At the time of the CS, the UK chart review study was ongoing and an interim data cut was used to inform the company cost-effectiveness. A separate report was not developed for the interim data cut.

An updated report was recently made available for the UK chart review. The company will submit a short report to the EAG and NICE, along with updated cost-effectiveness scenarios as a separate appendix, within approximately one week.

C2. Priority question: The company references Appendix F to describe the targeted literature review in various places in Section 3 of the CS. However, Appendix F presents details of the HRQoL SLR. Please provide details of the targeted literature review that was supposed to be Appendix F.

Details of the targeted literature reviews referenced in Section 3 of the Company Submission are supplied in the accompanying document ('TLRs to support CE analysis of efgartigimod in CIDP.pdf').

C3. On review of the provided appendices, the EAG notes many of the details and results of the multiple SLRs appear to be missing. For example, Appendix F lacks a results Section (such as Section 1.2 in Appendix E) and it appears that no SLR was conducted to identify relevant healthcare resource use publications, with the company instead relying on UK expert interviews.

a) Please provide the results of the HRQoL SLR outlined in Appendix F.

See Appendix 1 for reference list.

The screening of records from electronic searches (n=5,906) and ad-hoc congresses (2022-2024) identified a total of 29 publications from 26 studies (20 full-texts^{1,3-21} and nine congress abstracts²²⁻³⁰). The studies reported data for adult patients living with CIDP;^{1,3-6,8-30} three studies reported data for progressive or relapsing patients;^{4,16,17} two reported data for clinically stable patients^{1,5} and one study each reported data for newly diagnosed patients,¹¹ and patients with typical and definite chronic

inflammatory demyelinating polyneuropathy (CIDP).⁹ Across the studies, the sample size ranged between 11⁷ to 542²⁶ and mean (SD) age ranged between 45 (13.22)¹⁸ to 67.2 (14.2) years.¹⁴ The studies used standardised criteria for the diagnosis of CIDP, including the European Federation of Neurological Societies/Peripheral Nerve Society 2010 (EFNS/PNS 2010) criteria,^{1,3-6,8,10,12,13,18,20,21} and the American Academy of Neurology (AAN), 1991 criteria.¹⁹

The outcomes in identified studies were classified into the following categories (not mutually exclusive):

- 18 studies reported the overall patient QoL^{1,4-7,9,11,12,14-18,21-24,26}
- A set of nine studies reported on functional disability in CIDP patients^{5,6,8-10,13,20,21,28}
- Seven studies assessed fatigue^{5,6,12,13,19,24,26}
- Six studies analysed the prevalence of pain^{3,5,6,8,14,18}
- Three studies reported on social functioning^{1,6,22}
- Two studies evaluated disease impact on sleep quality^{1,18}
- Two studies investigated depression levels in patients living with CIDP^{6,8}
- Seven studies assessed disease impact on activities of daily living^{4,14,15,19,20,27,30}
- Five studies reported on treatment satisfaction^{4,21,23,27,29}
- Two studies reported on patient experiences; one each, following treatment with IVIg⁵ and SCIg¹⁰

The ad-hoc searches on the websites of 28 health technology assessment (HTA) agencies did not identify any additional evidence of humanistic outcomes for CIDP.

b) Please explain why an SLR was not performed for costs and healthcare resource use SLR, given SLRs were conducted for the identification for relevant cost-effectiveness studies and HRQoL studies.

Costs and healthcare resource use (HCRU) were included in the economic systematic literature review (SLR) (please see the search strings described in Appendix E of the CS: Table 19 #3&4; Table 20 #3&4; Table 21 #3&4).

- Nine publications evaluated and compared the cost of Ig treatment.^{34,75–82}
- Seven publications evaluated the annual total cost-of-illness (direct and indirect costs) and identified cost-driving factors.^{83–89}
- Five publications assessed HCRU including healthcare visits and inpatient visits/admissions.^{86,90–93}

The inclusion and exclusion criteria used in the economic SLR in patients living with CIDP are presented in Table 58 below.

Table 58: Eligibility criteria for selection of relevant studies on economic SLR

PICOST	Inclusion criteria	Exclusion criteria
Population	Adults (≥ 18 years old) with CIDP	• Patients without CIDP • Paediatric patients • For trials that qualify for inclusion as per the defined criteria but include a mixed population of participants, such studies shall be excluded unless separate data are reported for the population of interest
Intervention	Induction/maintenance treatment including any of the following: • Efgartigimod alfa and hyaluronidase–qvfc (Vyvgart Hytrulo). Also known as ◦ ARGX–113 ◦ Efgartigimod PH20 ◦ Efgartigimod PH20 SC ◦ Efgartigimod–argenx ◦ Efgartigimod alfa–fcab ◦ Efgartigimod alfa–fcab–argenx • Immunoglobulins (IV/SC or both) • Corticosteroids (oral/IV)–dexamethasone, prednisone, prednisolone, methylprednisolone • PLEX • Non-steroidal immunomodulatory drugs (rituximab, cyclophosphamide, ciclosporin, mycophenolate mofetil, azathioprine)	Interventions which are not administered in accordance with licensed indications such as herbal and traditional medicines
Comparator	Any or none	-
Outcomes	• Costs of illness (direct and indirect costs) ◦ Total costs ◦ Direct costs ◦ Indirect costs • HCRU, including but not limited to: ◦ Inpatient stays ◦ Outpatient visits ◦ Emergency visits ◦ ICU admissions ◦ Specialist visits ◦ Days hospital visits ◦ Duration of inpatient stays ◦ Duration of ICU admissions ◦ Disease monitoring tests and procedures, e.g. ▪ Laboratory tests ▪ Radiology tests or procedures ▪ Physiotherapy • Economic analysis/burden ◦ CEA ◦ CUA ◦ CCA ◦ CBA ◦ CMA	• Outcomes other than economic

PICOST	Inclusion criteria	Exclusion criteria
	○ ICER ○ QALYs • Data-related to ○ Productivity loss ○ Premature retirement ○ Unemployment ○ Sick leave ○ Absenteeism/presenteeism	
Study design	• Observational studies • Real world studies • Randomised controlled study • Clinical trial (≥10 cases) • Clinical studies (RCTs and nRCTs; ≥10 cases)	• Case reports/case series • Animal/in-vitro studies • Experimental studies • Clinical studies with <10 patients
Timeframe	2014–2024	Congress abstracts pre–2022
Publication type	• Primary publications • Letter and notes (research with relevant data) • Congress abstracts (2022–2024)	• Secondary publication • Letter to editor • Correspondence • Editorial • Erratum • Opinion • Reviews • Flag for bibliographic references ○ Systematic review (flag) ○ Meta-analysis (flag) ○ Network meta-analysis (flag) ○ Recommendations/Consensus/ Guidelines (flag)
Language	English	Non-English

Abbreviations: CCA: Cost-comparison analysis; CBA: Cost-benefit analysis; CMA: Cost-minimisation analysis; CEA: Cost-effectiveness analysis; CUA: Cost-utility analysis; CIDP: Chronic inflammatory demyelinating polyneuropathy; HCRU: Healthcare resource utilisation; ICER: Incremental cost-effectiveness ratio; ICU: Intensive care unit; IV: Intravenous; nRCT: Non-randomised controlled trial; PICOST: Population, Intervention, Comparator, Outcome, Study Design, Timeframe; PLEX: Plasma exchange; QALY: Quality-adjusted life year; RCT: Randomised controlled trial; SC: Subcutaneous injection.

While HCRU outcomes were included within the economic SLR scope (see Table 58), the systematic search yielded limited UK-specific evidence suitable for model parameterisation. Identified studies predominantly reported aggregate costs rather than granular resource use patterns (e.g., frequency of healthcare professional visits, caregiver hours by severity, mobility aid requirements), and most originated from non-UK healthcare systems with limited transferability to NHS practice.

To ensure model parameters reflected current UK clinical practice, the Company Submission supplemented SLR findings with high-quality UK-specific sources (as described in Appendix G of the CS):

- Mahdi-Rogers et al. (2014): UK prospective study providing NHS-relevant disease monitoring estimates (GP visits, specialist neurology consultations, physiotherapy, occupational therapy).⁸⁴
- Adelphi CIDP Dataset: Real-world UK data for parameters not consistently reported in published literature:⁴⁷
 - Professional caregiving requirements by disease severity
 - Mobility aid usage patterns
 - Hospitalisation length of stay by severity and ICU admission
- Structured Expert Elicitation (SEE): Five UK CIDP specialists validated assumptions and informed parameters where published evidence was insufficient (e.g., corticosteroid treatment duration, remission probabilities).¹³

This triangulated approach aligns with NICE methodology guidance emphasising use of the most appropriate data for the decision problem.⁹⁴ For context-dependent resource use parameters, UK primary sources often provide more directly applicable evidence than international systematic reviews. All data sources are documented transparently (Tables 75-80 in the CS) and tested in sensitivity analyses.

C4. In Section 3 of the CS, there are numerous instances where it is reported that parameters have been adjusted for a monthly cycle, rather than a 6-monthly cycle. This is particularly evident in Section 3.4.5 for Adverse Events. Please clarify that all inputs in the model are adjusted for the 6-monthly model cycle.

The company confirms that all inputs in the model are adjusted for the 6-monthly model cycle.

C5. The data in Tables 62, 63, 74, and 76 of the CS do not align with the data in the economic model. Please clarify if the data presented in the CS are correct and amend as necessary.

Amended tables are presented below (please note that the table numbers in the table titles refer to the tables presented in the CS).

CS Table 62: AE disutilities

AE	Decrement	Source
Arthralgia and pain in the extremities	-0.165	NICE TA706, ⁴⁹ Sullivan et al (2011) ⁵⁰
Asthenia	-0.102	Not available in the literature. The average disutility value was used.
Back pain	-0.177	NICE TA706, ⁴⁹ Sullivan et al (2011) ⁵⁰
Dizziness	-0.102	Not available in the literature. The average disutility value was used.
Fatigue	-0.102	Not available in the literature. The average disutility value was used.
Headache	-0.104	NICE TA706, ⁴⁹ Sullivan et al (2011) ⁵⁰
Haemolysis	-0.061	Sullivan et al (2011) ⁵⁰
Hypertension	-0.046	Sullivan et al (2011) ⁵⁰
Influenza	-0.080	NICE TA706 ⁴⁹
Infusion/injection site reaction	-0.010	NICE TA706 ⁴⁹
Nasopharyngitis	-0.019	NICE TA706 ⁴⁹ Sullivan et al (2011) ⁵⁰
Nausea	-0.073	Sullivan et al (2011) ⁵⁰
Pyrexia	-0.102	Not available in the literature. The average disutility value was used.
Upper respiratory tract infection	-0.119	NICE TA706 ⁴⁹ Sullivan et al (2011) ⁵⁰
Infections	-0.102	Not available in the literature. The average disutility value was used.
Sleep disorders	-0.095	Sullivan et al (2011) ⁵⁰
Psychiatric disorders	-0.143	Sullivan et al (2011) ⁵⁰
Abdominal pain	-0.044	Sullivan et al (2011) ⁵⁰
Endocrine disorders	-0.030	Sullivan et al (2011) ⁵⁰
Anaemia	-0.022	Sullivan et al (2011) ⁵⁰
Gastrointestinal disturbances	-0.044	Sullivan et al (2011) ⁵⁰
Renal dysfunction	-0.101	Sullivan et al (2011) ⁵⁰
Peripheral oedema	-0.040	Sullivan et al (2011) ⁵⁰

Abbreviations: AE: Adverse event.

CS Table 63: Disutilities related to intravenous access

Complication	Decrement	Duration (days)	Source
Permanent PICC, surgically implanted CVC, infusion port	-0.250	7	Average values
Catheter-related infections	-0.520	7	TA804 ⁵⁵
Catheter-related blood infections	-0.520	7	TA804 ⁵⁵
Thrombophlebitis	-0.063	7	Sullivan 2011 ⁵⁰
Infiltration and extravasation	-0.083	7	Sullivan 2011 ⁵⁰
Thromboembolic events	-0.065	7	Sullivan 2011 ⁵⁰

Abbreviations: CVC: Central Venous Catheter; PICC: Peripherally Inserted Central Catheter.

CS Table 74: Drug administration costs per-cycle

Treatment	Cost per cycle (£)
Efgartigimod	
One off cost for Induction (corresponding to 12 in-hospital administrations)	██████
Maintenance phase, q1w	██████
Maintenance phase, q2w	██████
Ig	
Privigen	██████
Gamunex	██████
Flebogamma DIF	██████
Hizentra	██████
Ig administration cost per 6-month period	██████
Basket of other treatments	
PLEX	██████
Corticosteroids	██████
Immunosuppressants	██████

Abbreviations: Ig: Immunoglobulin; PLEX: Plasma exchange.

CS Table 76: Disease monitoring - unit cost per healthcare professional

Service	Unit cost	Reference
General practitioner visit	£268.00	PSSRU, Unit Costs of Health and Social Care 2024. Cost per hour - GP Unit cost including direct care (Table 9.4.2.) ⁷¹
Specialist visit, neurology out-patient	£236.00	NHS England. NHS National Cost Collection 2023/24. HRG code AA32Z – Neuropsychology test ⁴¹
Physiotherapist	£41.00	PSSRU, Unit Costs of Health and Social Care 2024 Document. Section 6.2 (Table 6.2.1.) Cost per hour community services (one-to-one). Physiotherapy ⁷¹
Occupational therapist	£68.00	PSSRU, Unit Costs of Health and Social Care 2024 Document. Section 6.2 (Table 6.2.1.) Cost per hour community services (one-to-one). Occupational therapy ⁷¹

Abbreviations: GP: General practitioner; PSSRU: Personal Social Services Research Unit.

C6. Please supply the following papers, which are missing from the reference pack:

- **Jørgensen *et al.* (missing from the reference list in the CS, but noted as reference 168 in the main body of the report)**
- **Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. 2011; 31:800–4 (reference 166 of the CS, only abstract supplied in reference pack)**

The company has provided these within the reference pack as requested by the EAG. Please note that Jørgensen et al is a conference abstract.

References

1. argenx. ADHERE (ARGX-113-1802) Statistical analysis plan. Data on file.
2. Allen JA, Lin J, Basta I, Dysgaard T, Eggers C, Guptill JT, et al. Safety, tolerability, and efficacy of subcutaneous efgartigimod in patients with chronic inflammatory demyelinating polyradiculoneuropathy (ADHERE): a multicentre, randomised-withdrawal, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2024 Oct;23(10):1013–24.
3. argenx. ADHERE (ARGX-113-1802) Tables, figures and listings. Data on file.
4. Rajabally YA, Nazeer KK, Min YG. Minimal Clinically Important Differences in Measuring Treatment Effects in CIDP: History, Current Use, Limitations, and Prospects. *Muscle Nerve*. 2025 Nov;72(5):1042–51.
5. Van den Bergh PYK, Hadden RDM, Bouche P, Cornblath DR, Hahn A, Illa I, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision. *Eur J Neurol*. 2010 Mar;17(3):356–63.
6. Llauradó A, Quintana M, Gratacós-Viñola M, Vidal-Taboada JM, Restrepo-Vera JL, Alemañ J, et al. Gait Assessment in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. Colosimo C, editor. *Acta Neurol Scand*. 2024 Jan;2024(1):7037704.
7. argenx. Clinical study report ARGX-113-1802, Efgartigimod PH20 SC—CIDP. Data on file. 2023.
8. argenx. Analyses for NICE clarification questions. Data on file.
9. Rajabally YA, Fatehi F. Outcome measures for chronic inflammatory demyelinating polyneuropathy in research: relevance and applicability to clinical practice. *Neurodegener Dis Manag*. 2019 Oct;9(5):259–66.
10. Katzberg HD, Latov N, Walker FO. Measuring disease activity and clinical response during maintenance therapy in CIDP: from ICE trial outcome measures to future clinical biomarkers. *Neurodegener Dis Manag*. 2017 Apr;7(2):147–56.
11. Bus SRM, Broers MC, Lucke IM, Bunschoten C, Van Lieverloo GGA, Adrichem ME, et al. Clinical outcome of CIDP one year after start of treatment: a prospective cohort study. *J Neurol*. 2022 Feb;269(2):945–55.
12. Jacob S, Farrugia ME, Hewamadduma C, Norwood F, Hill M, Leite MI, et al. Association of British Neurologists (ABN) autoimmune myasthenia gravis management guidelines (2025 update). *Pract Neurol*. 2025 Oct;25(5):422–37.

13. argenx. Qualitative clinical validation and structured expert elicitation. Data on file. argenx;
14. Nagelkerke SQ, Kuijpers TW. Immunomodulation by IVIg and the Role of Fc-Gamma Receptors: Classic Mechanisms of Action after all? *Front Immunol*. 2014;5:674.
15. Summary of product characteristics - Vyvgart [Internet]. European Medicines Agency. [cited 2025 Aug 27]. Available from: https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf
16. Liu J, Wang W, Xue J, Zhao C, You H, Lu J, et al. Comparing the Autoantibody Levels and Clinical Efficacy of Double Filtration Plasmapheresis, Immunoabsorption, and Intravenous Immunoglobulin for the Treatment of Late-onset Myasthenia Gravis. *Ther Apher Dial*. 2010 Apr;14(2):153–60.
17. argenx. Market research survey report - Treatment patterns for chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. Data on file. 2025.
18. Sun C, Hu J, Zhao Y, Zheng Y, Meng Q, Luo S, et al. Short-term treatment of CIDP with efgartigimod: a case series in China. *Front Immunol*. 2025 May 1;16:1533167.
19. ClinicalTrials.gov. NCT06637072. A Study to Assess Adults With CIDP Transitioning From IVIg to Efgartigimod PH20 SC. [Internet]. [cited 2025 Nov 20]. Available from: <https://clinicaltrials.gov/study/NCT06637072>
20. argenx. ADHERE+ Top-line results report. Interim analysis 2. Data on file.
21. Markvardsen LH, Sindrup SH, Christiansen I, Olsen NK, Jakobsen J, Andersen H, et al. Subcutaneous immunoglobulin as first-line therapy in treatment-naïve patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study. *Eur J Neurol*. 2017 Feb;24(2):412–8.
22. van Schaik IN, Bril V, van Geloven N, Hartung HP, Lewis RA, Sobue G, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2018 Jan;17(1):35–46.
23. Goyal NA, Karam C, Sheikh KA, Dimachkie MM. Subcutaneous immunoglobulin treatment for chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve*. 2021 Sept;64(3):243–54.
24. Cocito D, Peci E, Torrieri MC, Clerico M. Subcutaneous Immunoglobulin in Chronic Inflammatory Demyelinating Polyneuropathy: A Historical Perspective. *J Clin Med*. 2023 Nov 7;12(22):6961.

25. Hizentra 200 mg/ml solution for subcutaneous injection - Summary of Product Characteristics (SmPC) - (emc) | 4643 [Internet]. [cited 2025 Oct 13]. Available from: <https://www.medicines.org.uk/emc/product/4643/smpc#gref>
26. Bril V, Hadden RDM, Brannagan TH, Bar M, Chroni E, Rejdak K, et al. Hyaluronidase-facilitated subcutaneous immunoglobulin 10% as maintenance therapy for chronic inflammatory demyelinating polyradiculoneuropathy: The ADVANCE-CIDP 1 randomized controlled trial. *J Peripher Nerv Syst JPNS*. 2023 Sept;28(3):436–49.
27. Léger JM, De Bleecker JL, Sommer C, Robberecht W, Saarela M, Kamienowski J, et al. Efficacy and safety of Privigen(®) in patients with chronic inflammatory demyelinating polyneuropathy: results of a prospective, single-arm, open-label Phase III study (the PRIMA study). *J Peripher Nerv Syst JPNS*. 2013 June;18(2):130–40.
28. Katzberg HD, Rasutis V, Bril V. Home IVIG for CIDP: A Focus on Patient Centred Care. *Can J Neurol Sci J Can Sci Neurol*. 2013 May;40(3):384–8.
29. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014 Dec;14(1):135.
30. Clinical Commissioning Policy for the use of therapeutic immunoglobulin (Ig) England (2025) [Internet]. NHS England; 2025 Apr [cited 2025 Oct 11]. Available from: <https://www.england.nhs.uk/publication/commissioning-criteria-policy-for-the-use-of-therapeutic-immunoglobulin-ig-in-england/>
31. argenx. Patient survey research report - Patient experiences living with chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. 2025.
32. NHS England. Health Survey for England, 2021 part 1. [Internet]. 2022 [cited 2025 Nov 24]. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2021/part-4-trends>
33. Rajabally Y, Narasimhan M. Distribution, clinical correlates and significance of axonal loss and demyelination in chronic inflammatory demyelinating polyneuropathy. *Eur J Neurol*. 2010;18(2):293–9.
34. Koay S, Chen YC, Ransley G, Compton L, Lunn MP, Carr AS. Safety and Cost Analysis of Immunoglobulin Cessation Trials in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *J Peripher Nerv Syst JPNS*. 2025 Mar;30(1):e70007.
35. Substudy ARGX-113-1902 - IA2 : Substudy of Phase 2 OLE of ARGX-113-1802 in CIDP with efgartigimod PH20 SC. Data on file. argenx; 2025.
36. van Schaik IN, Mielke O, Bril V, van Geloven N, Hartung HP, Lewis RA, et al. Long-term safety and efficacy of subcutaneous immunoglobulin IgPro20 in CIDP:

PATH extension study. *Neurol Neuroimmunol Neuroinflammation*. 2019 Sept;6(5):e590.

37. Kim PJ, Lansang RP, Vender R. A Systematic Review and Meta-Analysis of Injection Site Reactions in Randomized-Controlled Trials of Biologic Injections. *J Cutan Med Surg*. 2023 July;27(4):358–67.
38. Turner PJ, Ansotegui IJ, Campbell DE, Cardona V, Carr S, Custovic A, et al. Updated grading system for systemic allergic reactions: Joint Statement of the World Allergy Organization Anaphylaxis Committee and Allergen Immunotherapy Committee. *World Allergy Organ J*. 2024 Mar;17(3):100876.
39. MedRA MSSO. Medical Dictionary for Regulatory Activities Terminology (MedDRA). [Internet]. 2025 [cited 2025 Nov 24]. Available from: <https://bioportal.bioontology.org/ontologies/MEDDRA>
40. Dorst J, Fillies F, Dreyhaupt J, Senel M, Tumani H. Safety and Tolerability of Plasma Exchange and Immunoabsorption in Neuroinflammatory Diseases. *J Clin Med*. 2020 Sept 5;9(9):2874.
41. National Cost Collection for the NHS [Internet]. NHS England. [cited 2025 Oct 13]. Available from: <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>
42. Narayanaswami P, Sanders DB, Thomas L, Thibault D, Blevins J, Desai R, et al. Comparative effectiveness of azathioprine and mycophenolate mofetil for myasthenia gravis (PROMISE-MG): a prospective cohort study. *Lancet Neurol*. 2024 Mar;23(3):267–76.
43. Querol L, Crabtree M, Herepath M, Priedane E, Viejo Viejo I, Agush S, et al. Systematic literature review of burden of illness in chronic inflammatory demyelinating polyneuropathy (CIDP). *J Neurol*. 2021 Oct;268(10):3706–16.
44. Hahn AF, Bolton CF, Pillay N, Chalk C, Benstead T, Bril V, et al. Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy. A double-blind, sham-controlled, cross-over study. *Brain J Neurol*. 1996 Aug;119 (Pt 4):1055–66.
45. CIDP Healthcare Resource Use Survey - Redacted Summary. Data on file. argenx; 2025.
46. Hernández-Alava M, Pudney S. Mapping between EQ-5D-3L and EQ-5D-5L: A survey experiment on the validity of multi-instrument data. *Health Econ*. 2022 June;31(6):923–39.
47. argenx. Analysis of Adelphi dataset on patients with CIDP in support of NICE submission. Data on file. argenx; 2025.
48. argenx. Caregiver research survey report - Experiences of individuals supporting adults living with chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. Data on file. 2025.

49. National Institute for Health and Care Excellence. Overview | Ozanimod for treating relapsing–remitting multiple sclerosis | Guidance | NICE [Internet]. NICE; 2021 [cited 2025 Sept 24]. Available from: <https://www.nice.org.uk/guidance/ta706>
50. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Mak Int J Soc Med Decis Mak*. 2011;31(6):800–4.
51. Ghabri S, Dawoud D, Drummond M. Methods for Including Adverse Events in Economic Evaluations: Suggestions for Improvement. *Value Health*. 2024 July;27(7):936–42.
52. National Institute for Health and Care Excellence. Ocrelizumab for treating relapsing–remitting multiple sclerosis. TA533. [Internet]. 2018 [cited 2025 Nov 24]. Available from: <https://www.nice.org.uk/guidance/ta533>
53. National Institute for Health and Care Excellence. Cladribine for treating relapsing–remitting multiple sclerosis. TA616. [Internet]. 2019 [cited 2025 Nov 24]. Available from: <https://www.nice.org.uk/guidance/ta616>
54. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active Crohn’s disease after prior therapy. TA352. [Internet]. 2015 [cited 2025 Nov 24]. Available from: <https://www.nice.org.uk/guidance/ta352>
55. National Institute for Health and Care Excellence. Teduglutide for treating short bowel syndrome. TA804. [Internet]. NICE; 2022 [cited 2025 Sept 24]. Available from: <https://www.nice.org.uk/guidance/ta804>
56. Jørgensen T, Worbes-Cerezo M, Lelli F, Lee X, Bøgelund M, Alulis S. Preferences for Route of Administration, Frequency and Location – A Time-Trade-Off Study in the United Kingdom General Population. *Value Health*. 2017 Oct;20(9):A637.
57. Matza LS, Cong Z, Chung K, Stopeck A, Tonkin K, Brown J, et al. Utilities associated with subcutaneous injections and intravenous infusions for treatment of patients with bone metastases. *Patient Prefer Adherence*. 2013;7:855–65.
58. Bril V, Lampe J, Cooper N, Kiessling P, Gardulf A. Patient-reported preferences for subcutaneous or intravenous administration of parenteral drug treatments in adults with immune disorders: a systematic review and meta-analysis. *J Comp Eff Res*. 2024 Sept;13(9):e230171.
59. UK Government. Fit for the Future. 10 Year Health Plan for England. [Internet]. 2025. Available from: <https://assets.publishing.service.gov.uk/media/6888a0b1a11f859994409147/fit-for-the-future-10-year-health-plan-for-england.pdf>

60. NHS England. Advice and Guidance – operational delivery framework for integrated care boards for 2025/26. [Internet]. 2025. Available from: <https://www.england.nhs.uk/wp-content/uploads/2025/04/advice-and-guidance-operational-delivery-framework-for-integrated-care-boards.pdf>
61. MD/SAS. NHS Immunoglobulin Database Annual Report 2023/24 [Internet]. 2025. Available from: https://igd.mdsas.com/wp-content/uploads/Igd_AnnualReport_202324.pdf
62. Ripellino P, Fleetwood T, Cantello R, Comi C. Treatment of chronic inflammatory demyelinating polyneuropathy: from molecular bases to practical considerations. *Autoimmune Dis.* 2014;2014:201657.
63. Medicinal forms | Mycophenolate mofetil | Drugs | BNF content published by NICE [Internet]. [cited 2025 Nov 25]. Available from: <https://bnf.nice.org.uk/drugs/mycophenolate-mofetil/medicinal-forms/>
64. Appointments - Safe working in general practice - BMA [Internet]. The British Medical Association is the trade union and professional body for doctors in the UK. [cited 2025 Nov 25]. Available from: <https://www.bma.org.uk/advice-and-support/gp-practices/managing-workload/safe-working-in-general-practice/appointments>
65. Costa J, De Carvalho M. Chronic inflammatory demyelinating polyneuropathy, phrenic nerve and respiratory symptoms. *Eur J Neurol.* 2005 Jan;12(1):64–6.
66. Živković SA, Peltier AC, Iacob T, Lacomis D. Chronic inflammatory demyelinating polyneuropathy and ventilatory failure: report of seven new cases and review of the literature: CIDP and ventilatory failure. *Acta Neurol Scand.* 2011 July;124(1):59–63.
67. Stojkovic T, De Seze J, Hurtevent J, Fourrier F, Vermersch P. Phrenic nerve palsy as a feature of chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve.* 2003 Apr;27(4):497–9.
68. Sheth P, Rodriguez Lopez A, Acharya S, Dunn B. A Rare Presentation of Patient With CIDP Found to Have Respiratory Failure and Encephalopathy. Lazzeri C, editor. *Case Rep Crit Care.* 2025 Jan;2025(1):8875501.
69. Malka R, Muntean E. Chronic Inflammatory Demyelinating Polyneuropathy Presenting with Recurrent Ataxia, Bulbar Weakness, and Respiratory Dysfunction (P06.135). In *Neurology*; 2012. p. P06.135.
70. Stamboulis E, Katsaros N, Koutsis G, Iakovidou H, Giannakopoulou A, Simintzi I. Clinical and subclinical autonomic dysfunction in chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve.* 2006 Jan;33(1):78–84.
71. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2024 Manual [Internet]. Personal Social Services Research Unit (University of Kent) & Centre for Health Economics

(University of York); 2025 [cited 2025 Sept 26]. Available from: <https://kar.kent.ac.uk/id/eprint/109563>

72. NHS continuing healthcare - Social care and support guide [Internet]. nhs.uk. 2023 [cited 2025 Nov 25]. Available from: <https://www.nhs.uk/social-care-and-support/money-work-and-benefits/nhs-continuing-healthcare/>
73. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *PharmacoEconomics*. 2008;26(7):617–27.
74. National Institute for Health and Care Excellence. Inotersen for treating hereditary transthyretin amyloidosis (HST9). 2019 May 22; Available from: <https://www.nice.org.uk/guidance/hst9>
75. Burt RK, Tappenden P, Balabanov R, Han X, Quigley K, Snowden JA, et al. The Cost Effectiveness of Immunoglobulin vs. Hematopoietic Stem Cell Transplantation for CIDP. *Front Neurol*. 2021 Mar 22;12:645263.
76. Guptill JT, Runken MC, Eaddy M, Lunacsek O, Fuldeore RM. Treatment Patterns and Costs of Chronic Inflammatory Demyelinating Polyneuropathy: A Claims Database Analysis. *Am Health Drug Benefits*. 2019 May;12(3):127–35.
77. Kapoor M, Compton L, Rossor A, Hutton E, Manji H, Lunn M, et al. An approach to assessing immunoglobulin dependence in chronic inflammatory demyelinating inflammatory polyneuropathy. *J Peripher Nerv Syst JPNS*. 2021 Dec;26(4):461–8.
78. Piscitelli E, Massa M, De Martino BM, Serio CS, Guglielmi G, Colacicco G, et al. Economic evaluation of subcutaneous versus intravenous immunoglobulin therapy in chronic inflammatory demyelinating polyneuropathy: a real-life study. *Eur J Hosp Pharm*. 2021 Nov;28(e1):e115–9.
79. Rajabally YA, Afzal S. Clinical and economic comparison of an individualised immunoglobulin protocol vs. standard dosing for chronic inflammatory demyelinating polyneuropathy. *J Neurol*. 2019 Feb;266(2):461–7.
80. Miah S, Japzon N, Elsaddig A, Koay S, Compton L, Lunn MP, et al. Mycophenolate Facilitates Improvement in Outcome Measures in Treatment Resistant Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *Muscle Nerve*. 2025 Aug;72(2):250–7.
81. Chen Y, Koay JS, Ransley G, Lunn M. Intravenous Immunoglobulin Cessation Trials in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *Journal of the Peripheral Nervous System* 2024:S261. *J Peripher Nerv Syst*. 2024;S361.
82. Amar E, Nicole J, Shamim M, Aisling C, Michael L. Mycophenolate facilitates IVIG dose reduction in CIDP with improvement in clinical outcomes measures. In: Association of British Neurologists: Annual Meeting Abstracts 2023 [Internet].

BMJ Publishing Group Ltd; 2023 [cited 2025 Nov 20]. p. A87.2-A87. Available from: <https://jnnp.bmj.com/lookup/doi/10.1136/JNNP-2023-ABN.269>

83. Guptill JT, Bromberg MB, Zhu L, Sharma BK, Thompson AR, Krueger A, et al. Patient demographics and health plan paid costs in chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve*. 2014 July;50(1):47–51.
84. Mahdi-Rogers M, McCrone P, Hughes RAC. Economic costs and quality of life in chronic inflammatory neuropathies in southeast England. *Eur J Neurol*. 2014 Jan;21(1):34–9.
85. Mengel D, Fraune L, Sommer N, Stettner M, Reese JP, Dams J, et al. Costs of illness in chronic inflammatory demyelinating polyneuropathy in Germany. *Muscle Nerve*. 2018 Nov;58(5):681–7.
86. Cai Q, Zhang Q, Borsum J, Batista A, Heerlein K, Di Scala L. Productivity loss in patients with chronic inflammatory demyelinating polyneuropathy: A nationwide population-based study in Sweden. *J Peripher Nerv Syst*. 2022;S13.
87. Lim J, Van Groenestijn A, Merkies I, Van Doorn I, Bus S, Zambreanu L, et al. OPTIC Trial: Work-related Participation Following Intravenous Methylprednisolone And/Or Immunoglobulin Treatment in Chronic Inflammatory Demyelinating. *J Peripher Nerv Syst*. 2024;S272.
88. Guptill J, Blein C, Arvin-Berod C, Deborah G, Sergio BS, Hashmath UTAS, et al. Burden of illness for adults with chronic inflammatory demyelinating polyneuropathy in the United States [Internet]. ISPOR; 2024 May 5; Atlanta, USA. Available from: <https://argenxmedical.com/content/dam/medical-affairs/congress-posters/neurology/cidp/isor/Burden-Demyelinating-Polyneuropathy.pdf>
89. Paci S, Arvin-Berod C, Brackx F, Van de Veire L, Wright J, Taylor Y, et al. The impact of CIDP on patients' employment: Results from a real-world multinational survey. *Eur J Neurol*. 2025 June;32(S1):EPR-092.
90. Kuk D, Chen BPH, Kudesia V, Tsai R, Hoke A. RWD22 A Novel Patient-Centered Real-World Evidence Study Designed to Better Understand Chronic Inflammatory Demyelinating Polyneuropathy Using Longitudinal Data in the United States. *Value Health*. 2023 June;26(6):S364.
91. Hartung H, Alonso-Alonso M, Dormont F, Lopez-Grancha M, Saeed O, Nguyen M, et al. Leveraging Real-World Data To Understand Treatment Patterns And Disease Burden in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *J Peripher Nerv Syst*. 2024 Aug;S207.
92. Lewis R, Alonso-Alonso M, Dormont F, Lopez-Grancha M, Saeed O, Nguyen M, et al. Characterizing Treatment Patterns And Healthcare Use In Patients And Subgroups With Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *J Peripher Nerv Syst*. 2024 Aug;29(S3):S245.

93. Paci S, Arvin-Berod C, Brackx F, Van de Veire L, Wright J, Taylor Y, et al. Healthcare resource utilization and caregiver burden in CIDP: Results from a real-world multinational survey. *Eur J Neurol*. 2025 June;32(S1):EPR-095.
94. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. [Internet]. 2022 [cited 2022 Dec 13]. Available from: <https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation>

Appendix 1: Reference list for Question C3a

1. Englezou C, Nazeer, K.K. ,Rajabally, Y.A. Impact of social-functioning and sleep on quality of life in chronic inflammatory demyelinating polyneuropathy. *Clinical Neurology and Neurosurgery* 2023;234.
2. Burt RK, Tappenden, P., Balabanov, R., Han, X., Quigley, K., Snowden, J.A. ,Sharrack, B. The cost effectiveness of immunoglobulin vs. Hematopoietic stem cell transplantation for cidp. *Frontiers in Neurology* 2021;12.
3. Cocito D, Peci, E., Torrieri, M.C., Clerico, M. Ultramicronized palmitoylethanolamide in the management of neuropathic pain related to chronic inflammatory demyelinating polyneuropathy: A proof-of-concept study. *Journal of Clinical Medicine* 2024;13.
4. Hartung HP, Mallick, R., Bril, V., Lewis, R.A., Sobue, G., Lawo, J.P., Mielke, O., Durn, B.L., Cornblath, D.R., Merkies, I.S.J.,et al. Patient-reported outcomes with subcutaneous immunoglobulin in chronic inflammatory demyelinating polyneuropathy: The path study. *European journal of neurology* 2020; 27:196-203.
5. Adrichem ME, Lucke, I.M., Vrancken, A.F.J.E., Goedee, H.S., Wieske, L., Dijkgraaf, M.G.W., Voermans, N.C., Notermans, N.C., Faber, C.G., Visser, L.H., Kuitwaard, K., Van Doorn, P.A., Merkies, I.S.J., De Haan, R.J., Van Schaik, I.N. ,Eftimov, F. Withdrawal of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *Brain* 2022; 145:1641-1652.
6. Al-Zuhairy A, Sindrup, S.H., Andersen, H., Jakobsen, J. A population-based study of long-term outcome in treated chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2020; 61:316-324.
7. Bamrungsawad N, Upakdee, N., Pratoomsoot, C., Sruamsiri, R., Dilokthornsakul, P., Dechanont, S., Wu, D.B.C., Dejthevaporn, C. ,Chaiyakunapruk, N. Economic evaluation of intravenous immunoglobulin plus corticosteroids for the treatment of steroid-resistant chronic inflammatory demyelinating polyradiculoneuropathy in thailand. *Clinical Drug Investigation* 2016; 36:557-566.
8. Bjelica B, Peric, S., Bozovic, I., Kacar, A., Cobeljic, M., Dejanovic, I., Stevic, Z., Basta, I. One-year follow-up study of neuropathic pain in chronic inflammatory demyelinating polyradiculoneuropathy. *Journal of the Peripheral Nervous System* 2019; 24:180-186.
9. Cirillo G, Todisco, V., Ricciardi, D., Tedeschi, G. Clinical-neurophysiological correlations in chronic inflammatory demyelinating polyradiculoneuropathy patients treated with subcutaneous immunoglobulin. *Muscle and Nerve* 2019; 60:662-667.
10. Cocito D, Merola, A., Peci, E., Mazzeo, A., Fazio, R., Francia, A., Valentino, P., Liguori, R., Filosto, M., Siciliano, G., Clerici, A.M., Lelli, S., Marfia, G.A., Antonini, G., Cecconi, I., Nobile-Orazio, E. ,Lopiano, L. Subcutaneous immunoglobulin in cidp and mmn: A short-term nationwide study. *J Neurol* 2014; 261:2159-64.
11. Draak TH, Vanhoutte, E.K., van Nes, S.I., Gorson, K.C., Van der Pol, W.L., Notermans, N.C., Nobile-Orazio, E., Léger, J.M., Van den Bergh, P.Y., Lauria, G., Bril, V., Katzberg, H., Lunn, M.P., Pouget, J., van der Kooi, A.J., Hahn, A.F., Doorn, P.A., Cornblath, D.R., van den Berg, L.H., Faber, C.G. ,Merkies, I.S. Changing outcome in inflammatory neuropathies: Rasch-comparative responsiveness. *Neurology* 2014; 83:2124-2132.
12. Kuitwaard K, Brusse, E., Jacobs, B.C., Vrancken, A.F.J.E., Eftimov, F., Notermans, N.C., van der Kooi, A.J., Fokkink, W.J.R., Nieboer, D., Lingsma, H.F., Merkies, I.S.J. ,van Doorn, P.A. Randomized trial of intravenous immunoglobulin maintenance treatment regimens in chronic inflammatory demyelinating polyradiculoneuropathy. *European Journal of Neurology* 2021; 28:286-296.
13. Lawley A, Abbas, A., Seri, S. ,Rajabally, Y.A. Clinical correlates of fatigue in chronic inflammatory demyelinating polyneuropathy. *Muscle and Nerve* 2020; 62:226-232.

14. Mahdi-Rogers M, McCrone, P., Hughes, R.A.C. Economic costs and quality of life in chronic inflammatory neuropathies in southeast England. *European Journal of Neurology* 2014; 21:34-39.
15. Merkies ISJ, Bril, V., Dalakas, M.C., Deng, C., Donofrio, P., Hanna, K., Hartung, H.P., Hughes, R.A.C., Latov, N., Van Doorn, P.A. Health-related quality-of-life improvements in CIDP with immune globulin IV 10%: The ICE study. *Neurology* 2009; 72:1337-1344.
16. Merkies ISJ, Hughes, R.A.C., Donofrio, P., Bril, V., Dalakas, M.C., Hanna, K., Hartung, H.P., Latov, N., Van Doorn, P.A., Deng, C. Understanding the consequences of chronic inflammatory demyelinating polyradiculoneuropathy from impairments to activity and participation restrictions and reduced quality of life: The ICE study. *Journal of the Peripheral Nervous System* 2010; 15:208-215.
17. Merkies ISJ, Van Nes, S.I., Hanna, K., Hughes, R.A.C., Deng, C. Confirming the efficacy of intravenous immunoglobulin in CIDP through minimum clinically important differences: Shifting from statistical significance to clinical relevance. *Journal of Neurology, Neurosurgery and Psychiatry* 2010; 81:1194-1199.
18. Rayani M, Ansari, B., Boroujeni, S.A., Veshnavei, H.A., Basiri, K. Gabapentin versus pregabalin for management of chronic inflammatory demyelinating polyradiculoneuropathy. *American Journal of Neurodegenerative Diseases* 2021; 10:50-56.
19. Straver DC, van den Berg, L.H., van Doorn, P.A., Franssen, H. Symptoms of activity-induced weakness in peripheral nervous system disorders. *J Peripher Nerv Syst* 2011; 16:108-12.
20. Svacina MKR, Mehndiratta, M.M., Vedeler, C.A., Sharma, Y., Bobylev, I., Sprenger, A., Remke, G., Wüstenberg, H., Klein, I., Joshi, A., Lehmann, H.C. Clinical management of chronic inflammatory demyelinating polyneuropathy (CIDP) in Europe and India: An exploratory study. *J Neurol Sci* 2021; 427:117507.
21. Vu T, Anthony, N., Alsina, R., Harvey, B., Schleutker, A., Farias, J., Dang, S., Suresh, N., Gooch, C. Impact of subcutaneous immunoglobulin on quality of life in patients with chronic inflammatory demyelinating polyneuropathy previously treated with intravenous immunoglobulin. *Muscle and Nerve* 2021; 64:351-357.
22. Bjelica B, Saporilla Pietschmann, A., Siemer, J., Koch, M., Korner, G., Seeliger, T., Hummert, M., Skripuletz, T., Gingele, S. Switch from IVIG to SCIG in patients with CIDP: 6 months follow up study of quality of life. *European Journal of Neurology* 2022; 29:822.
23. Colin Anderson-Smits HA, Erin Greco, Shabbir Hasan. Patient-Reported Outcomes With Hyaluronidase-Facilitated Subcutaneous Immunoglobulin 10% And Intravenous Immunoglobulin 10%: The ADVANCE-CIDP 1 Study. *Journal of the Peripheral Nervous System* 2024: S211.
24. Pieter A. Van Doorn LQ, Hans-Peter Hartung, Richard A. C. Hughes, Mattea Orsini, Natalia HakimiHawken, Charles Minor, Jerome Mshid, Miguel Alonso-Alonso, Nazem Atassi, Richard Lewis. Phase 2 Trial of Riliprubart in Chronic Inflammatory Demyelinating Polyneuropathy: Quality-of-life and Fatigue. *Journal of the Peripheral Nervous System* 2024: S338.
25. Arnau Llauro JM, Margarida Gratacos, Maria Salvado, Daniel Sanchez-Tejerina, Javier Sotoca, Núria Raguera, Raul Juntas. Timed up and go test: effective tool for GAIT assessment in chronic inflammatory demyelinating polyneuropathy. *Journal of the Peripheral Nervous System* 2022;28: S85.
26. G. Boggia AB, C. Gary, W. Noel, W. Karmous, J. DeCourcy, J. Wright, Y. Taylor, H. Iqbal, G. Meyer zu Hörste. Diagnostic delay- and burden of- disease -in -chronic inflammatory-demyelinating polyneuropathy: -A -real-world survey. *European Journal of Neurology* 2024; 31:168.
27. Minor C MM, Hakimi-Hawken N, Coulouvrat C, Fine J, Shaffer D, O'Hara M. Disease Burden and Treatment Satisfaction Among Patients With Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): A Quantitative Patient Survey. *Value in Health* 2024;27.

28. Brackx F A-BC, Istas G, De Roeck A, Hofman E, Van Hoorick B, Dewilde S. The Association Between Disability Level and Health-Related Quality of Life in CIDP Patients. *Value in Health* 2024;27.
29. Dewilde S BF, Arvin-Berod C, Istas G, De Roeck A, Hofman E, Van Hoorick B. The Effect of Efgartigimod on Treatment Convenience, Effectiveness, and Overall Satisfaction in CIDP Patients. *Value in Health* 2024;27.
30. Roberts A, Williamson, N., Griffiths, N., Boparai, K., Wallace, S., Gater, A., Minor, C., Saeed, F.O., Hakimi-Hawken, N. Qualitative Exploration of the Patient Experience of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) Via Concept Elicitation Interviews with Patients and Neurologists. *Value in Health* 2023;26: S473.
31. Appendix H Quality appraisal checklist – qualitative studies. Third edition. 2012. Available from: <https://www.nice.org.uk/process/pmg4/chapter/appendix-h-quality-appraisal-checklist-qualitative-studies> (Accessed 31st January 2024).
32. Cumpston M, Li T, Page MJ et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019;10: Ed000142.
33. Excellence NIfHaC. NICE Process and Methods Guides. Developing NICE Guidelines: The Manual. London: National Institute for Health and Care Excellence (NICE), 2015.

Appendix 2: Updated base case results and sensitivity analyses

The updated base case incremental cost-effectiveness analysis results, probabilistic sensitivity analysis and deterministic sensitivity analysis are provided in a separate stand-alone document titled: '*ID6409 Appendix 2 updated base case results and sensitivity analyses*'

1. In CQ A17, the EAG requested ITCs between ADHERE and the first period (prior to the crossover period) of the ICE trial. Although the company provided ITCs between the two trials, comparisons were based on the extension phase of ICE.
 - a) Please perform an anchored MAIC between ADHERE and the first period (prior to the crossover period) of the ICE trial.
 - b) Please provide information on the relative weight distributions (as provided in the responses to CQ A15), unweighted and weighted baseline characteristics of the ADHERE trial and the change from baseline for the adjusted placebo group of ADHERE.

1a) The Company has carefully considered the feasibility of conducting indirect treatment comparisons (ITCs) where these are technically feasible and methodologically appropriate. To support this, the company conducted a structured ITC feasibility assessment to explore which comparisons could be credibly undertaken and to ensure that any analyses presented would be robust, transparent and consistent with NICE methodological guidance. The ICE trial was excluded from the initial ITC because its population did not align with the Ig pre-treated target population, i.e., it did not qualify for inclusion in the analysis. Specifically, ICE enrolled patients who had not received treatment in the three months prior to the study. A comparison of ICE extension phase vs ADHERE Stage B was only included as part of the sensitivity analysis presented in Section 20 (Appendix 9) of the ITC report (*argenx - indirect treatment comparison (ITC) report 2025 – DOF*).

A feasibility assessment was conducted to evaluate whether the first treatment period of ICE could be appropriately compared with ADHERE. This assessment indicated that a reliable comparison is not feasible due to structural differences between the trial designs. The reasons for excluding the first period of the ICE trial from eligibility for comparison with ADHERE are presented below.

An anchored MAIC between ADHERE and the ICE first period is not feasible due to several structural limitations. The ICE first period can be appropriately compared only with ADHERE Stage A, for the following reasons:

- **Population:** Patients entered the ICE first period only if they had not received IVIg, PLEX, or steroids >10 mg/day in the previous three months, meaning they were treatment-naïve or had been off treatment. Any comparison with Stage B would therefore be inappropriate, as Stage B includes only patients who had previously responded to efgartigimod induction therapy rather than those coming from an off-treatment period. Moreover, Stage B includes only responders, whereas the ICE first period includes patients before response was assessed.
- **Treatment:** Patients in the ICE first period received an initial IVIg loading dose, clearly representing an induction regimen. This cannot be compared with Stage B, which specifically evaluates efgartigimod in a maintenance context.
- **Study design:** Non-responders exited the ICE first period and entered the cross-over period, underscoring that the first period functions as an induction phase used to

identify responders for the subsequent extension phase. This design directly parallels ADHERE Stage A.

Therefore, a comparison is meaningful only with ADHERE Stage A. A comparison with ADHERE Stage B would contrast a treatment-naïve or off-treatment population that includes non-responders (ICE first period) with a population that has just completed an induction regimen and includes only treatment responders (ADHERE Stage B). The ICE first-period population enters from an off-treatment state, whereas patients in ADHERE Stage B have already achieved clinically meaningful improvement during Stage A, and Stage B is explicitly designed to assess maintenance of those gains. As a result, any such comparison would be structurally biased, with observed differences driven by prior treatment exposure and patient selection rather than by a valid assessment of relative treatment effects. This would almost certainly breach the assumption of consistent treatment effects that underpins MAIC.

After further evaluation, the company determined that conducting a MAIC for either approach was not feasible due to multiple structural limitations, as outlined below. Consequently, neither an anchored or unanchored MAIC approach were considered viable:

1. An anchored comparison, as requested by the review group, is not possible because ADHERE Stage A contains only an active arm and therefore provides no common anchor.
2. An unanchored MAIC, which relies on strong and often unrealistic assumptions about conditional constancy of absolute effects, is not feasible due to the endpoint definition and the design of the ICE first period.
 - The change in aINCAT is reported from baseline to Week 24 in ICE first period, but this cannot be derived for ADHERE Stage A because patients exited Stage A within the first 13 weeks, well before Week 24, and no efficacy data exist for those subsequently randomised to placebo.
 - Even when restricting the analysis to patients later randomised to efgartigimod in Stage B - where a 24-week aINCAT change from the Stage A baseline could theoretically be reconstructed - the comparison remains unfeasible. In ICE first period, non-responders exited the first period at any time after the initial infusion, meaning only responders remained until Week 24. Importantly, all patients not showing any improvement left ICE first period within the first 6 weeks. In contrast, all patients in ADHERE Stage A remained for the full 13 weeks regardless of response. These differing discontinuation rules introduce a substantial selection mechanism, whereby the observed ICE first-period outcomes are conditioned on early response, while ADHERE outcomes reflect the complete spectrum of patient responses observed over the fixed 13-week Stage A period. Consequently, any comparison would be inherently biased, as differences in observed 24-week outcomes would largely reflect differential patient retention and response-based selection rather than true differences in treatment effect between IVIg and efgartigimod.

There are additional secondary reasons why comparing the ICE first period with ADHERE Stage A is unfeasible. For example, ICE did not include a run-in period. This may introduce substantial bias when comparing the ICE first period with ADHERE Stage A.

Finally, it should be noted that because the ICE trial enrolled treatment-naïve patients, its population does not align with the target population defined in the submission, which limits the relevance of any comparison beyond feasibility considerations.

1b) This information has not been provided because, as outlined in the response to question 1a, it was concluded that ITCs between ADHERE and the first period of the ICE trial are not feasible.

- 2. In response to CQ A10, the company reported aINCAT score throughout ADHERE+ (Figure 2) and change in aINCAT score from the ADHERE+ baseline (Figure 3). Please clarify why aINCAT score in Figure 2 increases from Week 96 onwards for the prior efgartigimod group (indicating symptoms getting worse), while change from baseline in Figure 3 is negative (indicating improvements in symptoms).**

The company would like to clarify that the apparent difference between the two figures does not represent clinical deterioration. Because ADHERE+ has rolling entry and declining evaluable numbers over time, the absolute aINCAT values at later visits (from Week 96 onwards) reflect only a very small subset of participants who remain under observation. The mean absolute value at these later visits is higher compared to earlier timepoints, but this reflects the characteristics of the subset still contributing data rather than longitudinal follow-up of the same individuals.

Specifically, the participants who remain in follow-up beyond Week 96 had considerably higher aINCAT scores at their own ADHERE+ baseline compared to the broader study population, indicating they entered the extension with more severe baseline disability. Despite maintaining absolute aINCAT values around 4–4.5 at these late visits, these same individuals have experienced substantial improvement from their own baseline values, as demonstrated in Figure 3.

Change-from-baseline is the appropriate indicator of improvement. Figure 3 anchors each participant to their individual ADHERE+ baseline, and the sustained negative change-from-baseline values confirm ongoing improvement relative to each participant's starting point. This measure is unaffected by the sample-size fluctuation that shifts the absolute means in Figure 2. The pattern in Figure 2 simply reflects differences in baseline severity between the subset observed at later visits versus the full cohort, not any loss of treatment effect.

- 3. The EAG notes that the weighted baseline characteristics for ADHERE (reported in Tables 18 to 26) are identical to the baseline characteristics reported for each of the comparator trials. Please clarify if this is correct, or if there were any differences between baseline characteristics following weighting adjustments.**

Yes, this is correct. In the anchored MAIC, the weights for ADHERE were estimated so that the mean baseline values of the selected effect modifiers match the published baseline characteristics of each comparator trial. As a result, after weighting, the average baseline characteristics for the matched variables in ADHERE are identical (up to rounding) to those reported for the respective comparator study.

This is the aim of the MAIC re-weighting step: to ensure that the relative treatment effect is estimated in a population whose average baseline characteristics align with those of the comparator trial. Any residual differences would only relate to unknown modifier

4. Updated analysis of UK chart review data (relating to Clarification Question C1)

At the time of the company's original submission to NICE and EAG clarification questions, the UK Chart Review study was ongoing, and an interim data cut was therefore used to inform the cost-effectiveness. A standalone report was not produced for this interim dataset. An updated and final report for the UK Chart Review is now available. Full details on the estimation of the data from the Chart Review and resulting data are reported in a separate report shared together with this response document, as agreed with the NICE project manager.

The company proactively conducted a UK Chart Review study to provide real-world validation of treatment patterns in the target population and to ensure that assumptions used in the economic model reflect NHS clinical practice. This is particularly relevant in CIDP, a rare condition where routine data sources are limited, and treatment pathways may vary by centre.

As with most real-world evidence in rare diseases, the Chart Review has both strengths and limitations. Strengths include direct reflection of NHS clinical practice and validation of treatment sequencing and dosing patterns. Limitations include small sample sizes and missing treatment frequency data for some parameters. In addition, the data collection took place during July and August coinciding with the UK summer leave period, which may have further constrained site participation and data completeness. Despite these challenges argenx undertook this work to strengthen the evidence to support the submission.

Importantly, the scenario informed by the Chart Review data remains directionally consistent with the simulation-based evidence evaluation (SEE) results but generates more conservative cost-effectiveness estimates. Specifically, the Chart Review scenario in a higher ICER of [REDACTED] compared to the base case. This increase is driven directly by the following two factors:

- **SCIg dose distribution and treatment frequency:** Chart Review data show that patients are more uniformly distributed across SCIg dose categories compared to the SEE estimates, with 37% receiving <0.5 g/kg per treatment cycle. However, this is based on a small subset (n=16 SCIg patients), limiting precision for this specific parameter.
- **IVIg dose distribution:** Chart Review data indicate slightly lower treatment-course frequency than the SEE, with average intervals of 5 and 6 weeks for patients on 1–1.99 g/kg and 2 g/kg, respectively. However, treatment frequency data were missing for a substantial proportion of observations (n=442), which were replaced with the mean of the available values (32 days), likely inflating the estimated interval.

Despite this, efgartigimod remains dominant in the probabilistic analysis. The Chart Review therefore increases confidence in the base-case assumption for IVIg. However, the company maintains that the SEE approach provides more reliable estimates for SCIg- related parameters and treatment frequency. This reflects the structured, transparent and NICE aligned methodology underpinning the SEE process, which is particularly valuable in rare diseases where real-world datasets are sparse and heterogenous.

Taken together, the Chart Review and SEE analyses provide complementary evidence, strengthening the robustness and credibility of the economic evaluation.

Scenario	Deterministic results				Probabilistic results			
	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)	Incremental Cost	Incremental QALYs	ICER (Cost/QALY)	NMB (WTP £30K)
Revised base case	██████	4.26	██████	██████	██████	3.96	██████	██████
Source of Ig consumption data: UK chart review – final cut	██████	4.20	██████	██████	██████	3.97	██████	██████

Single Technology Appraisal

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	Inflammatory Neuropathies UK
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Inflammatory Neuropathies UK is the only UK charity which is completely dedicated to providing information and support to people impacted by Guillain-Barré Syndrome (GBS), CIDP, MMN, and other Inflammatory Neuropathies. These are rare, but life altering autoimmune conditions. The charity offers support, personal grants, local groups, online forums, and much more. We provide support through a community of people with lived experience, who can help each other. We raise funds for research, and carry out some social research ourselves. We work right across the UK. The charity is largely funded through donations and fundraising, which is supplemented by a small amount sales and other income.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company,	We received £1232.73 from argenx in July 2025 for support and input into a CIDP patient survey

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We work with people with lived experience of these conditions every day and collect information through discussions, feedback, surveys, forums, and other processes. We have been undertaking a significant amount of work around CIDP for a number of projects and have used some of this information to feed into this response. We also collected information on the impact of CIDP and related treatments that has directly fed into this response.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CIDP is an incredibly complex condition that can impact people differently depending on a whole range of variations and factors. Our biggest take away is that everybody's CIDP journey is different. This makes it difficult to summarise what it is like to live with the condition. However, there are a number of key impacts which cut across the CIDP experience. These include physical issues, mental and emotional issues, and social issues. In terms of physical issues people can lose their mobility, struggling to walk, stand, or get about. Some people will require mobility aids and may need to use a wheelchair (particularly outdoors). Another physical issue is around motor skills, when CIDP impacts on both gross and fine motor skills, impacting hands, feet, and limbs. CIDP can result in significant fatigue and 'brain fog' impacting on day to day living, as well as high levels of pain throughout the body. Patients may also be impacted by sensory issues, often seen as numbness, pins and needles, and changes to the toleration of touch. Some people are also impacted by co-morbidities. Emotional and mental health is a very real everyday factor for people impacted by CIDP. Physical symptoms, the burden of the condition and of treatment, and the impact of social issues can all lead to depression, anxiety, and low level mental and emotional health needs. These are largely undetected and untreated. On top of this, we often find that CIDP patients have been through trauma, often as the result of diagnosis of a life long progressive condition that can have impacts across all aspects of a person's life. The social impacts of CIDP are varied and include relationship breakdown (or changes within relationships), financial impact (through increased costs of living or loss of employment, with many people having to leave work), changes in social interactions and the loss of friendship circles, the need to move or relocate home, adaptations around living with the condition or changes in mobility, social isolation, and lack of support. A significant issue of living with CIDP, is the fluctuating nature of the condition, the fact that it can be progressive (especially if it is untreated or not treated well), and issues around the impact of relapse (or the fear of relapse). The impact on everyday life can vary day by day, and a relapse or an increase in symptoms means that the condition often can have different impacts everyday. This means living a 'normal life' can be challenging. There are a number of variants of CIDP, as well as related conditions, which means obtaining support, input, and treatment can vary widely. On top of this, different clinicians and trusts have different approaches to providing support and treatment, which means what support and treatment people receive can vary significantly depending

	on where you live, or even which clinician within the same hospital you see. This means that patients are subject to a number of inequalities and inequity of approach around access, treatment, and support. Like patients, carer experience can differ significantly. Care can often fall on spouses and partners, although with other conditions, the caring responsibility can impact parents and children as well. Most carers provide informal care, and the amount of care is linked to the severity of the condition for a patient or the severity of the impacts of the condition. Caring responsibility obviously impacts on the carers own physical and emotional health, as well as on a number of social factors. This can manifest as tiredness, ill health, mental health impact, impact on employment, and changes to social life. Many carers (and patients) report financial issues across the family unit, as well as relationship issues as the impact of caring, and CIDP itself changes the definition of the relationship. Many carers do not feel supported within their caring role. Many carers of people with CIDP do not identify as a carer, and feel that they are just doing what they have to do to support their loved one or the person they support. Some carers have reported that they are concerned that they will not be able to cope if the CIDP of the person they support progresses, relapses, or if treatment isn't (or is no longer) provided.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	As you would expect with a broad church of people, opinions on treatment and care through the NHS varies widely. Many people are happy or generally happy with the support and treatment they receive, but we do hear reports of people stating that they don't want to complain due to fear of losing their treatment. Most people with CIDP who receive treatment, receive an Immunoglobulin (Ig) treatment. In general, people have mixed feelings about both the outcomes from treatment and the burden of treatment. Some people report that they Ig works well for them and they are happy to accept the inconvenience of hospital delivery, while others find (or have found) that Ig doesn't work for them, has a mixed response, is not provided consistently, or has significant burdens and impacts. We have reports of some people having to travel several hours for their treatment to be provided; treatment leaving people drained or ill; people having to take leave from work for treatment, or having to balance treatment around employment or parental duties; and some patients receiving treatment inconsistently against both their peers, and their own treatment regime. The biggest reported issue with Ig treatment is linked to the up and down nature of response. Once Ig is provided, people find functionality and ability improves, before declining over time. While this is to be expected with the nature of the treatment, for many people the fluctuation is significant, and the low point before an infusion is debilitating. While attempts can be made to 'flatten the curve', variabilities in different approaches by clinicians or trusts means that individual patients can have a very different experience to each other. This is linked to some people receiving infusions every few weeks, and others up to every six months. In our experience, patients find this variation in provision both unfair and unacceptable, but are unlikely to complain due to fear of losing their existing treatment, or through lack of knowledge about treatments other people receive. Some patients would like to be offered choice in treatment (especially in terms of community treatment or sub-cutaneous treatment they could administer themselves at home, but which isn't available in their area). Some people are not at all satisfied with their treatment, and some people receive no treatment at all. People live in fear of any treatment being removed and relapse of their CIDP occurring. At present, there is no fixed treatment pathway in the UK, so different people will receive different treatments. This is especially true of initial treatments. Some people are only offered steroid treatment which can have very negative impacts on health. The current systems provides a 'menu of treatments' that a clinician can call off, but patients would like more input into this decision making, and more choice of treatments to choose from.

	In terms of overall NHS report, people tend to be satisfied (most but not all) with their clinicians, but find access to physiotherapy and ongoing support incredibly difficult.
8. Is there an unmet need for patients with this condition?	There are a number of unmet needs at present. These include: • Some patients having no appropriate treatment available due to negative reactions, lack of response to existing options, or additional needs that prevent the use of current treatments • Some people have their treatment stopped and then their condition relapses leading to further issues • Some people's treatment does not fully control their symptoms • There is an inconsistent and unequal approach to treatment and treatment options • A lack of understanding across clinicians around the treatment options available • People are unable to cope with the burden of existing treatments, or treatment burden has negative impacts on quality of life

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Having spoken to a range of patients, there are a number of advantages to be considered. These are: • Choice – Patients want a range of treatments available, so that their treatment can be tailored to their individual needs. They (as do we) want to see a more person centred approach to CIDP treatment that results in better outcomes for people • Location – The ability to undertake treatment at home, at a time and location that works for individuals is hugely beneficial. This would reduce time needed to travel, stress and anxiety linked to going to hospital sites, time taken off work, and time in actual hospital • Time – The suggestion is that the new treatment would be taken over a very short period at home. This quick infusion appeals to many patients against long drawn out infusions, or large amounts of sub-cutaneous volume • Efficacy – Current treatments do not work for everyone, and an additional treatment may deliver improved outcomes for some people • Hope – There are a number of people who receive no treatment, or poor results from treatments. Faced with a progressive condition, a new potential treatment has provided some people with hope

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	From feedback received or picked up from discussions, disadvantages are: • Understanding – As this is a new treatment/technology, there are some concerns around what the treatment is, how it works, and what it does • Fear of change – As seen during recent changes in IVIg and SCIg treatments, people are fearful of change, and a risk of losing what they have, even if the impact isn't as good as it should be • Limited size of trial – We have heard some limited comments around the fact that the cohort involved in the trial was small, and therefore some people have mentioned concerns around evidence generated. However from experience, this is the same for most trials

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Our view is that anyone could benefit from different treatments if it works for them, both physically and emotionally. However, in terms of this appraisal we believe that the most benefit will be for people where existing treatments do not work so well. These are mainly those laid out in section 8 above, but especially those people who: • Are not currently able to receive a treatment (or who are not being offered a treatment) and whose condition is progressing or whose symptoms are getting worse • Are not able to tolerate a current treatment, have side effects, where there are safety issues, or where existing health conditions or co-morbidities contra-indicate or prevent the use of an exiting treatment • Find that existing treatments are too burdensome or intrusive and impact negatively on their physical or mental health, or on their overall quality of life

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Many patients should be considered as disabled, so consideration should be taken into account the impact on disability, especially in terms of access to a treatment that may reduce disability. Demographics suggest that people with CIDP are generally older, so age may be a factor to consider in any decision making.

Other issues

13. Are there any other issues that you would like the committee to consider?	There have been no new treatments for CIDP for a generation, and for a number of people with CIDP current treatments do not meet their needs, nor treat their condition effectively. For some people there is no treatment, and for others, the burden of treatment and of the condition is very high. A new potential treatment has brought hope to the Inflammatory Neuropathies community after many years of negativity. There is a real opportunity to improve the lives of people through this appraisal, and to transform lives for the better

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Current treatments do not work for everyone • Some people with CIDP and its variants receive no treatment at all • The burden of current treatments can be excessive • There is significant inequality and variation around treatment options and access • The need for choice and options for clinicians and patients is vital in delivering improved outcomes for people

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

Patient organisation submission

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	Association of British Neurologists, Neuromuscular advisory group
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists' is a professional membership organisation and its mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. The ABN receives funding mainly from its member subscriptions and annual conference income. Additional funding from external charity organisations is received to solely fund fellowships. Additionally, the ABN receives sponsorship from pharmaceutical companies. Sponsoring companies have no input, control nor opportunity to influence the ABN.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	In the past 12 months, the ABN has received sponsorship from the following companies to support the ABN Annual Conference. Sponsorship companies have no editorial input, control over the agenda, speaker selection, content development nor opportunity to influence the conference. Sponsorship is £18,020 per company. • Abbvie • Alnylam • Angelini • argenx • Biogen • Eisai • Eli Lilly • Janssen • Pfizer • Roche • Sanofi • Teva • UCB

**5c. Do you have any
direct or indirect links
with, or funding from,
the tobacco industry?**

No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reverse disability and prevent progression to irreversible neurological deficit (through axonal loss). To improve quality of life through improved physical, psychological, social and financial wellbeing of patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) by maintaining stability and preventing relapse.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response in CIDP is defined in the EFNS/PNS 2021 guidelines as improvement on at least one disability scale and one impairment scale. Specific objective response criteria, used in clinical trials and guidelines, include changes in the Inflammatory Rasch-built Overall Disability Scale (I-RODS ≥ 4 points) and Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale (≥ 1 point), Overall Neuropathy Limitations Score (ONLS, ≥ 1 point) and/or increases in the Medical Research Council (MRC) Sum Score ($\geq 2-4$ points), modified INCAT Sensory Sum Scale (miSS ≥ 2 points) or grip strength measured by dynamometry (Jamar ≥ 10 kPa, Martin $\geq 8-14$). Reference EFNS/PNS 2021 Guidelines: Van den Bergh PYK , van Doorn PA , Hadden RDM , et al . European academy of neurology/peripheral nerve society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force-second revision. J Peripher Nerv Syst 2021;26:242–6 DOI:10.1111/ene.14859 In clinical practice in the UK, some specialist clinicians use a modified MRC score, for example focused on the muscles involved and responsive in the individual patient, to evaluate treatment response. NHSE Immunoglobulin treatment guidelines recommend clinical monitoring in CIDP with at least 3 disease specific clinical outcome measures, including those recommended in EFNS/PNS guidance as well as MRC SS, using a contiguous improvement in at least 2 outcome measures as indicative of response. [https://www.england.nhs.uk/wp-content/uploads/2021/12/ccp-for-the-use-of-therapeutic-immunoglobulin-england-2025.pdf] Stable is defined using the new CIDP Task Force consensus criteria (manuscript in preparation). No-evidence of disease activity (NEDA) will include the following parameters: 1. Worsening in Patient Global Impression of Change (PGIC) 2. Disability: I-RODS ≥ 4-point (centile) change or INCAT ≥ 1-point change 3. Impairment: Grip strength vigorimeter ≥ 8 kPa or Jamar dynamometer $\geq 10\%$ (requires 3 consecutive day average) or MRC 60 sum score ≥ 2-point change. For relapse necessitating treatment change we will use three categories for analysis: 1) NEDA-1: No patient perception of worsening AND either no decline in disability OR no decline in impairment for a duration of 6 months or more. 2) NEDA-2: No patient perception of change AND no decline in disability AND no decline in impairment components for a duration of 6 months or more.

	3) Non-specified relapse according to the physician and/or patient leading to change in treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There is a need for therapeutic options as many patients have relative or definite contraindications so some or all of the current SOC options. Many of the current treatment options require frequent and long hospital visits, blood sampling and time away from work and family, or have unfavourable long term side effect profiles. In addition, for patients who have refractory CIDP or an incomplete response to treatment, an additional option would be welcomed as some research has suggested Efgartigimod may be helpful in this setting. Sun C, Hu J, Zhao Y, Zheng Y, Meng Q, Luo S, Qiao K, Sun J, Lu J, Lin J, Zhao C. Short-term treatment of CIDP with efgartigimod: a case series in China. Front Immunol. 2025 May 1;16:1533167. doi: 10.3389/fimmu.2025.1533167. PMID: 40375986; PMCID: PMC12078319.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The current treatment pathway for CIDP typically includes a combination of immunomodulatory therapies aimed at reducing inflammation and improving nerve function. We will refer to this below as standard of care (SOC). First line: - Corticosteroids OR IVIg OR PLEX chosen according to individual patient risk profile and availability and continued on the basis of recorded evidence of response according to CIDP specific outcome measures. - 60-70% of patients with CIDP will respond well to one of the three first line options - In those who do not respond, switching to another first line option results in meaningful response in up to 80% (Cocito et al 2010) - The proportion of CIDP patients who receive steroids vs IVIG vs PLEX as first line treatment in current NHS practice This varies and there are no clear data. As patients get offered one of the these three first line therapies depending on patient preference, comorbidities, cost and availability of each treatment option which has some geographical variation. 80% of patients will respond to one of the three first line options, if a patient is initially treated with steroids and does not enter remission IVIg (or SCIg) is used for maintenance in chronically active disease in greater than 80% of cases in UK clinical practice with small

	proportions of patients maintained on either PLEX or low dose steroids/ steroid sparing agents (for which there is limited evidence). The preference for immunoglobulin maintenance is backed up by the MDSAS database: ○ CIDP (including IgG or IgA associated paraprotein associated demyelinating neuropathy) 1,650 patients/ 1,381,729g/year (2023/24) ○ With a prevalence of 5/100,000 this represents over half of NHSE CIDP patients on maintenance Ig. If 60-70% have active disease at any time, this would be around 80% if those with active CIDP maintained on Ig (which reflects my personal experience and ad hoc surveys preformed at the BPNS) Second line: - In those who show suboptimal or transient response to any of the first line options, the addition of an immunosuppressive steroid or immunoglobulin sparing agent is indicated - But reappraisal of the diagnostic security is essential (EFNS/ PNS criteria) Third line / refractory disease: - This is very rare in CIDP and thorough re-evaluation of the case and consideration of a second opinion is sensible - Treatment options are limited but might include cyclophosphamide References: Cocito, D et al (2010), A nationwide retrospective analysis on the effect of immune therapies in patients with chronic inflammatory demyelinating polyradiculoneuropathy. European Journal of Neurology, 17: 289-294. https://doi.org/10.1111/j.1468-1331.2009.02802.x Kapoor M et al. Immunoglobulin use in neurology: a practical approach. Practical Neurology Published Online First: 03 August 2024. doi: 10.1136/pn-2022-003655 –
9a. Are any clinical guidelines used in the	EFNS/PNS 2021 Guidelines: Van den Bergh PYK , van Doorn PA , Hadden RDM , et al . European academy of neurology/peripheral nerve society guideline on diagnosis and treatment of chronic inflammatory demyelinating

treatment of the condition, and if so, which?	polyradiculoneuropathy: report of a joint task force-second revision. J Peripher Nerv Syst 2021;26:242–6 DOI:10.1111/ene.14859
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	It is recognised that there is varying access to treatments and resources across different regions of the NHS, and some variation in the practice of individual clinicians. However the practice of peripheral nerve subspecialists typically adheres to EFNS/PNS 2021 guidelines on CIDP. . Examples would include resource-intensive treatments like PLEX and SCIg therapy (which are not available at all in some geographical areas and would be available through MDSAS)
9c. What impact would the technology have on the current pathway of care?	For CIDP patients in the NHS, efgartigimod would offer an additional therapeutic option with a different mechanism of action. This might be appropriate for the subgroup of patients shown to have persistent, active disease dependent on maintenance IVIg or PLEX at regular intervals, or to those who have contraindications to or poor tolerance of any of the three first line therapeutic options. In those with definite CIDP but suboptimal control despite standard therapies there may be benefit to be gained from the novel mechanism of action but data is poor on the role of Efgartigimod in refractory CIDP. Please see also the answer to question 13.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	For CIDP to our knowledge it is currently only used in trial settings. It is listed in the BNF as a treatment for myasthenia gravis in specialised settings. This would be a new indication for use in CIDP and would need to fit into the current treatment algorithm in a sensible way.
10a. How does healthcare resource use differ between the technology and current care?	Healthcare resource for Efgartigimod would differ from current care in a number of ways: - Current maintenance therapies for active CIDP require regular hospital attendance (IVIg: average maintenance regimen 1g/kg/month infused over 2-3 days/ PLEX: 3-5 exchanges of 1.5 plasma volume over 3-5 days every 4-6 weeks). IVIg is provided via hospital day care settings or by home infusion (subcutaneous immunoglobulin) with nursing support for training and troubleshooting and consumables requiring a delivery company - o Efgartigimod is a 90 second subcutaneous injection self-delivered at home by the patient: REDUCED healthcare resource - Not all patients who responded to SOC in ADHERE were efgartigimod responsive (70% in trial). Therefore there is potential for relapse during the changeover period.

	○ This will require appropriate infrastructure (access to prompt review and prompt re-establishment of previous treatment/ rescue treatment) if a relapse occurs: INCREASED healthcare resource - Efgartigimod is immunomodulatory (regular infusions required to maintain remission) and there is no evidence for it to induce remission therefore regular assessment of efficacy, safety and ongoing disease activity (planned treatment cessation trials with close clinical monitoring) along the lines of IVIg monitoring in CIDP are likely to be required: EQUIVALENT healthcare resource
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Initially we would envisage treatment with efgartigimod to be in consultation with a specialist who is an expert in peripheral neuropathy in a secondary or tertiary care setting (Eg. Regional specialist peripheral nerve clinics). Patients should meet diagnostic criteria for CIDP (EFNS/ PNS diagnostic criteria). Disease activity should be established before treatment commenced and appropriate efficacy monitoring continue during treatment to ensure appropriate response maintained. Adequate infrastructure to support the potential for relapse on transfer from other maintenance (IVIg or PLEX or previous corticosteroids) to Efgartigimod, acknowledging that there may be some who do not respond. In cases with suboptimal response or if efgartigimod if being considered to treat potentially refractory CIDP an expert clinical review is essential to ensure alternative diagnoses have been excluded and adequate efficacy monitoring and criteria for defining response are established.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Staff with appropriate training in administering subcutaneous injections are likely already available. We would expect that first dose would likely be given in a setting with facilities to manage drug reactions, though these would be unlikely. Facilities, staffing and time for delivering training to patients about the drug and its administration would be required. While safety data appears favourable, we would imagine that some blood monitoring of e.g. albumin and lipids might be desired, but this is likely to be less than current monitoring for all other treatment options. Appropriate infrastructure to support safe transfer from other maintenance treatments is required. This will be akin to the support required to facilitate safe Ig cessation trials and prompt rescue in those who do not respond. • S Koay, Y-C Kiki Chen, G Ransley, L Compton, MP Lunn, AS Carr. Safety and cost analysis of immunoglobulin cessation trials in CIDP. JPNS Feb 2025. DOI:10.1111/jns.70007
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The ADHERE trial suggested equivalent efficacy to other first line CIDP treatment in a proportion of patients with definite CIDP who were treatment naïve or responsive to either IVIg or corticosteroids. Benefits to SOC include improved convenience (does not require venous access or administration in a hospital setting, rapid subcutaneous injections self-administered at home) and favourable side effect profile. Please also see answer in Q13.

11a. Do you expect the technology to increase length of life more than current care?	No current evidence that this will increase length of life more than current care. CIDP does not limit life expectancy.
11b. Do you expect the technology to increase health-related quality of life more than current care?	It is expected that efgartigimod will increase health-related quality of life (HRQoL) more than current SOC for a proportion of CIDP patients, particularly those who experience high burden from existing therapies (from safety, tolerance and convenience perspective). Please also see answer in Q13.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Stage B of the study was enriched with a subset of CIDP patients shown to be treatment responsive and to have active disease (i.e. not refractory CIDP). Some of the trial patients did not respond in stage A (28+8/322), and some patients in the treatment arm of stage B experienced relapses despite efgartigimod. However in the absence of head to head trials against SOC, these data would suggest that efgartigimod will be suitable for a proportion of patients currently receiving SOC. Anecdotal cases of benefit in refractory CIDP have been reported but evidence is limited to small cases series: (Sun C, Hu J, Zhao Y, Zheng Y, Meng Q, Luo S, Qiao K, Sun J, Lu J, Lin J, Zhao C. Short-term treatment of CIDP with efgartigimod: a case series in China. Front Immunol. 2025 May 1;16:1533167. doi: 10.3389/fimmu.2025.1533167. PMID: 40375986; PMCID: PMC12078319.) Though further study is needed, and depending on cost efgartigimod may be particularly clinically appropriate/cost effective in: (1) Individuals with impaired mobility, who may require hospital transport or carer support to attend regular daycare /inpatient hospital admissions for IVIg or PLEX (2) Individuals of working age or with other significant responsibilities for whom a self-delivered home treatment option would save considerable time compared to regular hospital visits for maintenance IVIg or PLEX (typically 1-3 days per month in patients with active disease). (3) In patients with significant thrombo-embolic risk profile or previous thrombo-embolic events where the number needed to harm with IVIg treatment is 6.

	(4) The patient cohort who have partial response to SOC may benefit from a treatment with an alternative mechanism of action (limited evidence). (5) Patients receiving current treatment with IVIG or PLEX who have difficulty with venous access.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Easier for patients: - convenience of home treatment over much shorter infusion time. - No intravenous access required - Reduced complication risk: - o from IVIG (e.g. arterial and venous thromboembolism management, headache management, blood monitoring, renal and liver dysfunction, venous access) - o PLEX (risk from line placement, risk from line infection or thrombosis, loss of blood volume, haemorrhage or thrombosis, electrolyte abnormalities). - o Efgartigimod may provide an alternative to steroids in high-steroid risk patients (diabetes, hypertension, cataract, weight gain, redistribution of body fat, impact on bone health including osteoporosis and avascular necrosis of the femoral head, gastro intestinal from dyspepsia to significant gastric ulceration, Addisonian crisis)

	Easier for healthcare provision: - reduction in attendance/occupancy in daycase/daycare or PLEX units, . - Organising IVIG or PLEX for multiple patients has a considerable clinician, nursing, pharmaceutical and administrative time burden. - Reduced pressure on PLEX services: PLEX facilities are labour intensive, requiring line placement and care, and specialist haematology nursing care, and are expensive and in high demand. - Improved availability of IVIg which is an expensive and limited resource (essential/ life saving and without alternative in certain conditions: acquired and inherited immunodeficiency syndromes) Required healthcare support: - Infusion and safe administration/ disposal of sharps training: in line with current training models in place for homecare SCIg (subcutaneous immunoglobulin) which is already an established treatment option in CIDP - Support for possible relapse on transfer from alternative maintenance treatment/ if lack of response in treatment naïve cases: in line with infrastructure required to support NHSE mandated annual treatment cessation trials in Ig maintenance patients with stable CIDP.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• Response is defined as MCID improvement in at least 2 of 3 disease specific, clinimetrically validated outcome measures (as per the EFNS/ PNS guidelines and NHSE Ig commissioning guidelines). Furthermore, response may also refer to halting progression: expectation of response depends on the degree of established axonal loss prior to treatment and so is individualised. • We would expect the need for clinical examination and collection of outcome measure data not to change. We do not expect/ there is no data to support efgartigimod induces remission but the

	regular re-assessment of ongoing disease activity is likely to be required for this immunomodulatory therapy: in line with NHSE immunoglobulin commissioning guidance for maintenance in CIDP: [https://www.england.nhs.uk/wp-content/uploads/2021/12/ccp-for-the-use-of-therapeutic-immunoglobulin-england-2025.pdf] References: Mahima Kapoor, Laura Compton, Alex Rossor, Elsbeth Hutton, Hadi Manji, Mike Lunn, Mary Reilly, Aisling Carr. An approach to assessing immunoglobulin dependence in chronic inflammatory demyelinating inflammatory polyneuropathy. J Peripher Nerv Syst. 2021 Dec;26(4):461-468. doi: 10.1111/jns.12470. S Koay, Y-C Kiki Chen, G Ransley, L Compton, MP Lunn, AS Carr. Safety and cost analysis of immunoglobulin cessation trials in CIDP. JPNS Feb 2025. DOI:10.1111/jns.70007 Adrichem ME et al. Withdrawal of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy, Brain, Volume 145, Issue 5, May 2022, Pages 1641–1652, https://doi.org/10.1093/brain/awac054 -
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There is randomised placebo-controlled trial evidence suggesting this therapeutic appears to be as effective as standard of care first line therapy (SOC) in controlling CIDP symptoms in a subset of individuals who have shown previous response to SOC treatment and in treatment naive CIDP. Furthermore, it was well tolerated, with fewer side effects than corticosteroids and IVIg. Importantly, it is deliverable at home by the patient as a subcutaneous injection rather than requiring hospital led administration via intravenous access (as is the case for IVIg or PLEX), with potential cost-savings for the NHS when considering resources (venous access/staffing/transportation/inpatient/daycare hospital beds) required to administer hospital-based treatments. The self-administration option potentially gives patients greater flexibility and independence, which are important considerations in treatment for a chronic disease, where individuals may have impaired mobility with difficulty accessing hospital-based treatments. This new therapy offers an important point of difference from a lifestyle perspective to individuals requiring maintenance immunomodulatory therapy to control CIDP. There is a clinical and socioeconomic argument

	to support its availability as a therapeutic option in this disease group where the affected demographic is often people of working age.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	For the patients who have high adverse event risk to current SOC options, including limited access or VTE risk. For patients who have significant lifestyle impacts as a result of the need to take time away from work and family to attend hospital to receive treatment. There may be benefit to those who have not responded or inadequately respond to SOC given the novel mechanism of action of efgartigimod but evidence to support this is currently lacking.
16a. Is the technology a 'step-change' in the management of the condition?	Yes it is step change as a treatment for CIDP via a new mechanism/mode of action with a new option of route of administration. (We accept that SCIg is also subcutaneous, but it is likely not as convenient or quick as a simple 90second injection, requires nursing infrastructure and is not widely available in the UK)
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. - Offers another potential treatment option, patients with venous access limitations, and patients for whom the side effect profile of SOC therapies is unfavourable. - Potential socioeconomic, travel, and quality of life benefits of self-administered therapy at home as discussed, affecting both patients and their families. References: -

	Adrichem ME et al. Withdrawal of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy, Brain, Volume 145, Issue 5, May 2022, Pages 1641–1652, https://doi.org/10.1093/brain/awac054 - Kapoor M et al. Immunoglobulin use in neurology: a practical approach. Practical Neurology Published Online First: 03 August 2024. doi: 10.1136/pn-2022-003655 – S Koay, Y-C Kiki Chen, G Ransley, L Compton, MP Lunn, AS Carr. Safety and cost analysis of immunoglobulin cessation trials in CIDP. JPNS Feb 2025. DOI:10.1111/jns.70007 Mahima Kapoor, Laura Compton, Alex Rossor, Elsbeth Hutton, Hadi Manji, Mike Lunn, Mary Reilly, Aisling Carr. An approach to assessing immunoglobulin dependence in chronic inflammatory demyelinating inflammatory polyneuropathy. J Peripher Nerv Syst. 2021 Dec;26(4):461-468. doi: 10.1111/jns.12470.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Rates of side effects were similar between the placebo and treatment groups in ADHERE. Commonly reported SE were injection site bruising and erythema, infections, CIDP worsening and headache. Three deaths occurred. One receiving treatment who died after cardiac arrest in the context of COVID-19, one during follow up due to CIDP deterioration, and one due to pneumonia, though they were in the placebo arm. The study reported that no clinically meaningful changes were seen in ECGs, vital signs or laboratory assessments. Pooled safety data has been published which suggests that most side effects were mild or moderate, and include headache, nasopharyngitis, UTI, COVID-19 and injection site

	reactions and described that severe or serious reactions were similar between treatment and placebo groups. The paper was funded by argenx. References Allen, JA, Lin J, Dysgaard T, ... Safety, tolerability and efficacy of subcutaneous efgartigimod in patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (ADHERE) Lancet 2024. Gwathmey, K. G., Broome, C. M., Goebeler, M., Murai, H., Bata-Csörgo, Z., Newland, A. C., ... Howard, J. F., Jr. (2025). Safety profile of efgartigimod from global clinical trials across multiple immunoglobulin G-mediated autoimmune diseases. <i>Expert Review of Clinical Immunology</i>, 21(5), 627–638. https://doi.org/10.1080/1744666X.2025.2497840 [note funded by argynx]

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	In general UK clinical practice respects EFNS/ PNS guidance on CIDP treatment with patients treated with one of three proven first line treatments (corticosteroids, IVIg or PLEX) depending on individual characteristics/ risk and choice of the patients, cost and local availability of either infrastructure or access. Therefore the entry criteria for this trial align with this approach.

	ADHERE used relapses (in keeping with criteria used in UK clinical practice as set out in previous CIDP RCTs, the EFNS/ PNS CIDP guidelines and NHSE Ig commissioning guidance) as a method of recruitment to confirm the population have active CIDP. Long term efficacy, potential to induce remission and timing or monitoring of treatment cessation trials has not yet been demonstrated. Data collection is ongoing in the OLE : ADHERE+ (NCT04280718)
18a. If not, how could the results be extrapolated to the UK setting?	We do not think ADHERE represents a significant difference to UK clinical practice which can be extrapolated easily to current CIDP care. It would be interesting to explore efgartigimod in the subgroup of SOC treatment suboptimal or refractory CIDP patients to see if they have a meaningful response
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	We suggest the use of CIDP-specific clinical outcome measures and minimally clinically important differences in the recording of treatment response is appropriate. In the current NHSE IVIg commissioning guidelines outcome measures include: MRC sum score, INCAT sensory sum score, ONLS, Hand dynamometry, I-RODS score, 10m walk time, timed up and go, and Berg Balance scale. Those used in the EFNS/PNS 2021 guidelines are listed in question 7. In our experience, it is not possible to perform all of these for each patient due to resource limitation, and often practice is to select a suitable outcome measure for the patient, for example a Berg Balance scores will not help you in a patient whose main symptoms relate to intrinsic hand muscle weakness, so you might chose an MRC

	sum score, perhaps also measuring MRC scores in other hand and arm muscles to look for responsiveness, Martin virgometry and an I-RODS as suitable outcome measures for that patient. NHSE immunoglobulin commissioning guidelines recommend the use of at least 3, disease specific, clinicimetrically validated outcome measures for effective disease activity monitoring. The choice of which three is dependent on the patient, the infrastructure and CIDP pattern. The ADHERE Trial used INCAT, Grip and I-RODS.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not used
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No but a clinical practice study has revealed that 4/9 patients previously stable on SOC experienced clinically significant relapse on transfer to efgartigimod. Appropriate support infrastructure will be required to appropriately identify and retreat/ rescue these individuals. Levine T, Muley S. Early deterioration of CIDP following transition from IVIG to FcRn inhibitor treatment. J Neurol Sci. 2025 Jan 15;468:123313. doi: 10.1016/j.jns.2024.123313. Epub 2024 Nov 17. PMID: 39578164.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No to our knowledge. We are aware there are various trials on FcRn modulators, complement inhibitors and Rituximab pending.

20. How do data on real-world experience compare with the trial data?	Real world data on potential for significant relapse on transfer from SOC maintenance to efgartigimod highlight need for supportive infrastructure to facilitate safe transfer/ rescue if ineffective. Levine T, Muley S. Early deterioration of CIDP following transition from IVIG to FcRn inhibitor treatment. J Neurol Sci. 2025 Jan 15;468:123313. doi: 10.1016/j.jns.2024.123313. Epub 2024 Nov 17. PMID: 39578164. Otherwise no major real-life large case series studies have yet been published that we are aware of.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	It is known that socioeconomic status and geographical location impact access to new therapies at tertiary care settings, but this is both true of SOC, and outside scope of this assessment. To our knowledge, there is no safety data regarding efgartigimod in pregnancy.
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• ADHERE suggests that efgartigimod may result in clinically meaningful improvement at similar rates to existing first line therapies. • Existing treatments are associated with significant risk and lifestyle implications, including days away from work and family at hospital for infusions, need for venous access, and significant complications both acute and chronic with their own associated economic and health cost and treatment burden. • Efgartigimod has a favourable side effect profile, can be self-administered at home rapidly via subcutaneous injection, and requires considerably less blood monitoring and nursing intervention than current therapies. • For a proportion of patients with CIDP, Efgartigimod may be life-changing. • It is possible that efgartigimod may be beneficial in refractory CIDP patients or those with sub-optimal response to SOC therapies given novel mechanism of action of FcRN blockage, although data to support this is currently limited. A significant unmet need exists in CIDP treatment, with over 30% of patients being refractory to current standard-of-care therapies.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory

demyelinating polyneuropathy [ID6409]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Tuesday 24 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Part 1: Treating chronic inflammatory demyelinating polyneuropathy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Aisling Carr
2. Name of organisation	National Hospital for Neurology and Neurosurgery
3. Job title or position	Consultant Neurologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic inflammatory demyelinating polyneuropathy (CIDP)? ☐ A specialist in the clinical evidence base for CIDP or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

8. What is the main aim of treatment for CIDP? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To reverse motor and sensory deficit, improve function and reverse disability. And maintain control of optimal clinical response to facilitate independence and stability in a disease mediated by chronic inflammatory attack of the peripheral nervous system
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	• Meaningful and measurable (see below) improvement in strength and function Disease specific outcome measures can be used to document clinical improvement, there are clinimetrically validated changes which reflect meaningful improvement (MCID). A range of measures exist and clinicians use a variety in clinical decision making. These include: ○ MRC sum score: at least 2 point improvement ○ CIDP-RODS: minimum 4 point improvement (raw score), 8 point on logit scale ○ Grip strength (kPa): minimum improvement of 8kPa ○ 10m timed walk: 17% improvement (borrowed from multiple sclerosis literature but a meaningful functional measure) ○ INCAT: at least 1 point improvement Although the NHSE immunoglobulin commissioning guidelines recommend the use of at least 3 outcome measures in the judgement of treatment responsiveness not all measures are sensitive to meaningful changes in the patient due to the heterogeneity of the disease. Often subjective improvement as reported by the individual or a contiguous (sub-MCID) change in at least 2 outcome measures is sufficient to reflect treatment response.
10. In your view, is there an unmet need for patients and healthcare professionals in CIDP?	Although 70-80% of patients demonstrate meaningful improvement to at least one of the first line approved therapies (either corticosteroids, immunoglobulin or PLEX) there is significant associated tolerance and treatment burden implications of these options:

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

	- Corticosteroids cause weight gain, have bone health/ infection and GI complications and can induce diabetes. Corticosteroids are effective in remission induction in 60-70% of CIDP patients. They are rarely used as longterm maintenance in CIDP due to tolerance issues and adverse events. - Ig (including IVIg and SCIg) and PLEX are immunomodulatory therapies and must be delivered regularly at 3-6 week intervals to maintain control in active CIDP and represent the mainstay of management for chronic active CIDP. This means patients attend hospital, travel to regional centres, miss work days, incur personal cost for travel and parking or spend hours infusing at home (with medicalisation of the home environment as consumables to support homecare subcutaneous immunoglobulin are significant). - Alternatives to longterm maintenance management of CIDP which are effective, well tolerated and reduce treatment burden would be beneficial to the patient cohort, the NHS and society as a whole - There is a small proportion of CIDP patients who require high dose, high frequency Ig to maintain control and a smaller number who are refractory to current proven treatments. Although there is very limited evidence to suggest efgartigmod is more effective than Ig or useful in Ig/ corticosteroid or PLEX non-responders, this is a group where novel therapeutics could be highly impactful
11. How is CIDP currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	• Guidance used in the UK: ○ van den Bergh, P. Y. K., et al. (2021). European Academy of Neurology/Peripheral Nerve Society Guideline on the diagnosis and treatment of chronic inflammatory demyelinating polyneuropathy. European Journal of Neurology, 28(5), 1379-1392. [DOI:10.1111/ene.14859]

Clinical expert statement

Efgartigmod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

What impact would the technology have on the current pathway of care?	https://www.england.nhs.uk/wp-content/uploads/2021/12/ccp-for-the-use-of-therapeutic-immunoglobulin-england-2025.pdf - Kapoor M et al. Immunoglobulin use in neurology: a practical approach. Practical Neurology Published Online First: 03 August 2024. doi: 10.1136/pn-2022-003655 - Practical Neurology is the official journal of the Association of British Neurologists - There are 3 first-line treatment options in CIDP: corticosteroids, Immunoglobulin and PLEX. In real life clinical practice corticosteroids and Ig are used as induction treatments much more frequently, choice is influenced by individual patient factors (co-morbidities, patient choice, aggressiveness of disease onset) and local factors (availability of PLEX: not uniform across the UK, consideration of cost: corticosteroids significantly less expensive than Ig). For maintenance management in chronic active CIDP immunoglobulin is the predominant therapeutic used in the UK because of inequity of access to PLEX. The approach is broadly similar between peripheral nerve sub-specialist neurologists as documented by a survey by the British Peripheral Nerve Society (BPNS - to be presented at the ABN meeting 2026) and a marketing survey performed by Argenx (publication in draft). - Based on the proposed positioning, the technology could shift a proportion of patients requiring maintenance Ig treatment for chronic active disease out of daycare delivered infusions to homecare, self-delivered therapy. This would increase DCU capacity for the NHS, improve availability of Ig (a notoriously limited and in-demand resource), improvement lifestyle of patients, reduce treatment burden, reduce missed work days.

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	• Efgartigimod will differ from existing immunomodulatory treatments used for chronic active CIDP in that it is a 90sec subcutaneous injection delivered by the individual at home. Secondary care/ speciality neuromuscular service prescription and monitoring will be required (in line with how CIDP is currently managed with Ig) but drug delivery will move from hospital/ day case unit delivery to the home • Current maintenance treatment in chronic active CIDP is predominantly intravenous immunoglobulin delivered over 1-3 days per month on a day case unit. Alternatives include PLEX (hospital delivered) or subcutaneous Ig (home case delivered but not available throughout the UK) • Clinical setting: efgartigimod should be used to treat chronic active CIDP as judged by clinical monitoring by a peripheral nerve/ neuromuscular specialist neurologist in a secondary/ tertiary care setting. This aligns with how Ig is managed and delivered to CIDP patients already. This is safely facilitated with a consultant overseeing clinical decision making in the outpatient setting with ongoing support available from a neuromuscular/ neurology Clinical Nurse specialist who is needed to provide the responsiveness essential to maintaining disease control and responding to change in clinical status around treatment changes. • No extra training will be required as this is the approach used in the assessment of treatment response in CIDP already (in line with NHSE Ig commissioning guidance). And used to assess disease activity during Ig cessation trials as recommend. An important note to consider for transfer on patients from Ig to efgartigimod, as demonstrated in stage A of the ADHERE trial, a proportion will not respond, and these patients should have access to previously effective treatment in a timely manner.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	• CIDP is not a life shortening disease. But untreated the associated physical disability has significant negative impact on an individuals mobility, independence and general well being. Optimal treatment with

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

- Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	immunomodulatory therapy (including efgartigimod) results in meaningful improvements in strength and function with reduction in disability. The ADHERE trial showed comparable improvement in INCAT, I-RODS and grip strength There is potential for efgartigimod to significantly increase health-related quality of life compared to current care because of the meaningful reduction in burden of care. Ig maintenance is typically delivered over 1-3 days per month in a hospital day case unit while efgartigimod is a 90sec subcutaneous injection (well tolerated) delivered by the patient at home. This will reduce missed work days, reduce time and cost associated with travel to and from hospital and improve social engagement of individuals with less time lost to receiving treatment
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The regular assessment of disease activity should not differ from that recommended for immunoglobulin treatment in CIDP (as per NHSE Ig commissioning guidelines: annual review of ongoing disease activity for individuals with stable disease on stable treatment regimen over 12 months). The assessment of response to efgartigimod induction (in treatment naïve patients) would be identical to the process applied to all treatment modalities: measurement of improvement on disease specific outcome measures. The changeover from established maintenance (either Ig or PLEX) to efgartigimod will require hospital-supervised support from a responsive clinician/ clinical nurse specialist and rescue treatment infrastructure to facilitate prompt

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

	treatment if deterioration occurs so as axonal damage/ irreversible nerve deficit does not occur due to delay in access to re-treatment. Most specialist centres already provide this set up to facilitate intermittent assessment of disease activity for other maintenance treatments.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Rules for starting and continuing this immunomodulatory treatment should align perfectly with those set out in the NHSE Ig commissioning guidance for CIDP: - Patients should be assessed for treatment response using at least 3 disease specific clinical outcome measures - In responders who have been clinically stable (according to outcome measure monitoring) on a stable dose and regimen for at least 12 months should have re-assessment of disease activity - Intolerance or treatment failure should be the indications to stop There is some potential for increase clinical workload in the changeover phase. Not all patients who respond to Ig will respond to efgartigimod and therefore there may be need to rescue management in a proportion if deterioration occurs. Appropriate counselling for the patient will be part of the consent procedure - Stage A (ADHERE trial) - Levine T et al., Early deterioration of CIDP following transition from ICIg to FcRN inhibitor treatment. J Neurol Sci. Nov 17, 2024. Doi:10.1016/j.jns.2024.123313
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	• There are many elements of living with CIDP that are not adequately captured by QALY: ○ The additional financial impact of missing 2-3 workdays/ month for maintenance Ig treatment delivered in hospital ○ The additional cost of travel to and parking at a hospital to attend treatments

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	○ With short (90 sec) self-delivered subcutaneous treatment delivered at home there is likely to be improved independence and feeling of self-sufficiency alongside the monetary benefits as listed above. ○ For those with established, irreversible disability the challenge and danger associated with regular hospital attendance will also be beneficial (even if employment is not a factor)
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	• Efgartigimod is innovative in its molecule specificity. Previous maintenance options (immunoglobulin) have multifaceted mechanisms of action. Although this provides wide-reaching effect across multiple autoimmune diseases it makes the prediction and appreciation of rare but significant adverse reactions very difficult. There is a real increase in thromboembolic rate risk with Ig, which is clinically significant in individuals with established cardiovascular risk at baseline. No thromboembolic events were recorded in the ADHERE trial. Although open label use will be needed to definitely exclude this, it would appear that efgartigimod would reduce this risk. • The step-change from a patient perspective is the reduction in time spent receiving treatment. This will have huge benefits from a quality of life and treatment burden perspective. With likely financial benefits to the individuals as well (as documented above). The stepchange for the NHS will be the potential for shift of a significant number of day care unit treated patients to home based delivery. Although overarching care for these patients will remain the responsibility of secondary care clinicians it is a move away from hospital care, improving DCU capacity. • The unmet need that will be most impactful to patients, in my opinion, is the possibility of home based, rapidly delivered treatment. And how much of their life it will give them back for just living. • There is an argument that a novel therapeutic with a molecule specific mechanism of action may provide additional clinical benefit to a proportion of patients who do not respond well to existing therapeutics. We do not have

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

	strong evidence to support this possibility. But it would be exciting if OLE data from ADHERE shows this
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Local injection reactions were the most common adverse event in the ADHERE trial. In my experience (greater than 10 years of managing patients who transfer from IV to SC immunoglobulin treatment) these skin reactions become less bothersome and more easy to manage over time.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The ADHERE trial placed efgartigimod as an alternative to SOC maintenance therapy in CIDP patients with active disease and as a firstline treatment option in treatment naïve patients. Only those who responded to efgartigimod in Stage A were then transferred on to the Stage B efgartigimod versus placebo arm. There was a 61% lower risk of relapse in the efgartigimod group with benefit measured in INCAT, I-RODS and grip strength. • Efgartigimod is unlikely to compare well from a cost perspective to corticosteroid induction therapy. But in those who relapse after initial steroid response (those who require longterm maintenance treatment, efgartigimod is a viable option) • Efgartigimod has patient-centred benefits as a first-line, longterm maintenance treatment option in patients with chronic active CIDP compared to hospital delivered immunoglobulin and PLEX treatment. • The outcomes used in the clinical trial reflect disease specific clinical improvement on the treatment and were appropriate to prove efficacy. Markers of patient satisfaction were encouraging. • CIDP is a chronic, relapsing-remitting autoimmune disease. Some individual require longterm maintenance immunomodulatory therapy: efgartigimod provides as alternative to the current options we have (Ig in the main). We do not have data on whether efgartigimod has the potential to induce remission or whether it is clinically more effective than comparators at this time. When

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

	CIDP is optimally managed by a responsive clinical team there should not be longterm accrual of deficit and disability over years. - Although this is not an adverse effect of the medication the possibility that a proportion of individual who previously responded to Ig maintenance may not respond to efgartigimod is a significant event which would have adverse consequences to the individual. Therefore, this will need to be part of the consent procedure for any patients wishing to move from maintenance Ig to efgartigimod and there must be adequate, responsive clinical services in place to monitor for decline and re-institute previous effective therapy as required. - Levine T et al., Early deterioration of CIDP following transition from ICIg to FcRN inhibitor treatment. J Neurol Sci. Nov 17, 2024. Doi:10.1016/j.jns.2024,123313
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Nothing further to the references added within this document.
22. How do data on real-world experience compare with the trial data?	- Real world data form use in the USA is interesting for thelack of response in some patients who previously responded to Ig. This could be interpreted from the trial design. As the placebo arm (stage B) was enriched with efgartigimod responders from stage A. - Levine T et al., Early deterioration of CIDP following transition from ICIg to FcRN inhibitor treatment. J Neurol Sci. Nov 17, 2024. Doi:10.1016/j.jns.2024,123313 We do not have much more real world data on CIDP as yet. In the real world setting it would be interesting to: - assess whether individuals experience greater treatment effect with efgartigimod treatment compared to optimised dosing regimen of previous maintenance therapies is the treatment effect greater in all or

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

	some patients as is shown in the real world data from efgartigimod use in myasthenia gravis: ○ Dionisio et al., Efgartigimod efficacy and safety in refractory myasthenia gravis: UK's first real-world experience. JNNP, 96(4): 322-328. - There is treatment response if refractory cases (individuals who either require ultrahigh dose Ig maintenance: greater than 2g/kg/month) or those who do not respond in a meaningful way to any of the established first line therapies (corticosteroids, Ig or PLEX).
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	No

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. Efgartigimod is an alternative to maintenance Immunoglobulin or PLEX as treatment for chronic active CIDP
2. Efgartigimod presents a significant quality of life improvement to patients requiring maintenance treatment for CIDP through reduced treatment burden, reduced time spent traveling to and receiving treatment in hospital.
3. Efgartigimod is well tolerated
4. Efgartigimod presents a novel molecule specific therapy for CIDP, it is not yet know whether this will provide superior clinical benefit to existing treatment options or if it will be effective in CIDP deemed refractory to existing therapies.
5. The introduction of efgartigimod into UK clinical practice will not incur extra clinical service costs (either staffing or training) but should have a positive impact on bother day case unit capacity and immunoglobulin availability

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our [privacy notice](#).

Clinical expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Clinical Expert Statement: Efgartigimod in CIDP

Chinar Osman / 05 March 2026

Unmet Need

There is a clear and significant need for additional therapeutic options in chronic inflammatory demyelinating polyneuropathy (CIDP). Many patients have relative or absolute contraindications to one or more standard-of-care (SOC) treatments. Furthermore, existing options frequently necessitate repeated hospital visits, intravenous access, extensive blood monitoring, and prolonged periods away from work and family commitments. Some carry unfavourable long-term side effect profiles. For patients with refractory CIDP or an incomplete response to current treatments, an alternative option with a distinct mechanism of action would address a meaningful clinical gap.

Current Treatment Pathway

First-line therapeutic options—corticosteroids, intravenous immunoglobulin (IVIg), or plasma exchange (PLEX)—are selected according to individual patient risk profile, disease severity, local infrastructure availability, and patient preference. Treatment is continued on the basis of documented evidence of response using validated CIDP-specific outcome measures.

- Approximately 60–70% of patients demonstrate a favourable response to one of the three first-line options
- In non-responders, switching to an alternative first-line agent yields a meaningful response in up to 80%
- Suboptimal or transient response to any first-line option warrants consideration of an adjunctive immunosuppressive or steroid-/immunoglobulin-sparing agent; however, reappraisal of diagnostic security using European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society (PNS) criteria is essential before escalating therapy
- Truly refractory CIDP is uncommon; thorough case re-evaluation and specialist second opinion are strongly recommended, with limited options including cyclophosphamide

Role of Efgartigimod in NHS Practice

For NHS CIDP patients, efgartigimod offers an additional therapeutic option via a novel mechanism of action—FcRn blockade, leading to IgG degradation and reduced circulating autoantibody levels. It would be most appropriately considered for:

- Patients with persistent, active disease dependent on maintenance IVIg or PLEX therapy
- Patients with documented contraindications to, or significant intolerance of, any first-line option
- Potentially those with suboptimal disease control despite optimised standard therapies, although the evidence base in this refractory subgroup currently remains limited

Evidence Base: The ADHERE Trial

The randomised, placebo-controlled ADHERE trial demonstrated that efgartigimod achieves clinically meaningful improvement at rates comparable to first-line therapies. Stage B was deliberately enriched with patients confirmed to have active, treatment-responsive CIDP—not refractory disease. The trial entry criteria align closely with established UK clinical practice as defined by EFNS/PNS guidance, and findings are broadly extrapolatable to current NHS CIDP care.

Approximately 70% of patients who responded to SOC in Stage A also demonstrated response to efgartigimod. Consequently, a meaningful proportion (~30%) may experience relapse during the transition period. Long-term efficacy, the potential to induce remission, and the optimal timing of treatment cessation remain undemonstrated; prospective data collection is ongoing in the open-label extension trial ADHERE+ (NCT04280718). Anecdotal cases reporting benefit in refractory CIDP have been reported; however, robust evidence in this population is currently lacking.

Safety Profile

Adverse event rates were distributed similarly between treatment and placebo arms in ADHERE. Commonly reported adverse events included injection site bruising and erythema, infections, CIDP worsening, and headache. Three deaths occurred during the trial: one in the treatment arm following cardiac arrest in the context of COVID-19 infection; one during follow-up due to CIDP deterioration; and one in the placebo arm due to pneumonia. No clinically meaningful changes were observed in electrocardiograms (ECGs), vital signs, or laboratory assessments. Pooled safety data indicate that the majority of adverse events were mild-to-moderate in severity, with serious adverse events distributed similarly across treatment and placebo groups. Blood monitoring requirements (e.g. albumin and lipid assessment) are anticipated to be substantially less burdensome than for current SOC options. Currently, no safety data regarding efgartigimod use in pregnancy are available.

Healthcare Resource Implications

Efgartigimod is administered as a rapid (90-second) subcutaneous injection self-delivered by the patient at home, representing a substantive departure from hospital-based intravenous infusion models. Key resource considerations include:

Training and Administration

Staff training in subcutaneous injection delivery is likely already established given existing homecare subcutaneous immunoglobulin (SCIg) programmes. Patient education regarding drug use and self-administration will require dedicated time, staffing, and appropriate facilities—akin to established SCIg training frameworks already operational in CIDP services.

The first dose should ideally be administered in a setting equipped to manage potential drug reactions, although these are anticipated to be rare.

Transition and Safety Infrastructure

Approximately 30% of SOC-responsive patients will not respond to efgartigimod. Robust infrastructure for prompt clinical review and expedited re-establishment of prior treatment or alternative rescue therapy is essential, mirroring the support required for NHSE-mandated annual Ig cessation trials in stable CIDP patients. Some published real-world data have revealed that patients previously stable on SOC experienced clinically significant relapse following transfer to efgartigimod, emphasising the need for supportive transition protocols.

Ongoing Monitoring

Efgartigimod does not induce remission; therefore, ongoing efficacy and safety monitoring—including planned treatment cessation trials with close clinical surveillance—will be required, analogous to current frameworks for IVIg maintenance therapy monitoring.

System-Level Benefits

Widespread adoption has the potential to reduce demand on daycare infusion units, PLEX services, and overall IVIg supply—an expensive and increasingly resource-constrained component of NHS provision.

Cost-Effectiveness and Patient Selection

The annual cost of efgartigimod treatment (at a dose of 1,000 mg per week) is estimated at approximately £15,307 per patient per annum based on a cost of £780k per treatment course. This is broadly comparable to the cost of IVIg maintenance therapy.

Efgartigimod may be particularly cost-effective and clinically appropriate for:

- Patients with significant mobility impairment requiring hospital transport or carer support to attend repeated daycare or inpatient hospital admissions for IVIg or PLEX

- Working-age patients or those with substantial caring responsibilities, for whom hospital attendance for frequent infusions represents a considerable occupational and social burden
- Patients with documented high thrombo-embolic risk or prior venous thrombo-embolic (VTE) events; the number needed to harm with IVIg therapy in this setting is 6
- Patients with persistent difficult venous access or an unfavourable or intolerable SOC side effect profile

Clinical Criteria for Treatment Initiation

Treatment with efgartigimod should initially be initiated in consultation with a specialist with expertise in peripheral neuropathy, within a secondary or tertiary care setting (e.g. regional specialist peripheral nerve clinics). The following criteria should be met prior to commencement:

1. Confirmed diagnosis of CIDP according to EFNS/PNS diagnostic criteria
2. Established and documented disease activity prior to treatment initiation
3. Planned ongoing efficacy monitoring utilising validated CIDP-specific outcome measures
4. For cases of suboptimal response, or where efgartigimod is being considered for potentially refractory CIDP, expert clinical review is essential to exclude alternative diagnoses and establish appropriate efficacy monitoring and response criteria before proceeding

Conclusion

Efgartigimod represents a meaningful therapeutic advance in CIDP management: a novel FcRn-blocking mechanism, a distinct route of self-administered home delivery, and substantially reduced clinical monitoring burden. The ADHERE trial provides randomised controlled evidence of efficacy comparable to first-line SOC within a well-defined population of patients with active, treatment-responsive disease. It offers a favourable safety profile and significant quality-of-life benefits—particularly for working-age patients, those with impaired mobility, and those experiencing high burden from existing therapies. A substantial unmet need persists, with over 30% of CIDP patients remaining refractory to current SOC, and whilst evidence for efgartigimod in this refractory cohort remains limited, its novel mechanism warrants further investigation.

References

- [1] EFNS/PNS guidelines on CIDP management and diagnostic criteria
- [2] ADHERE trial (Efficacy and Safety of Efgartigimod in Patients with CIDP): NCT03375697
- [3] ADHERE+ open-label extension: NCT04280718

[4] NHS England immunoglobulin commissioning guidance and CIDP treatment protocols

Single Technology Appraisal

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with chronic inflammatory demyelinating polyneuropathy (CIDP) or caring for a patient with CIDP. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm on Tuesday 24 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Part 1: Living with this condition or caring for a patient with chronic inflammatory demyelinating polyneuropathy (CIDP)

Table 1 About you, CIDP, current treatments and equality

1. Your name	Nadia Mulliner
2. Are you (please tick all that apply)	☒ A patient with CIDP? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with CIDP? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with CIDP? If you are a carer (for someone with CIDP) please share your experience of caring for them	Having moved from using a wheelchair to being fully able to walk and go to the gym and being able to self administer Efgartigimod my experience has been long and distressing. My legs started to fully fold in and I was falling down without any notice. In hotels and driveways I was unable to continue to work and had to move downstairs to live in my home. My weight was 15 stones (now 10st 4 lb) CIDP also affected my family especially my Husband and daughter.
7a. What do you think of the current treatments and care available for CIDP on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	The NHS offered IVG which did help a lot and got me walking again. However very tiring and left me with severe headache. Timing was also an issue and distance to the Hospital as not available nationwide. I was also given the IVG over 4 consecutive days every 8 weeks. A number of people that I meet and sat with in the hospital didn't fair as well the IVG seemed to maintain their condition only. I was lucky and improved almost from the start.
8. If there are disadvantages for patients of current NHS treatments for CIDP (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Time in hospital as some needed to go every 4 weeks for 4 days. Headaches

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

9a. If there are advantages of efgartigimod with recombinant human hyaluronidase PH20 over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does efgartigimod with recombinant human hyaluronidase PH20 help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	Main advantage and most important is I am able to administer at home. I am diabetic and have no fear of injection myself. However it is important to note not all patients are able to do this or want to. No longer need a stick for balance and able to walk c 2 miles for a coffee A ...One has Shaking hands and the drug is thick and takes some strength B...One is Not comfortable to self inject. Their partner not happy to administer So a nurse would need to home visit once a week. Keeping out of the hospital setting. Self sufficient in administration Less clinical time and driving.
10. If there are disadvantages of efgartigimod with recombinant human hyaluronidase PH20 over current treatments on the NHS please describe these. For example, are there any risks with efgartigimod with recombinant human hyaluronidase PH20? If you are concerned about any potential side effects you have	No disadvantages I am suffering from lower abdominal pain and it is under investigation this may be due to diabetic treatment or CIPD drug.

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

11. Are there any groups of patients who might benefit more from efgartigimod with recombinant human hyaluronidase PH20 or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Only 3 on efgartigimod in my group A ... Has mobility and dexterity issue and would not be able to self administer.
12. Are there any potential equality issues that should be taken into account when considering CIDP and efgartigimod with recombinant human hyaluronidase PH20 ? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Unknown
13. Are there any other issues that you would like the committee to consider?	As above less time in hospital and less clinical time.

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Able to self administer
- Able to enjoy a full life with ability to walk unaided
- Less time in the hospital
- Less risk of infection (Sorry not a dig at the NHS) Just a fear removed
- Wheel chair not need via treatment of IVG then part 2 delivered by Efgartigimod

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see [NICE's privacy notice](#).

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Single Technology Appraisal

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with chronic inflammatory demyelinating polyneuropathy (CIDP) or caring for a patient with CIDP. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm on Tuesday 24 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Part 1: Living with this condition or caring for a patient with chronic inflammatory demyelinating polyneuropathy (CIDP)

Table 1 About you, CIDP, current treatments and equality

1. Your name	Richard Gedge
2. Are you (please tick all that apply)	☒ A patient with CIDP? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with CIDP? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with CIDP? If you are a carer (for someone with CIDP) please share your experience of caring for them	I was diagnosed with CIDP in 2015 and since then I have been treated with IVIg, initially every 3 months and now every 4 weeks. I find the treatment to be effective with few side effects and issues. My hands and feet are most effected by the condition and I have limited sensation in those areas. I have also lost significant strength and stamina and have gone from being able to walk 20 miles a day to sometimes struggling to do 1-2. I have lost the use of the intrinsic muscles in my right hand but still have a reasonable grip. My life has always revolved around practical hands on activities and I have a substantial workshop where I now spend much of my time now that I'm retired. Unfortunately these activities, as much as I still love them, do emphasise the impact that CIDP has had on me which does make me down at times. My life now revolves around the 4 weekly IVIg treatment cycle. I feel low and fatigued on the days leading up to treatment and on the days afterwards and I hence avoid arranging any activities during those times. Day to day I have found that it's often the simple things that catch you out. For instance, how do you buy a pair of shoes when you can't feel your feet? Having lost the sensation and fine motor control of my hands I tend to drop things a LOT, if I can't see something in my hand then I can't be sure that I'm still holding it. I have

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

	installed rubber mats in my workshop to try and prevent tools and created items from breaking when I inevitably drop them on the floor. It's heartbreaking when have spent days making something only to destroy it by dropping, on the plus side it does get me out of the washing up! I also find that the mundane process of going to the loo to be hard as I no longer have the strength in my fingers to adequately use toilet paper. At home we have a bidet but it does make trips away more difficult. I also struggle to flush loos that have recessed buttons. My fingers tend to seize up if they get cold and I wear gloves much of the time. Once cold I cannot undo zips, buttons and shoe laces and have to rely on my someone to help or wait until I get some movement back. Typing is also effected and I frequently miskey unless I watch carefully what I am doing.
7a. What do you think of the current treatments and care available for CIDP on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I feel that the NHS treats my condition better than caring for me as an individual. I have never been offered any form of support or help in living with CIDP or help for dealing with the days when I feel down and despondent. To be fair, being an independent person, I have never asked. I now receive 80mg of IVIg every 4 weeks which I understand is the maximum for my body weight. This is carried out as an outpatient at the main hospital which is about 45 minutes drive away The process is straightforward and well run although as many patients are treated in a single room it can be noisy and not ideal when a common side effect for me is a headache. Steroids were also tried as an alternative treatment but proved to be ineffective. I'm not aware of any alternative treatments, I certainly haven't been offered any. I generally avoid speaking with other CIDP patients as my experience so far has been that people are effected very differently so their experiences can cause more worry than help. I'm led to believe that IVIg treatment is costly with limited availability and therefore has to be carefully controlled. The process of being evaluated each year for

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

	continued treatment is always a concern particularly when the tests seem very subjective.
8. If there are disadvantages for patients of current NHS treatments for CIDP (for example, how they are given or taken, side effects of treatment, and any others) please describe these	During my evaluation of a steroid treatment I experience several unpleasant side effects and was glad when the trial was over. In general I have found IVIg to have few side effects, I do get a headache during and after treatment but it is not severe and when it is then paracetamol is an effective treatment. For me the only real issue with IVIg treatment is the peaks and troughs of the treatment cycle. The week before my treatment I start to feel more fatigued and the sensation in my feet and hands gradually worsens. This continues until my treatment day after which I have one day of feeling poorly before I start to feel my symptoms lessen once again. If a new treatment eliminated this roller coaster then I would see it as a big advantage all other things being equal.
9a. If there are advantages of efgartigimod with recombinant human hyaluronidase PH20 over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does efgartigimod with recombinant human hyaluronidase PH20 help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	I have no knowledge or experience of the efgartigimod treatment.

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

10. If there are disadvantages of efgartigimod with recombinant human hyaluronidase PH20 over current treatments on the NHS please describe these. For example, are there any risks with efgartigimod with recombinant human hyaluronidase PH20? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have no knowledge or experience of the efgartigimod treatment.
11. Are there any groups of patients who might benefit more from efgartigimod with recombinant human hyaluronidase PH20 or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I have no knowledge or experience of the efgartigimod treatment.
12. Are there any potential equality issues that should be taken into account when considering CIDP and efgartigimod with recombinant human hyaluronidase PH20 ? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	I have no knowledge or experience of the efgartigimod treatment.

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- IVIg is an effective treatment with few side effects
- There are currently no alternative treatments, which is a concern in case IVIg stops being effective.
- My life revolves around my 4 weekly IVIg treatment cycle
- CIDP effects my daily life and that of my wife.
-

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see [NICE's privacy notice](#).

Patient expert statement

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy
[ID6409]

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 175573.

Title:	Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Clare Dadswell, Clinical Evidence Manager, BMJ-TAG, London Sophie Ip, Senior Health Economist, BMJ-TAG, London Victoria Wakefield, Principal Clinical Evidence Analyst, BMJ-TAG, London Tracey Jhita, Health Economics Manager, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ Group, 5th Floor, 90 Whitfield Street, London W1T 4EZ, UK.
Date completed:	23/02/2026
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 175573.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Tatyana Yermakova (Consultant Physician in Clinical Neurophysiology, ABUHB, Newport, South Wales), Dr Graham Warner (Consultant Neurologist, Royal Surrey County Hospital) and Dr David Gosal (Consultant Neurologist, Manchester Centre for Clinical Neurosciences) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Dadswell C, Ip S, Wakefield V, Jhita T. Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]: A Single Technology Appraisal. BMJ Technology Assessment Group, 2026.

Copyright is retained by argenx for Figures 1-11 and content reproduced in Tables 21, 27, 29, 31, 32, 34, 35, and 49-63.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Clare Dadswell	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Sophie Ip	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

Table of Contents.....	4
List of Tables	8
List of Figures	15
List of Abbreviations	17
1 Executive summary	20
1.1 Overview of the EAG's key issues.....	20
1.2 Overview of key model outcomes.....	21
1.3 EAG's key issues.....	22
1.4 Secondary issues identified by the EAG	32
1.5 Company's modelling errors identified by the EAG	37
1.6 Summary of EAG's preferred assumptions and resulting ICER	37
1.7 Outline of confidential comparator or subsequent treatment prices.....	42
2 Background	43
2.1 Critique of the company's description of underlying health problem	43
2.2 Critique of the company's overview of current service provision	46
2.3 Critique of the company's definition of the decision problem	50
2.3.1 Population	55
2.3.2 Intervention.....	57
2.3.3 Comparators.....	59
2.3.4 Outcomes	61
3 Clinical effectiveness.....	64

3.1	Critique of the methods review.....	64
3.2	Critique of trials of the technology of interest.....	66
3.2.1	ADHERE study design	66
3.2.2	ADHERE+ study design	68
3.2.3	Summary and critique of ADHERE and ADHERE+ methods	68
3.3	Critique of the clinical effectiveness analysis and interpretation	76
3.3.1	ADHERE Stage A efficacy results	76
3.3.2	ADHERE Stage B efficacy results (double blinded, randomised).....	79
3.3.3	ADHERE+ efficacy results	84
3.4	Subgroup results.....	89
3.4.1	ADHERE Stage A subgroup analyses.....	89
3.4.2	ADHERE Stage B subgroup analyses.....	90
3.5	Safety.....	91
3.5.1	ADHERE	91
3.5.2	ADHERE+	93
3.6	Critique of the indirect treatment comparison.....	93
3.6.1	Critique of studies identified and included in the indirect treatment comparison	93
3.6.2	Statistical methods.....	100
3.6.3	Clinical effectiveness results	107
3.7	Conclusions of the clinical effectiveness section.....	110
4	Cost effectiveness	112
4.1	Critique of the review of cost effectiveness evidence	112

4.2	Critique of the submitted economic evaluation.....	114
4.2.1	NICE reference case checklist	114
4.2.2	Population, intervention and comparators.....	115
4.2.3	Model structure	120
4.2.4	Treatment pathway.....	125
4.2.5	Patient baseline characteristics	128
4.2.6	Perspective, time horizon and discounting.....	129
4.2.7	Treatment effectiveness	130
4.2.8	Other events.....	138
4.2.9	Mortality.....	142
4.2.10	Adverse Events.....	142
4.2.11	Health-related quality of life.....	146
4.2.12	Resource use and costs.....	153
4.2.13	Caregiver burden	169
5	Cost effectiveness results	176
5.1	Company's cost effectiveness results.....	176
5.1.1	Company's sensitivity analyses	179
5.2	EAG additional analyses	187
5.2.1	Model validation and face validity check.....	187
5.2.2	EAG's exploratory analyses using the company's base case.....	187
5.2.3	EAG preferred assumptions	194
5.2.4	Scenario analyses using EAG's preferred assumptions.....	206

5.3	Decision Modifiers	214
5.3.1	QALY weighting for severity	214
5.3.2	Uncaptured benefits	214
5.3.3	Health inequalities	215
5.4	Confidential comparator and subsequent treatment prices.....	215
5.5	Conclusions of the cost effectiveness sections	215
6	References	218
7	Appendices.....	222
7.1	EAG corrections in the economic model	222
7.2	Quality assessment.....	225
7.3	Study design of ADHERE and ADHERE+.....	229
7.4	EAG-preferred three-month transition probabilities	230
7.5	Company's approach to modelling adverse events in the economic analysis	231
7.5.1	Adverse events for efgartigimod.....	231
7.5.2	Adverse events for Ig.....	232
7.5.3	Adverse events for PLEX.....	233
7.5.4	Adverse events for corticosteroids	233
7.5.5	Adverse events for immunosuppressants.....	233
7.6	Price sources for treatments included in the confidential appendix	234
7.7	Full list of scenario analyses performed by the company	235
7.8	Results of EAG analyses with mixed population	241
7.8.1	EAG's exploratory analyses using the company's base case.....	241

7.8.2	EAG preferred assumptions: base case results	242
7.8.3	EAG preferred assumptions: deterministic sensitivity analyses	247
7.8.4	Scenario analyses using EAG's preferred assumptions	248
7.9	Probabilistic analysis convergence plots	251

List of Tables

Table 1.	Summary of key issues	20
Table 2.	Issue 1. Lack of alignment between the company's proposed population and the ADHERE trial	22
Table 3.	Issue 2. Concerns about the trial design of ADHERE, which may have overestimated the effectiveness of efgartigimod	23
Table 4.	Issue 3. Different outcomes are used to assess clinical deterioration and established clinical improvement in ADHERE	25
Table 5.	Issue 4. A high percentage of patients in the ADHERE trial who deteriorated following Ig discontinuation did not improve with efgartigimod.....	26
Table 6.	Issue 5. Considerable uncertainty interpreting the results of the ITCs due to substantial methodological limitations	26
Table 7.	Issue 6. Uncertainty around the use of Ig in clinical practice	28
Table 8.	Issue 7. Choice of cycle length for first-two years	29
Table 9.	Issue 8. Uncertainty around treatment pathway after discontinuing efgartigimod.....	29
Table 10.	Issue 9. Lack of treatment effectiveness data for patients with severe disease	30
Table 11.	Issue 10. Approach to modelling treatment effectiveness and discontinuation in the comparator arm	31
Table 12.	Issue 11. Uncertainty around AEs	31

Table 13. Issue 12. Approach to modelling caregiver burden	32
Table 14. Issue 1. Inclusion of biweekly dosing of efgartigimod	33
Table 15. Issue 2. Appropriateness of HSUVs	34
Table 16. Issue 3. Approach to modelling HRQoL impact of IV administrations	35
Table 17. Issue 4. Approach to modelling resource use and costs	36
Table 18. Summary of post-clarification errors in the economic model identified by the EAG	37
Table 19. Summary of EAG's preferred assumptions and resulting ICER (Ig maintenance population)	38
Table 20. Summary of EAG's preferred assumptions and resulting ICER (Ig-intolerant/refractory population).....	40
Table 21. EAN/PNS CIDP diagnostic guidelines (Reproduced from Table 44 of CS, Appendix J).....	44
Table 22. Summary of decision problem	51
Table 23. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal	65
Table 24. Summary of the clinical effectiveness studies of efgartigimod (adapted from Table 6 of the CS)	71
Table 25. EAG's summary of the design, conduct and analysis of ADHERE Stage B.....	74
Table 26. ADHERE Stage A – confirmed ECI responders (primary endpoint) by prior CIDP therapy in the sensitivity analysis (Stage A safety analysis set excluding participants ongoing in Stage A at the 88th relapse event in Stage B) (reproduced from Table 11 of the CS)	77
Table 27. ADHERE Stage A change from Stage A baseline in aINCAT score, I-RODS score, MGS score, MRC sum score, TUG test score and EQ-5D-5L VAS at Stage A last assessment (Stage A safety analysis set; reproduced from Table 12 of the CS).....	78

Table 28. Stage A clinical improvement based on aINCAT, by measure of clinically meaningful deterioration during run-in (Stage A safety analysis set) (adapted from clarification response Table 1)	79
Table 29. ADHERE Stage B – summary of secondary endpoint results of participants treated with efgartigimod or placebo (reproduced from Table 15 of the CS)	82
Table 30. Outcomes of ADHERE+ separated by patient entry route from Stage B of ADHERE.....	87
Table 31. Safety outcomes from Stage A of ADHERE. Reproduced from Table 20 of the CS.....	92
Table 32. Safety outcomes from Stage B of ADHERE. Reproduced from Table 22 of the CS	92
Table 33. EAG’s summary of the design, conduct and analysis of ADVANCE-CIDP-1 (Epoch 1).....	95
Table 34. Prognostic factors and treatment effect modifiers identified by the company’s clinical experts. Reproduced from Table 12 of CS (Appendix 1.3).....	101
Table 35. Comparison between baseline characteristics of ADHERE and ADVANCE-CIDP-1 before and after population weighting adjustments in ADHERE. Reproduced from Table 20-3 of the ITC report	102
Table 36. Change from baseline in aINCAT in the unweighted and weighted placebo arm of ADHERE and ADVANCE-CIDP-1	104
Table 37. Change from baseline in aINCAT in the unweighted and weighted placebo arm of ADHERE and comparator trials	105
Table 38. Change from baseline in the unweighted and weighted placebo arm of ADHERE and the comparator trials	106
Table 39. Results of the anchored MAIC for change from baseline in aINCAT. Values below 0 favour efgartigimod.....	107
Table 40. Results of the anchored MAICs for change from baseline in I-RODS and MGS. Values greater than 0 favour efgartigimod	109
Table 41. Company’s base case results.....	112
Table 42. EAG critique of company SLR methods.....	113

Table 43. NICE reference case checklist.....	114
Table 44. Distribution of patients across Ig products	116
Table 45. Distribution of patients across treatments in the comparator basket	116
Table 46. Scenario analyses varying the proportion of patients receiving each treatment in the 'alternative' basket	119
Table 47. Patient distributions at baseline	122
Table 48. Proportion of patients receiving each subsequent treatment (efgartigimod arm, Ig maintenance cohort)	126
Table 49. Patient baseline characteristics used in the economic model.....	129
Table 50. Patient numbers in each health state informing 24-week transition probabilities for efgartigimod.....	132
Table 51. Mean CfB in aINCAT over Stage B of the ADHERE trial (reproduced from Table 5 in the company's clarification response)	136
Table 52. Input values for parameters included in remission and relapse probability calculations ..	139
Table 53. Per-cycle permanent discontinuation probabilities for efgartigimod treatment	141
Table 54. Per-cycle permanent discontinuation probabilities for Ig treatment	141
Table 55. Adverse events included in the company's base case.	143
Table 56. Per-cycle probability of complications related IV administration (reproduced from Table 60 of the CS).....	144
Table 57. Health state utility values included in the model (reproduced from Table 53 of the CS) ..	147
Table 58. Adverse event disutilities included in the model (reproduced from Table presented in the company's clarification response to question C5).....	149
Table 59. Disutilities associated with complications related to IV access (reproduced from Table presented in the company's clarification response to question C5)	150

Table 60. IV administration disutility per cycle (reproduced from Table 64 of the CS).....	152
Table 61. Cost per six-month cycle of efgartigimod (with PAS).....	154
Table 62. Ig dose data included in the company's base case	155
Table 63. Ig dose data – company chart review study ¹⁸	158
Table 64. Treatment administration costs per cycle	160
Table 65. Health state resource use included in the model.	162
Table 66. Proportion of patients requiring mobility aids by severity (reproduced from Table 77 of the CS)	164
Table 67. Unit costs of mobility aids included in the model.....	164
Table 68. Mobility aid data by severity from Table 6 of the company Adelphi study ⁵⁸	165
Table 69. Adverse event unit costs included in the model.....	166
Table 70. Unit costs of complications related to IV access included in the model (reproduced from Table 82 of the CS)	168
Table 71. Caregiver disutilities by health state	170
Table 72. Proportion of patients requiring caregivers by aINCAT score, from the UK Adelphi dataset	172
Table 73. Professional care costs included in the model (reproduced from Table 77 of the CS).....	172
Table 74. Company's base case results.....	176
Table 75. Company's deterministic subgroup analysis results vs established clinical management .	178
Table 76. Key company scenario analyses: deterministic results	183
Table 77. Summary of EAG's exploratory analyses using company's base case	188
Table 78. Results of EAG's exploratory analyses using company's base case (Ig maintenance population).....	191

Table 79. Results of EAG’s exploratory analyses using company’s base case (Ig-intolerant/refractory population).....	192
Table 80. Results using the EAG’s preferred model assumptions (deterministic analysis, Ig maintenance population)	195
Table 81. Results using the EAG’s preferred model assumptions (deterministic analysis, Ig-intolerant/refractory population).....	197
Table 82. EAG base case results (Ig maintenance population)	199
Table 83. EAG base case results (Ig-intolerant/refractory population)	200
Table 84. Summary of EAG’s scenario analyses using the EAG preferred assumptions.....	206
Table 85. Deterministic results of EAG’s exploratory analyses using EAG’s preferred assumptions (Ig maintenance population)	209
Table 86. Results of EAG’s exploratory analyses using EAG’s preferred assumptions (Ig-intolerant/refractory population).....	211
Table 87. Full details of EAG corrections in the economic model	222
Table 88. EAG’s summary of the design, conduct and analysis of the PATH trial	225
Table 89. EAG’s summary of the design, conduct and analysis of the ICE trial	226
Table 90. EAG-preferred three-month transition probabilities, 0-6 months from response assessment	230
Table 91. EAG-preferred three-month transition probabilities, 6-12 months from response assessment.....	230
Table 92. EAG-preferred three-month transition probabilities, 12-18 months from response assessment.....	231
Table 93. EAG-preferred three-month transition probabilities, 18-24 months from response assessment.....	231
Table 94. Odds ratios of experiencing an AE for different doses of IVIg (Waheed <i>et al.</i> 2019) ³¹	233

Table 95. Source of the confidential prices used in the confidential appendix.....	234
Table 96. Deterministic results for all scenario analyses performed by the company.....	235
Table 97. Results of EAG’s exploratory analyses using company’s base case (mixed population)	241
Table 98. Results using the EAG’s preferred model assumptions (probabilistic analysis, mixed population).....	242
Table 99. EAG base case results (mixed population)	244
Table 100. Results of EAG’s exploratory analyses using EAG’s preferred assumptions (lg maintenance population).....	248

List of Figures

Figure 1. Current UK treatment pathway (reproduced from Figure 2 of CS)	48
Figure 2. Current UK treatment pathway including suggested positioning of efgartigimod (reproduced from Figure 3 of CS)	49
Figure 3. ADHERE Stage B – Kaplan–Meier analysis of the relative risk of CIDP relapse based on time to first aINCAT deterioration in participants treated with efgartigimod or placebo (mITT analysis set) (reproduced from Figure 6 of the CS)	81
Figure 4. ADHERE Stage B Kaplan–Meier analysis of time to I-RODS deterioration in participants treated with efgartigimod or placebo (mITT analysis set, reproduced from figure 8 of the CS).....	82
Figure 5. ADHERE longitudinal mean aINCAT scores of Stage A responders from run-in baseline to last assessment in Stage B (post-hoc analysis; run-in and mITT analysis sets [reproduced from Figure 9 of the CS]).....	84
Figure 6. aINCAT Score: Mean (SE) changes From OLE Baseline (mITT Analysis Set; reproduced from Figure 3 of company response to clarification questions).....	85
Figure 7. ADHERE+ substudy – Kaplan–Meier analysis of time to clinical deterioration during q2w dosing regimen (efficacy analysis set, reproduced from Figure 10 of the CS)	88
Figure 8. ADHERE+ substudy – Kaplan-Meier time to restabilisation on q1w after clinical deterioration during q2w dosing (reproduced from Figure 11 of the CS).....	89
Figure 9. ADHERE Stage A forest plot of a post-hoc analysis of confirmed ECI responders (primary endpoint) by subpopulation of participants treated with open-label efgartigimod (reproduced from Figure 12 of the CS)	90
Figure 10. Time to first occurrence of clinical deterioration in Stage B of ADHERE - overall and by stratification factors for randomisation (mITT analysis set, reproduced from Figure 13 of the CS)	91
Figure 11. Relative weight distributions of the ADHERE population following weighting adjustments. Reproduced from Appendix 8 of the ITC report	102
Figure 12. Model structure diagram, reproduced from Figure 18 in the company submission.....	120

Figure 13. Treatment pathway for the efgartigimod arm, Ig maintenance cohort (reproduced from Figure 14 of the company submission)	126
Figure 14. Treatment pathway for the efgartigimod arm, Ig maintenance cohort (reproduced from Figure 15 of the company submission)	127
Figure 15. Scatterplot of probabilistic analysis runs on a cost-effectiveness plane of efgartigimod versus established clinical management (reproduced from Figure 1 of Appendix 2 from the company's clarification response)	177
Figure 16. Cost-effectiveness acceptability curve (reproduced from Figure 2 of Appendix 2 from the company's clarification response)	177
Figure 17. Tornado plot (reproduced from Figure 3 of Appendix 2 from the company's clarification response)	180
Figure 18. Cost-effectiveness plane, Ig maintenance population.....	201
Figure 19. Cost-effectiveness plane, Ig-intolerant/refractory population.....	201
Figure 20. Cost-effectiveness acceptability curve, Ig maintenance population	202
Figure 21. Tornado plot of OWSA incremental NHB (Ig maintenance population).....	204
Figure 22. Tornado plot of deterministic sensitivity analysis incremental NHB (Ig-intolerant/refractory population).....	204
Figure 23. ADHERE and ADHERE+ study design. Reproduced from Figure 4 of the CS	229
Figure 24. Cost-effectiveness plane, mixed population.....	246
Figure 25. Cost-effectiveness acceptability curve, mixed population	246
Figure 26. Tornado plot of deterministic sensitivity analysis incremental NHB (mixed population) .	247
Figure 27. ICER convergence plot, Ig maintenance population	251
Figure 28. ICER convergence plot, Ig-intolerant/refractory population	251
Figure 29. ICER convergence plot, mixed population	252

List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
aINCAT	Adjusted Inflammatory Neuropathy Cause and Treatment score
BPI-SF	Brief Pain Inventory – Short Form
BNF	British National Formulary
CDAS	CIDP Disease Activity Status
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
CMAP	Compound muscle action potential
CS	Company submission
CVC	Central venous catheter
DSA	Deterministic sensitivity analysis
EAG	External Assessment Group
EAN/PNS	European Academy of Neurology/Peripheral Nerve Society
ECI	Evidence of clinical improvement
ECMD	Evidence of clinically meaningful deterioration
EFNS/PNS	European Federation of Neurological Societies/Peripheral Nerve Society
EQ-5D	EuroQol 5-Dimension
EQ-5D-5L	EuroQol 5-Dimension 3-Level
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EQ-5D-5L-VAS	EuroQol 5-Dimension 5-Level Visual Analogue Scale
ESS	Effective sample size
FcRn	Neonatal Fc receptor
fSCIg	Facilitated subcutaneous immunoglobulin
GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare professional
HCRU	Healthcare resource utilisation
HR	Hazard ratio
HRG	Healthcare Resource Groups
HRQoL	Health-related quality of life
HSE	Heath Survey for England
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
Ig	Immunoglobulin
IgG	Immunoglobulin G

INCAT	Inflammatory Neuropathy Cause and Treatment
IPD	Individual patient data
I-RODS	Inflammatory Rasch-built Overall Disability Scale
ITC	Indirect treatment comparison
IV	Intravenous
IVIg	Intravenous immunoglobulin
KM	Kaplan-Meier
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MGS	Mean grip strength
mITT	Modified intent to treat
MPSC	Medicines procurement supply chain
MRC	Medical Research Council
MS	Multiple sclerosis
NC	Not calculated
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds ratio
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PGIC	Patient's Global Impression of Change
PICC	Peripherally inserted central catheter
PLEX	Plasma exchange
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
q1w	Every week
q2w	Every two weeks
QALY	Quality-adjusted life year
rHuPH20	Recombinant human hyaluronidase PH20
RCT	Randomised controlled trial
RT-FSS	Rasch-transformed Fatigue Severity Scale
SAE	Serious adverse event
SC	Subcutaneous
SCIg	Subcutaneous immunoglobulin

SD	Standard deviation
SE	Standard error
SEE	Structured expert elicitation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SNAP	Sensory nerve action potential
STC	Simulated treatment comparison
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSQM-9	9-item Treatment Satisfaction Questionnaire for Medication
TUG	Timed up and Go
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

The EAG's key issues are summarised in Table 1.

Table 1. Summary of key issues

ID	Summary of issue	Impact on results	Report sections
1	Lack of alignment between the company's proposed population and the ADHERE trial	Large	2.3.1 and 3.2.3
2	Concerns about the trial design of ADHERE, which may have overestimated the effectiveness of efgartigimod	Large	3.2.1, 3.2.3, 3.3.2, 3.5.1, 3.6.1, 3.6.2 and 3.6.3
3	Different outcomes are used to assess clinical deterioration and established clinical improvement in ADHERE	Large	2.3.4, 3.2.1, 3.2.3 and 3.3.2
4	A high percentage of patients in the ADHERE trial who deteriorated following Ig discontinuation did not improve with efgartigimod	Medium	3.3.1.1
5	Considerable uncertainty in interpreting the results of the ITCs due to substantial methodological limitations	Large	3.6.1, 3.6.2 and 3.6.3

6	Uncertainty around the use of Ig in clinical practice	Large	4.2.2 and 4.2.12.1
7	Choice of cycle length for first two years	Large	4.2.3
8	Uncertainty around treatment pathway after discontinuing efgartigimod	Large	4.2.4
9	Lack of treatment effectiveness data for patients with severe disease	Large	4.2.7.1
10	Approach to modelling treatment effectiveness and discontinuation in the comparator arm	Large	4.2.7.2 and 4.2.8.2
11	Uncertainty around AEs	Large	4.2.10
12	Approach to modelling caregiver burden	Large	4.2.13

Abbreviations: AE, adverse event; EAG, External Assessment Group; Ig, immunoglobulin.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions in the economic analysis are as follows:

- The EAG considers that some of the company's modelling approaches are not robust or appropriate, and has suggested appropriate alternatives;
- The EAG considers that many of the company's assumptions are biased in favour of efgartigimod;
- There is a large amount of uncertainty in the model inputs, and the EAG considers that in some cases more appropriate parameter values are available.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing patients' disease severity;
- Reducing the HRQoL impact of treatment administration;
- Reducing the impact on caregivers' quality of life.

Overall, the technology is modelled to affect costs by:

- A higher price than currently available treatments;

- Being predominantly self-administered subcutaneously at home, rather than intravenously at hospital;
- Reducing disease severity, and therefore reducing costs for disease monitoring, mobility aids, and hospitalisation;
- Reducing costs for professional caregiving.

The modelling assumptions that have the greatest effect on the ICER are:

- The dosages and products of Ig used in current clinical practice;
- The treatment pathway for patients following discontinuation of efgartigimod;
- Disease severity and treatment discontinuation for patients receiving comparator treatments;
- The impact of efgartigimod on patients with severe disease;
- The impact of efgartigimod on caregivers, and the costs of professional caregiving.

1.3 EAG's key issues

Table 2. Issue 1. Lack of alignment between the company's proposed population and the ADHERE trial

Report section	Sections 2.3, 2.3.1, 3.2.1 and 3.2.3
Description of issue and why the EAG has identified it as important	The company's proposed positioning of efgartigimod is for adults with CIDP who have had prior, unsatisfactory treatment with Ig (IVIg or SCIg) or patients who are intolerant or refractory to Ig. The definition of unsatisfactory treatment included: • patients who have a high burden of treatment (at least 6 months of IVIg or SCIg treatment, which has a significant impact on their daily life, working or caregiving responsibilities); or • patients who remain symptomatic or require high doses of Ig to experience the benefits of treatment and avoid symptom variation between doses. A high burden of treatment was further defined as patients who need IVIg treatment more frequently than every four weeks, are unable to tolerate more than half-maximal intravenous infusion rates due to side effects or contraindications, experience AEs that impact treatment tolerability or quality of life or have a schedule of Ig infusions that significantly impacts their daily life. The EAG has concerns that this patient population is not clearly represented by the patients included in the ADHERE trial. The key inclusion criteria for ADHERE were: • Patients who received treatment with pulsed corticosteroids, oral corticosteroids and/or IVIg or SCIg within the previous 6 months and were willing to discontinue the treatment; or • Patients who were treatment-naïve (including those who had not previously received treatment for CIDP or those who had not been treated with monthly or daily corticosteroids, IVIg or SCIg in the previous 6 months).

	Patients in the first of these categories (51.2% of all patients in Stage A of the ADHERE trial; 43.4% in Stage B) are most likely to reflect the company's proposed population. However, patients were not required to have Ig treatment for 6 months prior to enrolment in the trial and insufficient information was collected during the trial to determine which of these patients met the company's criteria for unsatisfactory treatment. It is therefore unclear how many patients in ADHERE are relevant to the company's proposed population. Patients in the treatment-naïve group would not meet the company's criteria for a high burden of Ig treatment, and information about whether these patients were intolerant or refractory to Ig was not recorded in ADHERE. Additionally, 10.6% of patients in Stage A of ADHERE had no prior treatment for CIDP and are therefore not representative of the company's proposed population. It is unclear what percentage of these patients progressed to Stage B of ADHERE. The issues outlined above mean that it is not possible to determine how many patients in ADHERE met the company's criteria for a high burden of treatment, and there appears to be no evidence for patients who are intolerant or refractory to Ig.
What alternative approach has the EAG suggested?	ADHERE is the only trial which provides comparisons between efgartigimod and placebo. With insufficient information from ADHERE to determine whether patients met the company's criteria for unsatisfactory treatment, it is difficult to resolve concerns about the applicability of the trial evidence to the company's proposed population. The EAG has instead acknowledged the above concerns in its discussions regarding the population and the trial design and results of ADHERE.
What is the expected effect on the cost-effectiveness estimates?	The impact of this issue on cost-effectiveness is unclear, as the economic model is heavily reliant on model inputs sourced from the ADHERE trial, and no appropriate alternatives are available.
What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider it possible to resolve this issue with the evidence available from the ADHERE trial. The most appropriate approach would be to develop a clinical trial with inclusion criteria which are based on the company's proposed population. Alternatively, the company's definition of the population could be updated to more closely match the population included in the ADHERE trial.
Abbreviations: AEs, adverse events; CIDP, Chronic inflammatory demyelinating polyneuropathy; EAG, External Assessment Group; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin	

Table 3. Issue 2. Concerns about the trial design of ADHERE, which may have overestimated the effectiveness of efgartigimod

Report section	3.2.1, 3.2.3, 3.3.2, 3.5.1, 3.6.1, 3.6.2 and 3.6.3
Description of issue and why the EAG has identified it as important	ADHERE used a randomised withdrawal design, with the trial separated into 3 stages following the screening period: - Run-in period: All patients discontinued treatment for CIDP; - Stage A: 12-week open-label phase where all patients received efgartigimod;

	Stage B: Randomised withdrawal phase of up to 48 weeks, where patients were randomised to efgartigimod or placebo. Only patients with established clinical improvement with efgartigimod in Stage A progressed to the randomised phase of the trial (Stage B). Results of Stage B of ADHERE therefore, reflect only those patients who responded to efgartigimod, rather than the wider CIDP population. This may have resulted in an overestimation of treatment effects and an underestimation of adverse events with efgartigimod. These concerns impact both the direct comparison with placebo in the ADHERE trial, and the indirect comparisons with SCIg in the ADVANCE-CIDP 1 trial, which used an RCT design and did not exclude non-responders.
What alternative approach has the EAG suggested?	ADHERE is the only trial which provides comparisons between efgartigimod and placebo. It is therefore difficult to address the concerns about trial design for the comparison with placebo. For comparisons with Ig, the EAG notes that other trials identified in the company's SLR (PATH and ICE) had a more similar design to that of ADHERE. The PATH trial, on which the trial design of ADHERE was based, compared SCIg to placebo, and also included a run-in period, open-label phase and randomised withdrawal phase where non-responders were excluded. In the ICE trial, patients were randomised to IVIg or placebo. Patients who showed a response during the main phase of the trial progressed to the extension phase, where they were re-randomised to either IVIg or placebo. The EAG requested additional comparisons with the PATH and ICE trials. The company provided the requested ITCs for three outcomes (change in aINCAT, I-RODS and MGS). While the EAG considers the PATH and ICE trials to be associated with fewer concerns about heterogeneity in trial design than ADVANCE-CIDP 1, both trials are associated with other methodological concerns which limit their use in decision making (see Issue 3, Table 4). The EAG has therefore provided a critique of the ITCs with ADVANCE-CIDP 1, PATH and ICE and acknowledged the limitations associated with each comparison.
What is the expected effect on the cost-effectiveness estimates?	The impact of this issue on cost-effectiveness is unclear, as the economic model is heavily reliant on model inputs sourced from the ADHERE trial, and no appropriate alternatives are available. However, it is likely that the company's economic analysis overestimates the cost-effectiveness of efgartigimod.
What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider it possible to resolve this issue or determine the magnitude of the overestimation of the treatment effect with the evidence available from the ADHERE trial. The most appropriate approach would be to develop a clinical trial with an RCT design which does not exclude efgartigimod non-responders.
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, Chronic inflammatory demyelinating polyneuropathy; EAG, External Assessment Group; I-RODS, Inflammatory Rasch-built Overall Disability Scale; ITC, indirect treatment comparison; IVIg, intravenous immunoglobulin; MGS, mean grip strength; RCT, randomised controlled trial; SCIg, subcutaneous immunoglobulin	

Table 4. Issue 3. Different outcomes are used to assess clinical deterioration and established clinical improvement in ADHERE

Report section	2.3, 2.3.4, 3.2.1, 3.2.3 and 3.3.2
Description of issue and why the EAG has identified it as important	During the run-in stage of ADHERE, all patients discontinued CIDP treatment and clinical deterioration was assessed using a range of outcomes, including an increase in aINCAT score ≥ 1 point, a decrease in I-RODS ≥ 4 points or a decrease in mean grip strength (MGS) ≥ 8 kPa. The EAG's clinical experts indicated that this reflects clinical practice, where decisions are usually made based on a combination of measures, rather than on a single outcome. During Stage A of ADHERE, all patients were given efgartigimod and established clinical improvement was assessed using the same measures as those used during the run-in stage. Improvement was measured relative to Stage A baseline: - For patients who skipped the run-in phase or deteriorated on aINCAT during the run-in stage: aINCAT score improvement ≥ 1 point; - For patients with no aINCAT change during run-in but deterioration on I-RODS and/or MGS: improvement in either aINCAT score ≥ 1 point, I-RODS ≥ 4 points or mean grip strength of ≥ 8 kPa. During Stage B of ADHERE, patients who demonstrated established clinical improvement during Stage A were randomised to either efgartigimod or placebo. Unlike the previous stages of the trial, which assessed change in disease status using a range of outcomes, relapse in Stage B was assessed solely based on change in aINCAT score. The EAG considers that the use of aINCAT as the sole measure for identifying relapse following randomisation will have underestimated the number of patients who experienced relapse during Stage B. It notes that patients will not have been considered to have relapsed if they showed a decline in I-RODS or MGS during Stage A, but no accompanying decline in aINCAT scores.
What alternative approach has the EAG suggested?	The EAG requested clarification from the company about the potential effects of patients not being classified as having relapsed in Stage B if their deterioration was on I-RODS or MGS rather than aINCAT. The company acknowledged that this approach could underestimate the number of patients who relapsed, but expected that any underestimation would be similar for both trial arms due to consistency in visit schedules and the definition of relapse. The company also reported that I-RODS and MGS were secondary outcomes, the results of which were consistent with those reported for relapse in terms of benefits of efgartigimod over placebo. The EAG has acknowledged the company's justification for the choice of relapse outcome, alongside its own critique of the approach, when assessing the results from ADHERE.
What is the expected effect on the cost-effectiveness estimates?	The impact of this issue on cost-effectiveness is unclear, as the economic model is heavily reliant on model inputs sourced from the ADHERE trial, and no appropriate alternatives are available.

What additional evidence or analyses might help to resolve this key issue?	Additional analyses which assessed relapse based on a combination of changes in aINCAT, I-RODS and MGS would be useful to reduce the uncertainty in the magnitude of the benefits of efgartigimod over placebo.
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, Chronic inflammatory demyelinating polyneuropathy; EAG, External Assessment Group; I-RODS, Inflammatory Rasch-built Overall Disability Scale; MGS, mean grip strength	

Table 5. Issue 4. A high percentage of patients in the ADHERE trial who deteriorated following Ig discontinuation did not improve with efgartigimod

Report section	3.3.1.1
Description of issue and why the EAG has identified it as important	Only patients who demonstrated clinical deterioration during the run-in phase (following the discontinuation of CIDP treatment) progressed to Stage A of ADHERE, where all patients were given efgartigimod. In the subgroup of patients who had prior IVIg or SCIg (those most relevant to the company's proposed population), 59% demonstrated established clinical improvement by the end of Stage A. Consequently, 41% of patients who previously had stable disease with Ig did not experience similar benefits with efgartigimod. This is a concern, as it suggests that many patients may experience poorer outcomes if they decide to switch maintenance treatment from Ig to efgartigimod.
What alternative approach has the EAG suggested?	Stage A of ADHERE was designed to identify efgartigimod responders rather than to identify differences between patients who did, or did not, respond to efgartigimod. The EAG has acknowledged its concerns about the low efgartigimod response rate in its critique of the ADHERE trial.
What is the expected effect on the cost-effectiveness estimates?	The impact of this issue on cost-effectiveness is unclear, as the economic model is heavily reliant on model inputs sourced from the ADHERE trial, and no appropriate alternatives are available.
What additional evidence or analyses might help to resolve this key issue?	A <i>post-hoc</i> analysis comparing efgartigimod responders and non-responders in Stage A of ADHERE might provide an indication of which patients tend to respond to efgartigimod. An analysis of the patients previously treated with IVIg or SCIg would be most relevant to the company's proposed population.
Abbreviations: CIDP, Chronic inflammatory demyelinating polyneuropathy; EAG, External Assessment Group; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin	

Table 6. Issue 5. Considerable uncertainty interpreting the results of the ITCs due to substantial methodological limitations

Report section	3.6.1, 3.6.2 and 3.6.3
Description of issue and why the EAG has identified it as important	The EAG considers the company's ITC comparing change in aINCAT between efgartigimod and SCIg (ADHERE vs ADVANCE-CIDP 1 trials) to be associated with a number of limitations. These include: • Uncertainty over how many patients met the company's definition of unsatisfactory treatment; • Differences in trial design; • Comparisons between patients who previously responded to efgartigimod (ADHERE) and all patients (ADVANCE-CIDP 1); • Concerns about weighting adjustments in the MAIC; • Differences in placebo response between the trials.

	These issues result in considerable uncertainty when interpreting the results and make it difficult to draw any strong conclusions about the relative effectiveness of efgartigimod and SCIg. Concerns about the robustness of the ITC also has limitations for its use in the economic model.
What alternative approach has the EAG suggested?	The EAG identified two trials (PATH and ICE) which it considered had fewer concerns about trial design than comparisons between ADVANCE-CIDP-1 and ADHERE. The company provided ITCs for these trials for change in aINCAT, I-RODS and mean grip strength. However, in addition to the same concerns outlined above for ADVANCE-CIDP-1 (alignment with the company's proposed population, weighting adjustments and different placebo responses), PATH and ICE were each associated with additional limitations, leading to further uncertainties when interpreting the results. The EAG has acknowledged the limitations associated with comparisons with each of the three trials in its critique of the ITCs. Given the concerns about the robustness of these analyses, results of the ITCs have not been used to inform the economic modelling.
What is the expected effect on the cost-effectiveness estimates?	While the company has used the ITC to inform treatment effectiveness in the comparator arm in the economic model, the EAG considers that this approach is inappropriate (see Section 4.2.7.2 for further details). The ITC is not used in the EAG's preferred base case.
What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider it possible to resolve this issue without further information on the number of patients who meet company's criteria for unsatisfactory treatment in ADHERE and each of the comparator trials, or without additional baseline characteristics from the comparator trials. In the absence of this information, an RCT directly comparing efgartigimod with Ig would provide a more robust comparison, which would be directly relevant to the treatment pathway in the NHS.
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, Chronic inflammatory demyelinating polyneuropathy; EAG, External Assessment Group; ITC, indirect treatment comparison; I-RODS, Inflammatory Rasch-built Overall Disability Scale; RCT, randomised controlled trial	

Table 7. Issue 6. Uncertainty around the use of Ig in clinical practice

Report section	4.2.2 and 4.2.12.1
Description of issue and why the EAG has identified it as important	The company has made several assumptions about the dosages and brands of Ig that are used in clinical practice. In particular, the company assumed the following: • The proportion of patients on each dosage of Ig was sourced from the company's SEE; • The split of patients between IVIg and SCIg was informed by the company's chart review. These assumptions have a large impact on the cost-effectiveness of efgartigimod.
What alternative approach has the EAG suggested?	The EAG suggested the following approach: • The proportion of patients on each dosage of Ig was sourced from the final data cut of the company's chart review; • The split of patients between IVIg and SCIg was informed by the Immunoglobulin Database Annual Report. The EAG considers these sources of input values to be more robust than the sources used by the company.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY) Company base case after corrections + EAG-preferred approach for modelling Ig use (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY)
What additional evidence or analyses might help to resolve this key issue?	Further robust evidence related to the usage of Ig in clinical practice would resolve this key issue; however, the EAG has been unable to identify any appropriate alternative sources of data.
Abbreviations: EAG, External Assessment Group; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; NHB, net health benefit; SCIg, subcutaneous immunoglobulin.	

Table 8. Issue 7. Choice of cycle length for first two years

Report section	4.2.3
Description of issue and why the EAG has identified it as important	In the company's base case, the economic model used a six-month cycle length for the entire time horizon. The EAG considers that this approach gives insufficient granularity at early timepoints, and is misaligned with the timepoints at which the data informing various model inputs were observed.
What alternative approach has the EAG suggested?	The EAG's preference is to use a three-month cycle length for the first two years from baseline.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY) Company base case after corrections + three-month cycle length (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY)
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is necessary.
Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHB, net health benefit.	

Table 9. Issue 8. Uncertainty around treatment pathway after discontinuing efgartigimod

Report section	4.2.4
Description of issue and why the EAG has identified it as important	The company informed the proportion of patients receiving each subsequent treatment after discontinuing efgartigimod by the company's SEE. However, the EAG considers that these input values are implausible; in particular, the EAG's clinical experts considered that the proportion of patients returning to Ig treatment after discontinuing efgartigimod would be much higher than the estimate from the company's SEE, which was based on a potentially misleading question to the company's clinical experts. The input values for these parameters have a large impact on the cost-effectiveness of efgartigimod.
What alternative approach has the EAG suggested?	The EAG's preferred approach is to assume that all patients who were on Ig maintenance at baseline would return to Ig treatment after discontinuing efgartigimod.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY) Company base case after corrections + EAG-preferred approach for modelling treatment pathway after efgartigimod: ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY)
What additional evidence or analyses might help to resolve this key issue?	Further robust evidence related to the treatment pathway for patients after discontinuing efgartigimod would help to resolve this key issue; however, the EAG has been unable to identify any appropriate alternative sources of data.
Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; SEE, structured expert elicitation.	

Table 10. Issue 9. Lack of treatment effectiveness data for patients with severe disease

Report section	4.2.7.1
Description of issue and why the EAG has identified it as important	Very few patients in the ADHERE and ADHERE+ trials had aINCAT scores corresponding to the severe impairment and very severe impairment health states in the economic model at any point (i.e. aINCAT scores of 7-10). Therefore, there are very few data to inform treatment effectiveness for patients in these health states. The approach to modelling treatment effectiveness for these health states has a large impact on the cost-effectiveness of efgartigimod.
What alternative approach has the EAG suggested?	The EAG has suggested that, in the absence of more robust data, it is assumed that all patients in the severe impairment and very severe impairment health states remain in these health states indefinitely.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY) Company base case after corrections + EAG-preferred approach for modelling patients with severe disease: ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY)
What additional evidence or analyses might help to resolve this key issue?	The availability of more treatment effectiveness data for patients with aINCAT score of 7-10 would resolve this key issue.
Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; EAG, External Assessment Group; NHB, net health benefit.	

Table 11. Issue 10. Approach to modelling treatment effectiveness and discontinuation in the comparator arm

Report section	4.2.7.2 and 4.2.8.2
Description of issue and why the EAG has identified it as important	The company's approach to modelling treatment effectiveness for comparator treatments relies on an inappropriate methodology to derive transition probabilities, and is logically incompatible with the company's assumption that, in the long term, patients on maintenance treatment of any kind will not experience changes in disease severity. Similarly, the company's assumption that patients may discontinue Ig in the first few cycles of the model despite already on maintenance treatment, but would not discontinue comparator treatments thereafter due to being on maintenance treatment, is not logically coherent. The approach to modelling the comparator arm has a large impact on the cost-effectiveness of efgartigimod.
What alternative approach has the EAG suggested?	The EAG has suggested conservatively that patients in the comparator arm are assumed not to change disease severity or discontinue treatment at any point.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY) Company base case after corrections + EAG-preferred approach for modelling comparator arm: ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY)
What additional evidence or analyses might help to resolve this key issue?	The EAG has been unable to identify a more appropriate approach within the company's model framework.
Abbreviations: EAG, External Assessment Group; Ig, immunoglobulin; NHB, net health benefit; SEE, structured expert elicitation.	

Table 12. Issue 11. Uncertainty around AEs

Report section	4.2.10
Description of issue and why the EAG has identified it as important	There are very few data informing frequency, costs and HRQoL impact of AEs for any treatment included in the economic model. What data are available are extremely heterogeneous, and are not consistently reported between different treatments. The approach to modelling AEs has a large impact on the cost-effectiveness of efgartigimod.
What alternative approach has the EAG suggested?	Due to the flaws in the company's approach, the EAG has suggested removing the impact of AEs altogether.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY) Company base case after corrections + AEs removed: ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY)
What additional evidence or analyses might help to resolve this key issue?	More availability of robust and consistent data related to AEs would resolve this key issue.
Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; EAG, External Assessment Group; NHB, net health benefit.	

Table 13. Issue 12. Approach to modelling caregiver burden

Report section	4.2.13
Description of issue and why the EAG has identified it as important	The EAG does not agree with the company's approach to modelling caregiver burden. In particular: • The company's inclusion of both HRQoL impact on informal caregivers and costs for professional caregivers may lead to double-counting; • The source used to parametrise the HRQoL impact on informal caregivers is inappropriate; • The company's estimates of the number of caregivers required by each individual is too high; • The company's approach to costing professional caregiving likely overestimates the proportion of patients who will be able to access professional care funded by the NHS/PSS.
What alternative approach has the EAG suggested?	The EAG has suggested excluding costs for professional caregiving altogether. The EAG has also proposed alternative approaches for parametrising the HRQoL impact on informal carers and the number of informal carers per patient.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is [REDACTED], incremental NHB is [REDACTED] (£30,000/QALY) Company base case after corrections + EAG-preferred approach for modelling caregiver burden: ICER is [REDACTED], incremental NHB is [REDACTED] (£30,000/QALY)
What additional evidence or analyses might help to resolve this key issue?	More availability of robust data related to caregiver burden would resolve this key issue.
Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; EAG, External Assessment Group; NHB, net health benefit.	

1.4 Secondary issues identified by the EAG

The EAG has several secondary issues related to the company's approach and assumptions in the economic analysis, as described in the following tables.

Table 14. Issue 1. Inclusion of biweekly dosing of efgartigimod

Report section	3.3.3.2, 4.2.12.1
Description of issue and why the EAG has identified it as important	In the ADHERE+ open-label extension, patients were eligible to move from weekly to biweekly dosing of efgartigimod if they had remained on treatment for at least 24 weeks. Of the patients who switched to biweekly dosing, only [REDACTED] of patients remained stable on biweekly dosing. Of those who deteriorated on biweekly dosing, [REDACTED] did not return to stable levels of disease. The company also reflected this in the economic analysis, by assuming that [REDACTED] of patients receiving efgartigimod would be on a biweekly dosing schedule indefinitely, from six months from baseline. The EAG is unsure to what extent the use of biweekly dosing would be considered appropriate in clinical practice, given that a large proportion of patients were not stable on this dosing schedule. The inclusion of the biweekly dosing schedule has a considerable impact on the ICER.
What alternative approach has the EAG suggested?	The EAG has retained the biweekly dosing pattern in the EAG's base case, but has explored the impact of restricting all patients to a weekly dosing pattern in a scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is [REDACTED], incremental NHB is [REDACTED] (£30,000/QALY) Company base case after corrections + biweekly dosing is excluded: ICER is [REDACTED], incremental NHB is [REDACTED] (£30,000/QALY)
What additional evidence or analyses might help to resolve this secondary issue?	Further evidence around the proportion of patients who would be on a biweekly dosing schedule for efgartigimod in clinical practice may help resolve this issue.
Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IV, intravenous; IVIg, intravenous immunoglobulin; NHB, net health benefit; PLEX, plasma exchange.	

Table 15. Issue 2. Appropriateness of HSUVs

Report section	4.2.11.1
Description of issue and why the EAG has identified it as important	The HSUVs included in the model were informed by a regression model fitted to HRQoL data collected in the ADHERE trial. The EAG had several concerns around the company's approach, as follows: • The EAG considers that the derived HSUV for the most severe impairment health state lacks face validity; • The regression model fitted to HRQoL data was overly simplistic; • The attrition rate of HRQoL data collected from ADHERE appeared to be high, potentially resulting in bias in the resulting HSUVs; • The company used a complete case analysis approach rather than imputing missing values. The approach to modelling HSUVs has a moderate impact on the ICER.
What alternative approach has the EAG suggested?	The EAG was unable to identify appropriate alternative HSUVs, but has suggested using the company's HSUVs for all health states except for the very severe impairment health state, for which the HSUV was set to zero.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY) Company base case after corrections + EAG-preferred approach for modelling HSUVs: ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY)
What additional evidence or analyses might help to resolve this secondary issue?	A more robust analysis of HRQoL data from the ADHERE trial may help to resolve this issue.
Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; NHB, net health benefit.	

Table 16. Issue 3. Approach to modelling HRQoL impact of IV administrations

Report section	4.2.10.2 and 4.2.11.4
Description of issue and why the EAG has identified it as important	The company stated that a key benefit of efgartigimod is avoiding IV administrations, which can have a considerable negative impact on patients' HRQoL. The company, therefore, included utility decrements related to IV administrations, as follows: • A general utility decrement associated with IV administrations was applied; • An additional decrement was applied, related to IV administrations in a hospital setting; • An additional decrement was applied, related to the frequency of IV administrations; • An additional decrement was applied, related to the expected duration of IV administrations; • Additional decrements were applied to reflect the impact of complications associated with IV administration. The EAG considered that the company included too many utility decrements related to IV administrations, and that there was a high risk of double-counting. The approach to modelling the HRQoL impact of IV administrations has a moderate impact on the ICER.
What alternative approach has the EAG suggested?	The EAG has suggested excluding all utility decrements associated with IV administration, with the exception of the 'baseline' utility decrement.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY) Company base case after corrections + EAG-preferred approach to modelling HRQoL impact of IV administrations: ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY)
What additional evidence or analyses might help to resolve this secondary issue?	More robust evidence related to the HRQoL impact of IV administrations on patients treated with IVIg and PLEX may help to resolve this issue.
Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IV, intravenous; IVIg, intravenous immunoglobulin; NHB, net health benefit; PLEX, plasma exchange.	

Table 17. Issue 4. Approach to modelling resource use and costs

Report section	4.2.12.2, 4.2.12.3, 4.2.12.4 and 0
Description of issue and why the EAG has identified it as important	The EAG has multiple concerns around the company's assumptions around costs for disease monitoring, mobility aids and hospitalisation. In particular: • The company assumed that patients receiving Ig would require funded transportation to receive treatment in a hospital setting, but patients receiving efgartigimod would not; • The company assumed that if SCIg was administered in hospital, it would be administered over multiple days; • The company assumed that some patients would receive IVIg in an inpatient setting; • GP surgery consultations were assumed to have a duration of one hour; • The proportion of patients requiring a wheelchair was informed by an inappropriate source; • The cost for an ICU visit was informed by an inappropriate source. Individually, these issues have a small to moderate effect on the ICER for efgartigimod.
What alternative approach has the EAG suggested?	The EAG has suggested the following alternative approaches: • The EAG assumed that all patients requiring treatment administration in a hospital setting would require funded transportation; • The EAG assumed that SCIg would only be administered on one day per week in a hospital setting; • The EAG assumed that all patients would receive IVIg in an outpatient setting; • The EAG assumed that a GP surgery consultation would have a duration of ten minutes; • The EAG proposed more appropriate sources for the proportion of patients requiring a wheelchair, and the cost for an ICU visit.
What is the expected effect on the cost-effectiveness estimates?	Company base case after corrections (deterministic analysis): ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY) Company base case after corrections + EAG-preferred approach to modelling resource use and costs: ICER is ■■■, incremental NHB is ■■■ (£30,000/QALY)
What additional evidence or analyses might help to resolve this secondary issue?	More robust evidence around HCRU needs for patients with CIDP may help to resolve this issue.
Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; EAG, External Assessment Group; GP, general practitioner; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; IVIg, intravenous immunoglobulin; NHB, net health benefit; SCIg, subcutaneous immunoglobulin.	

1.5 Company's modelling errors identified by the EAG

The EAG identified multiple modelling errors, both at the clarification stage, and post-clarification. A summary of the key errors identified by the EAG is given in Table 18. A full list of the EAG's corrections is given in Appendix 7.1.

Table 18. Summary of post-clarification errors in the economic model identified by the EAG

Description of error	Impact of error
Multiple errors in the implementation of costs and AE impacts for the first cycle in the efgartigimod arm, when accounting for the induction period.	Affects EAG base case and company base case
Error in the baseline distribution for Ig-refractory population non-responders in the efgartigimod arm.	Affects EAG base case and company base case
Multiple errors in the implementation of the three-month cycle length, including failure to adjust mortality rates, failure to adjust starting point for biweekly dosing, and other minor errors.	Affects EAG base case but does not affect company base case
Error in the implementation of the analysis in which professional caregiver costs are removed (costs for all interactions with HCPs were mistakenly removed).	Affects EAG base case but does not affect company base case
Multiple errors in the implementation of the probabilistic analysis, including incorrect implementation of sampling of beta-distributed random variables, unstable implementation of Dirichlet distribution sampling for transition probabilities, and other minor errors.	Led to misalignment between probabilistic and deterministic results
Abbreviations: AE, adverse event; EAG, External Assessment Group; HCP, healthcare provider.	

1.6 Summary of EAG's preferred assumptions and resulting ICER

A summary of the EAG's preferred assumptions is given in Table 19 and Table 20. Results are presented separately for patients who are on Ig maintenance treatment at baseline, and patients who are intolerant of Ig or refractory to Ig at baseline, as the comparators are different: Ig is the comparator for the former population, and a basket of alternative treatments including corticosteroids, immunosuppressants, and plasma exchange (PLEX) is the comparator for the latter population. Results have been presented deterministically, due to time constraints, and the large number of assumptions considered.

For further details of the exploratory and sensitivity analyses done by the EAG, see Sections 5.2.2 and 5.2.4.

Table 19. Summary of EAG's preferred assumptions and resulting ICER (Ig maintenance population)

Scenario	Incremental costs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
Company base case (post-clarification, after EAG corrections)	■	4.27	■	■	■
Three-month cycle length applied for first two years (Key Issue 7)	■	4.50	■	■	■
Proportion of corticosteroids in alternative treatment basket sourced from company's chart review	■	4.26	■	■	■
Proportion of patients on PLEX who return to Ig: 95%	■	4.21	■	■	■
Assume 95% of cohort restarts Ig after discontinuation of efgartigimod (Key Issue 10)	■	4.19	■	■	■
Proportion of patients on each Ig dose sourced from company's chart review (final data cut) (Key Issue 6)	■	4.21	■	■	■
Ig-intolerant/refractory patients distributed according to baseline distribution from ADHERE run-in at model baseline	■	4.27	■	■	■
Patients do not move between aINCAT categories in the comparator arm (Key Issue 10)	■	2.17	■	■	■
Patients in the severe and very severe aINCAT categories do not move to other health states (Key Issue 9)	■	3.99	■	■	■
Half of patients move to a more severe health state following relapse	■	4.67	■	■	■
Remission is applied in the first two years, with three-month cycle length	■	4.20	■	■	■
Transition probabilities are derived from adjusted six-month probabilities, with three-month cycle length	■	5.37	■	■	■
Unplanned discontinuation of Ig is not included (Key Issue 10)	■	4.29	■	■	■
AEs excluded for all treatments (Key Issue 11)	■	4.17	■	■	■
AEs for IV administrations are excluded (Secondary Issue 3)	■	4.26	■	■	■
HSUV in the very severe health state is set to 0 (Secondary Issue 2)	■	4.18	■	■	■
Duration of Ig infusions based on data in the CS	■	4.13	■	■	■

Scenario	Incremental costs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
Disutility of IV administration based on Jørgensen <i>et al.</i> 2017 and considering only the coefficient for route of administration (Secondary Issue 3)	■	3.52	■	■	■
IVIg/SCIg split informed by the Immunoglobulin Database Annual Report (Key Issue 6)	■	4.06	■	■	■
Ig and efgartigimod patients require funded transportation (Secondary Issue 4)	■	4.27	■	■	■
Administration cost for SCIg set equal to efgartigimod (Secondary Issue 4)	■	4.27	■	■	■
SCIg treatment is administered once per week in hospital (Secondary Issue 4)	■	4.27	■	■	■
IVIg is administered in an outpatient setting (Secondary Issue 4)	■	4.27	■	■	■
Duration of GP surgery consultation is set to 10 minutes (Secondary Issue 4)	■	4.27	■	■	■
Proportion of patients requiring a wheelchair is informed by the company's Adelphi study, disaggregated by aINCAT score (Secondary Issue 4)	■	4.27	■	■	■
Cost of ICU visit sourced from PSSRU (Secondary Issue 4)	■	4.27	■	■	■
Professional care costs excluded (Key Issue 12)	■	4.27	■	■	■
Patient requirements for caregivers aligned with UK Adelphi study data, with maximum 1 caregiver (Key Issue 12)	■	3.79	■	■	■
Caregiver utility decrement sourced from company caregiver survey (Key Issue 12)	■	3.53	■	■	■
EAG's preferred base case (all above scenarios combined)	■	1.27	■	■	■

Abbreviations: AE, adverse event; aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; CS, company submission; EAG, External Assessment Group; GP, general practitioner; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; Ig, immunoglobulin; IV, intravenous; IVIg, intravenous immunoglobulin; NHB, net health benefit; PLEX, plasma exchange; PSSRU, Personal Social Services Research Unit; QALY, quality adjusted life year; SCIg, subcutaneous immunoglobulin.

Table 20. Summary of EAG's preferred assumptions and resulting ICER (Ig-intolerant/refractory population)

Scenario	Incremental costs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
Company base case (post-clarification, after EAG corrections)	■	4.04	■	■	■
Three-month cycle length applied for first two years (Key Issue 7)	■	3.72	■	■	■
Proportion of corticosteroids in alternative treatment basket sourced from company's chart review	■	3.93	■	■	■
Proportion of patients on PLEX who return to Ig: 95%	■	3.44	■	■	■
Assume 95% of cohort restarts Ig after discontinuation of efgartigimod (Key Issue 10)	■	4.04	■	■	■
Proportion of patients on each Ig dose sourced from company's chart review (final data cut) (Key Issue 6)	■	3.93	■	■	■
Ig-intolerant/refractory patients distributed according to baseline distribution from ADHERE run-in at model baseline	■	4.03	■	■	■
Patients do not move between aINCAT categories in the comparator arm (Key Issue 10)	■	1.70	■	■	■
Patients in the severe and very severe aINCAT categories do not move to other health states (Key Issue 9)	■	3.76	■	■	■
Half of patients move to a more severe health state following relapse	■	3.08	■	■	■
Remission is applied in the first two years, with three-month cycle length	■	3.76	■	■	■
Transition probabilities are derived from adjusted six-month probabilities, with three-month cycle length	■	4.49	■	■	■
Unplanned discontinuation of Ig is not included (Key Issue 10)	■	4.04	■	■	■
AEs excluded for all treatments (Key Issue 11)	■	4.03	■	■	■
AEs for IV administrations are excluded (Secondary Issue 3)	■	4.04	■	■	■
HSUV in the very severe health state is set to 0 (Secondary Issue 2)	■	3.95	■	■	■
Duration of Ig infusions based on data in the CS	■	4.11	■	■	■

Scenario	Incremental costs	Incremental QALYs	ICER	Incremental NHB at £20,000	Incremental NHB at £30,000
Disutility of IV administration based on Jørgensen <i>et al.</i> 2017 and considering only the coefficient for route of administration (Secondary Issue 3)	■	3.73	■	■	■
IVIg/SCIg split informed by the Immunoglobulin Database Annual Report (Key Issue 6)	■	4.04	■	■	■
Ig and efgartigimod patients require funded transportation (Secondary Issue 4)	■	4.04	■	■	■
Administration cost for SCIg set equal to efgartigimod (Secondary Issue 4)	■	4.04	■	■	■
SCIg treatment is administered once per week in hospital (Secondary Issue 4)	■	4.04	■	■	■
IVIg is administered in an outpatient setting (Secondary Issue 4)	■	4.04	■	■	■
Duration of GP surgery consultation is set to 10 minutes (Secondary Issue 4)	■	4.04	■	■	■
Proportion of patients requiring a wheelchair is informed by the company's Adelphi study, disaggregated by aINCAT score (Secondary Issue 4)	■	4.04	■	■	■
Cost of ICU visit sourced from PSSRU (Secondary Issue 4)	■	4.04	■	■	■
Professional care costs excluded (Key Issue 12)	■	4.04	■	■	■
Patient requirements for caregivers aligned with UK Adelphi study data, with maximum 1 caregiver (Key Issue 12)	■	3.45	■	■	■
Caregiver utility decrement sourced from company caregiver survey (Key Issue 12)	■	3.14	■	■	■
EAG's preferred base case (all above scenarios combined)	■	0.31	■	■	■

Abbreviations: AE, adverse event; aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; CS, company submission; EAG, External Assessment Group; GP, general practitioner; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; Ig, immunoglobulin; IV, intravenous; IVIg, intravenous immunoglobulin; NHB, net health benefit; PLEX, plasma exchange; PSSRU, Personal Social Services Research Unit; QALY, quality adjusted life year; SCIg, subcutaneous immunoglobulin.

1.7 Outline of confidential comparator or subsequent treatment prices

Confidential medicines procurement supply chain (MPSC) prices are available for some Ig products (Gamunex and Hizentra) and so the EAG has produced a confidential appendix to this report. Please refer to Section 5.4 for further details on analyses included in the confidential appendix.

2 Background

This report critiques the company submission (CS) for efgartigimod (Vyvgart®, argenx) for chronic inflammatory demyelinating polyneuropathy (CIDP). The anticipated marketing authorisation for efgartigimod in this indication is, “as monotherapy for the treatment of adult patients with progressive or relapsing active CIDP after prior treatment with corticosteroids or immunoglobulins”.

2.1 Critique of the company’s description of underlying health problem

The company submission (CS) provides an overview of CIDP, including the cause, prevalence, pathophysiology, diagnosis, and symptom burden (Section 1.3). It also provides a description of efgartigimod, its mechanism of action, indication, and methods of administration and dosage (Section 1.2 of the CS). Included below is the EAG’s summary of the key background information presented in the CS, supplemented by information provided by the EAG’s clinical experts.

CIDP is a rare autoimmune disorder, with up to 650 patients diagnosed every year in the UK.¹ It can occur at any age and has a higher prevalence in males. In CIDP, pathogenic autoantibodies, particularly immunoglobulin G (IgG), cause the inflammatory-mediated demyelination of nerve fibres, resulting in peripheral neuropathy alongside muscle weakness and sensory deficits which can affect both the upper and lower limbs. Numbness, paraesthesia, and diminished touch sensation are common symptoms, which can reduce balance and restrict mobility, resulting in many patients requiring a walking aid and experiencing difficulties in completing everyday tasks. Many patients with CIDP require assistance to manage their symptoms, with the CS reporting that almost 75% of patients in the UK receive support from a caregiver.²

The most common form of the disorder is typical CIDP, experienced by over half of all CIDP patients. Typical CIDP results in muscle weakness of the upper and lower limbs, sensory disturbances in at least two limbs and no, or reduced, tendon reflexes in all limbs. There are also variant phenotypes of CIDP, including distal, multifocal, focal, motor and sensory CIDP (Table 21). The reported frequency of each of these phenotypes varies (between 31% to 48% of the CIDP population) depending on the definition used by different studies.³ The CS notes that the symptoms experienced by patients who are initially diagnosed with one of the variant phenotypes tend to evolve into a more typical CIDP presentation as the disease progresses. In addition to the different phenotypes, patients can have either progressive (gradual neurological worsening developing over at least eight weeks) or relapsing-remitting (discrete relapses of neurological worsening separate by periods of improvement

or stability) disease. Despite these differences in diagnoses, all patients are considered part of a single treatment population who follow a similar treatment pathway.

Currently there is no specific guidance for the diagnosis and treatment of CIDP in the UK. The CS reports that diagnosis requires symptoms to persist for at least 8 weeks and includes the use of electrodiagnostic testing and clinical assessment, with different symptoms observed for typical CIPD and the variant phenotypes. In the absence of UK-based guidelines, clinicians predominantly use either the 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guideline (Table 21) or the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria when diagnosing patients.^{4, 5} A number of tools are commonly used for clinical assessment including the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, Inflammatory Rasch-built Overall Disability Scale (I-RODS), Medical Research Council (MRC) Sum score and the Timed Up and Go (TUG) test. Clinicians can also use the CIDP disease activity status (CDAS) scale to monitor a patient’s level of disease and treatment status, ranging from Level 1 (cure) to Level 5 (unstable active disease). The company’s advisory board and the EAG’s clinical experts highlighted variation in clinician preference over which of these tools are used for assessment, as discussed in more detail in Section 2.3.4. The EAG’s clinical experts also noted that response on one measure would not necessarily be reflected as a similar change in another measure, with each tool designed to capture a different aspect of patient function. For instance, if a patient demonstrates either a response, or a deterioration, on the aINCAT scale, this may not be accompanied by a similar change in the MRC sum score.

Table 21. EAN/PNS CIDP diagnostic guidelines (Reproduced from Table 44 of CS, Appendix J).

	Criteria
Clinical	Typical CIDP All of the following: • Progressive or relapsing, symmetric, proximal and distal muscle weakness of upper and lower limbs, and sensory involvement of at least 2 limbs • Developing over at least 8 weeks • Absent or reduced deep tendon reflexes in all limbs

	Atypical CIDP variants One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs): • Distal CIDP: distal sensory loss and muscle weakness predominantly in lower limbs • Multifocal CIDP: sensory loss and muscle weakness in a multifocal pattern, usually asymmetric, upper limb predominant, in more than 1 limb • Focal CIDP: sensory loss and muscle weakness in only 1 limb • Motor CIDP: motor symptoms and signs without sensory involvement • Sensory CIDP: sensory symptoms and signs without motor involvement
Electrodiagnostic	Motor nerve conduction At least 1 of the following: • Motor distal latency prolongation $\geq 50\%$ above ULN in 2 nerves • Reduction of motor conduction velocity $\geq 30\%$ below LLN in 2 nerves • Prolongation of F-wave latency $\geq 20\%$ above ULN in 2 nerves ($\geq 50\%$ if amplitude of distal negative peak CMAP $< 80\%$ of LLN) • Absence of F-waves in 2 nerves + ≥ 1 other demyelinating parameter in ≥ 1 other nerve • Partial motor conduction block • Abnormal temporal dispersion • Distal CMAP duration prolongation in ≥ 1 nerve + ≥ 1 other demyelinating parameter in ≥ 1 other nerve
	Sensory nerve conduction • At least 1 of the following abnormalities in at least 2 nerves: ○ Prolonged distal latency ○ Reduced SNAP amplitude ○ Slowed conduction velocity
Additional diagnostics	In patients with a possible diagnosis of CIDP based on clinical and electrodiagnostic criteria, 2 of the following supportive criteria are required for confirmation: • Objective response to treatment with immunomodulatory agents • Ultrasound revealing nerve enlargement in at least 2 sites in proximal median nerve segments and/or the brachial plexus • Magnetic resonance imaging showing enlargement and/or increased signal intensity of nerve root(s) on T2-weighted sequences • Elevated CSF protein • Nerve biopsy demonstrating thin myelination or demyelination, or perivascular macrophage clusters

Source: Van den Bergh 2023⁵

Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; CMAP: Compound muscle action potential; CSF: Cerebrospinal fluid; EAN: European Academy of Neurology; LLN: Lower limit of normal; PNS: Peripheral Nerve Society; SNAP: Sensory nerve action potential; ULN: Upper limit of normal.

2.2 Critique of the company's overview of current service provision

The National Institute for Health and Care Excellence (NICE) has no existing recommendations for the treatment of CIDP. The CS describes uncertainties over the current UK treatment pathway for CIDP due to a lack of clear recommendations on the most effective choice or sequence of treatments. Consequently, the company used structured expert elicitation (SEE) to understand how CIDP is currently managed in NHS clinical practice. The SEE highlighted variation in clinical practice, but the company reported that a consensus was reached on a clinical pathway that broadly reflects practice in the NHS (Figure 1), alongside consensus on the most appropriate positioning of efgartigimod (Figure 2).

Treatment of CIDP initially involves induction treatment, aimed at gaining rapid control over a patient's disease activity. This stage of treatment also provides clinicians with an opportunity to confirm the diagnosis of CIDP, with response to treatment often used as supportive evidence of the disease (Table 21). Either intravenous immunoglobulin (IVIg) or corticosteroids are recommended as induction treatment for most patients with CIDP, while IVIg is often recommended for motor CIDP.

Once a patient responds to induction treatment, maintenance treatment is used to maintain stable levels of disease control, avoid relapse and optimise long-term function. The CS highlights the heterogenous nature of treatment during the maintenance phase, with the choice of the most appropriate therapy based on a range of factors including disease severity, comorbidities, and availability of treatment. Options for maintenance treatment include IVIg, subcutaneous immunoglobulin (SCIg), corticosteroids and plasma exchange (PLEX).

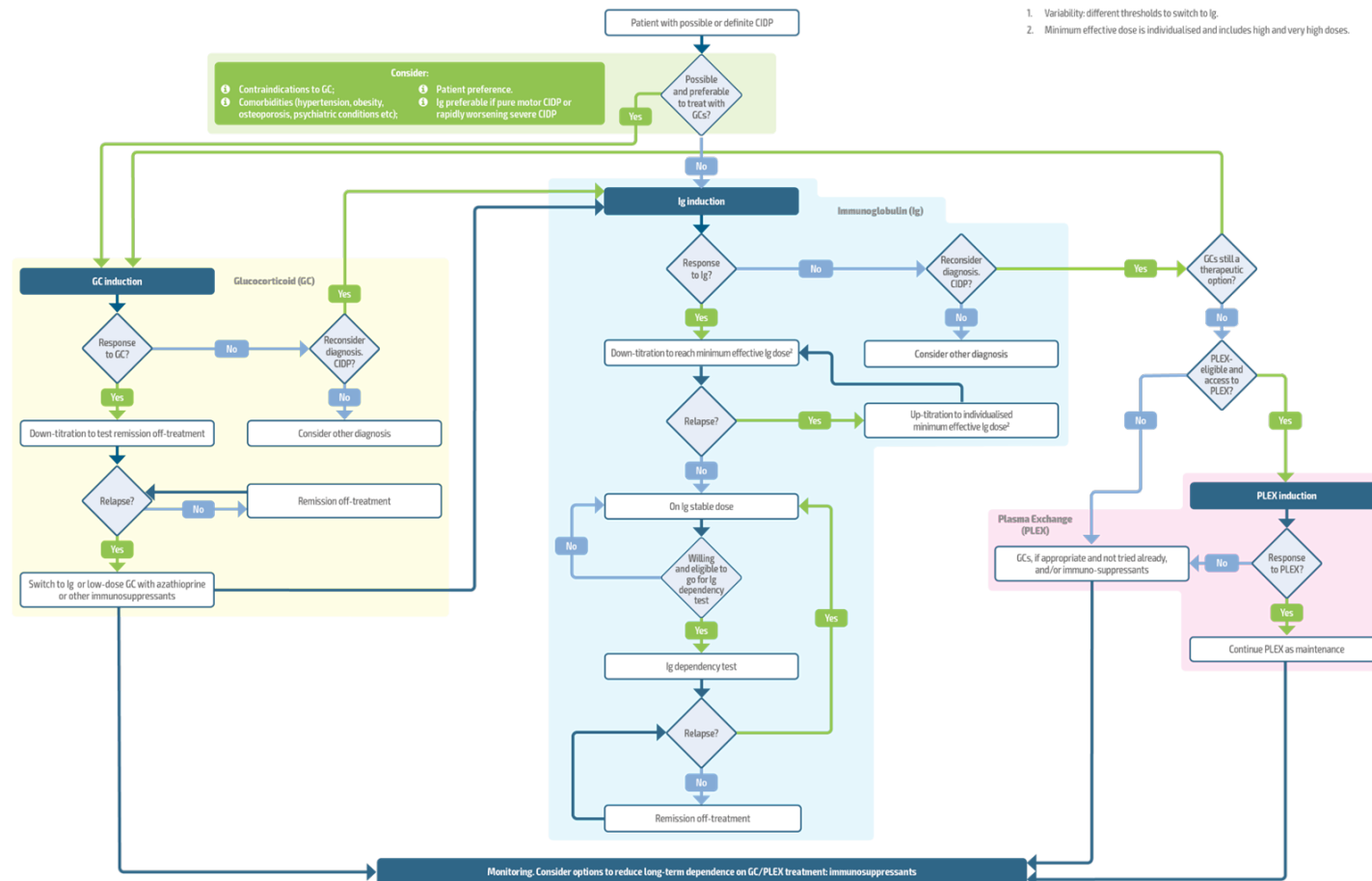
Immunoglobulin (Ig) is the most commonly used maintenance treatment in the NHS, favoured over corticosteroids due to a faster treatment response and fewer long-term adverse effects. The company reported that the average duration of Ig treatment is 3 years, with almost 45% of patients remaining on Ig treatment indefinitely. The EAG's clinical experts considered the average treatment duration to be slightly longer, reporting it to be 5 years, with approximately 65% to 70% of patients remaining Ig dependent. IVIg is the most common form of Ig administration, with the company's clinical experts estimating that 63% of all CIDP patients receive IVIg, compared to approximately 14% for SCIg. The lower uptake of SCIg was attributed to the training required for administration, the frequency and volume of dosing and logistical issues associated with treatment switching. The EAG's

clinical experts also highlighted that a lack of access to SCIg is a limiting factor in some NHS centres. While the choice of the administration of Ig is often influenced by patient preference, SCIg is most suitable for patients who only require low-dose or low-frequency IVIg to achieve stable disease control. The EAG's clinical experts agreed with the statements in the CS that the efficacy of IVIg and SCIg is generally considered to be comparable.

The company reported that corticosteroids and PLEX are rarely used for maintenance therapy. Corticosteroids are associated with risks, such as iatrogenic conditions, adverse events and lack of long-term benefits, while PLEX is an invasive treatment, associated with adverse events, often followed by relapse and only available in specialised units. The EAG's clinical experts also highlighted that many centres in the UK do not have access to PLEX, limiting the number of patients who can receive this treatment in the NHS. Given these limitations, PLEX is generally reserved for patients who have severe or refractory disease after other treatment options have failed. The company's clinician market research survey estimated that less than 5% of patients on maintenance therapy in the UK receive PLEX.⁶

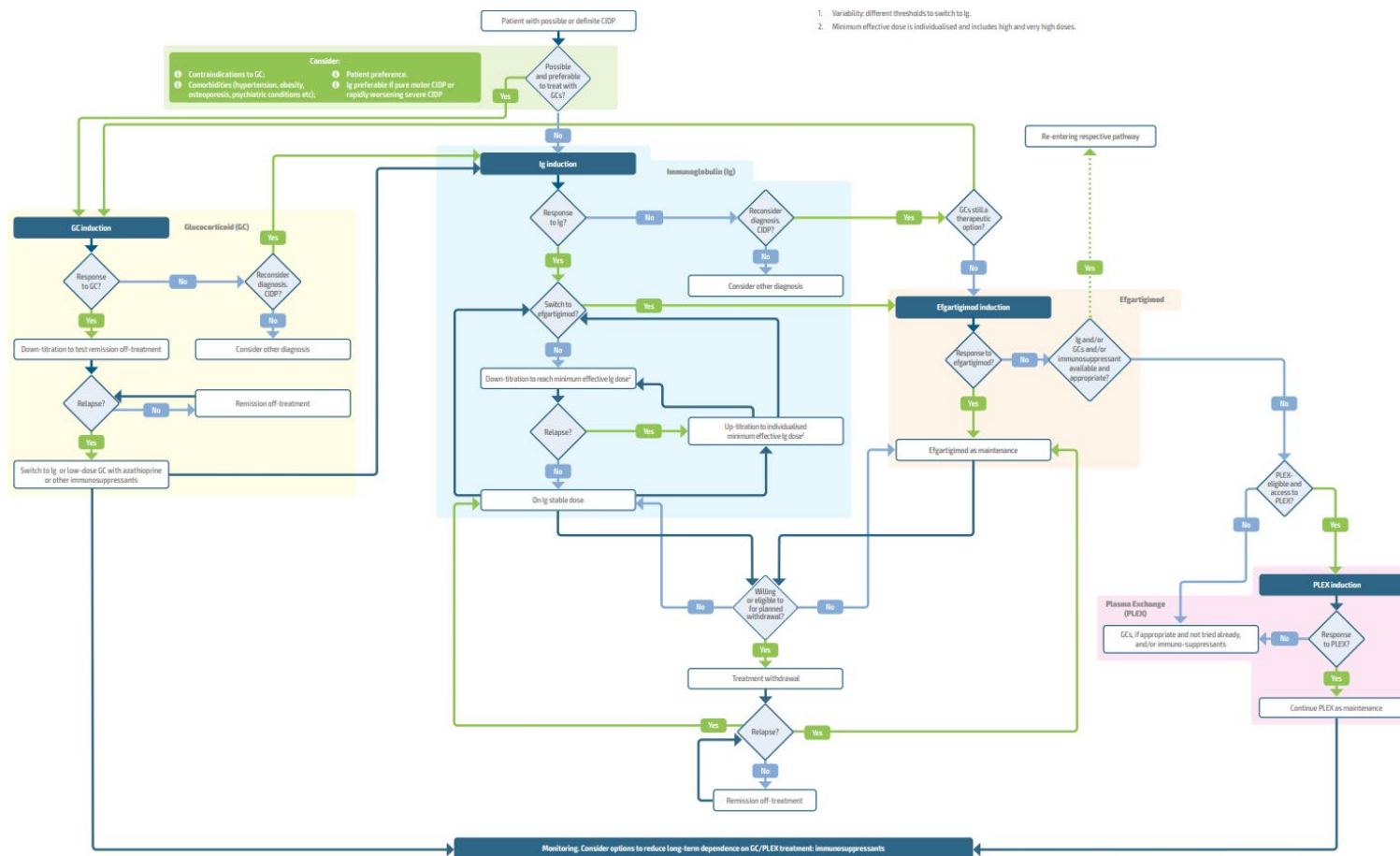
If patients have an inadequate response to Ig, alternative treatment options are available, such as cyclophosphamide, ciclosporin, or rituximab. Immunosuppressant or immunomodulatory agents may also be considered, although these treatments are used outside of their marketing authorisations, and have a more limited evidence base. As a result, they are generally only considered as a final treatment option, once other treatments have failed. Combination treatments can also be used, but are also reserved for late in the treatment pathway.

Figure 1. Current UK treatment pathway (reproduced from Figure 2 of CS)



Abbreviations: CIDP: Chronic inflammatory demyelinating polyneuropathy; CS: Corticosteroids; IVIg: Intravenous immunoglobulin; PLEX: Plasma exchange; SCIg: Subcutaneous immunoglobulin.

Figure 2. Current UK treatment pathway including suggested positioning of efgartigimod (reproduced from Figure 3 of CS)



Abbreviations: CIDP, Chronic inflammatory demyelinating polyneuropathy; CS, Corticosteroids; IVIg, Intravenous immunoglobulin; SCIG, Subcutaneous immunoglobulin; PLEX: Plasma exchange.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE, together with a rationale for any deviations from the decision problem. The CS covers a subpopulation of the anticipated marketing authorisation for efgartigimod and aligns with most of the NICE final scope, with some differences in the description of the population and the choice of comparators. A summary of the final scope issued by NICE, the decision problem addressed in the CS, and the EAG's critique of this is provided in Table 22. Further detail about the EAG's critique is provided in Sections 2.3.1 to 2.3.4.

Table 22. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with CIDP	Adults with CIDP after prior, unsatisfactory, treatment with immunoglobulin (IVIg or SCIg).	The company's definition reflects an optimised population of the anticipated UK marketing authorisation. The company considered their definition to most closely reflect patients who would be eligible for efgartigimod in NHS clinical practice. The definition, validated by the company's clinical experts, specified that patients should have had unsatisfactory treatment with Ig. Unsatisfactory treatment was defined as: • A high burden of Ig treatment: patients who have received at least 6 months of treatment with Ig (IVIg or SCIg for whom ongoing Ig infusions or injections significantly impact daily life, work, or caregiving responsibilities). This category includes patients who remain symptomatic or require high	The population in the CS reflects a subpopulation of that stated in the NICE final scope. The company stated that their chosen population reflected the patients who would be most likely to receive efgartigimod in UK clinical practice, based on a survey with nine clinicians, an advisory board of five specialist nurses and structured expert elicitation (SEE). The EAG's clinical experts confirmed that this is a population that is readily identifiable in clinical practice. Although the EAG considers this definition of the population to be a reasonable reflection of clinical practice, it notes that the population in the key trial of interest (ADHERE) does not fully align with the company's definition. The inclusion criteria of ADHERE does not specify that patients had to receive at least 6 months of Ig treatment, or that they should have been receiving a high dose or high frequency of treatment. Furthermore, patients who were intolerant or refractory to Ig were not included in the ADHERE trial. These

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
			doses or frequency of Ig to maintain benefit and avoid peri-dose fluctuations. Patients who are intolerant or refractory to Ig: patients who are unable to continue Ig due to adverse events, safety concerns (e.g. thromboembolism and heart failure), or relevant comorbidities.	discrepancies lead to concerns about the applicability of the trial evidence to the company's proposed population. The EAG notes that, while there was no evidence for patients who were intolerant or refractory to Ig, the company's economic evaluation modelled these patients separately to patients who were on Ig maintenance before starting treatment with efgartigimod.
Intervention	Efgartigimod with recombinant human hyaluronidase PH20.	As per the NICE scope	N/A	N/A
Comparator(s)	Established clinical management without efgartigimod with recombinant human hyaluronidase PH20, including but not limited to: - Corticosteroids - Igs (IVIg or SCIg) - Plasma exchange (PLEX) - Immunosuppressive therapies	As per the NICE scope	Although the company included the same comparators as the NICE final scope, it considered Ig (IVIg or SCIg) to be the primary comparator. The company reported that Ig most closely reflects the point in the treatment pathway where patients would be eligible for efgartigimod, stating that this decision was validated by five clinical experts. PLEX, corticosteroids and immunosuppressants were	The EAG's clinical experts considered Ig to be an appropriate comparator for efgartigimod. They noted that other treatments were used less frequently than Ig and tended to be reserved for patients with more severe or refractory disease. They also noted that PLEX and SCIg are not readily available in all centres in the UK, limiting their access for some patients in the NHS. Based on the frequency of its use as maintenance treatment, the EAG considers Ig to be an appropriate comparator for efgartigimod for most

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
			incorporated in the economic model as a basket of alternative treatments, which the company considered to reflect the broader population eligible for efgartigimod. These alternatives were not considered as comparators in the evaluation of clinical effectiveness, with the company's clinical experts emphasising that they are rarely used for long-term maintenance treatment of CIDP.	patients. However, it notes that some of the patients included in the company's proposed population, such as those who are intolerant or refractory to Ig, were not identified and examined as a subgroup in the ADHERE trial. As such, the EAG does not consider it possible to assess the effectiveness of efgartigimod for these groups.
Outcomes	- Physical function change from baseline - Disease progression - Hospitalisations - Adverse effects of treatment - HRQoL	- Physical function change from baseline - Disease progression - Hospitalisations - Adverse effects of treatment - HRQoL	N/A	N/A
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the	As per the NICE scope	N/A	N/A

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
	technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.			
Subgroups	No subgroups identified	No subgroups identified	Although the company did not identify any subgroups of interest, the CS focused on patients who have unsatisfactory treatment with Ig. The company's economic model considered three subgroups who would be eligible for efgartigimod, including patients who have a high burden of Ig treatment, patients who are intolerant to Ig and patients who are refractory to Ig.	As discussed above in relation to the company's definition of the population, the inclusion criteria in the ADHERE trial was not restricted to patients with a high burden of treatment, raising some concerns about the applicability of the evidence for this group. In addition, it was not possible to identify which patients were intolerant or refractory to Ig, preventing an assessment of the effects of efgartigimod for these patients. The subgroups that make up the company's population are discussed in the EAG's critique of the population (Section 2.3.1).
Special considerations, including issues related to equity or equality	None identified	None identified	N/A	N/A

Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment score; CIDP, Chronic inflammatory demyelinating polyneuropathy; EAG, External Assessment Group; HRQoL, health-related quality of life; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PLEX, plasma exchange; SCIg, Subcutaneous immunoglobulin; SEE, structured expert elicitation ; UK, United Kingdom

2.3.1 Population

The population proposed by the company reflects a subpopulation of the NICE scope (all adults with CIDP) and an optimised population of the anticipated UK marketing authorisation (adult patients with progressive or relapsing active CIDP after prior treatment with corticosteroids or Igs). The company stated that the population was selected to best reflect the patients who are most likely to receive efgartigimod in NHS clinical practice. In the absence of UK-based guidelines for the treatment of CIDP, the definition of the population was validated through surveys with clinicians, an advisory board of specialist nurses and using structured expert elicitation (SEE).

The population proposed by the company was adults with CIDP who have had prior, unsatisfactory treatment with Ig (IVIg or SClg). Unsatisfactory treatment was defined as patients who either:

- Have a high burden of Ig treatment. This includes patients who have received at least 6 months of treatment with either IVIg or SClg, which has a significant impact on their daily life, work, or caregiving responsibilities. It also includes patients who remain symptomatic or require high doses or frequency of Ig to continue to experience the benefits of treatment and avoid variation in symptoms between doses; or
- Who are intolerant or refractory to Ig. This includes patients who are unable to continue Ig treatment due to comorbidities, adverse events or safety concerns, such as concerns about the risk of developing thromboembolism or heart failure.

The EAG's clinical experts considered the definition of a high burden of treatment to be relatively subjective and potentially difficult to measure in clinical practice. In response to clarification questions, the company provided additional information about how this population would be defined, stating that it would include patients who:

- require IVIg treatment more frequently than every four weeks;
- are unable to tolerate more than half-maximal intravenous infusion rates due to side effects or contraindications;
- experience AEs that impact the tolerability of treatment or quality of life;
- have a schedule of regular Ig infusions or injections which significantly impacts their daily life.

The EAG's clinical experts considered the expanded definition of a high burden of treatment to be more easily identifiable in clinical practice, capturing issues which are often faced when treating

patients who have CIDP. However, they noted that there were still limitations, such as a lack of an accepted definition of a half-maximal intravenous infusion rate or uncertainty over what would be considered a significant impact on someone's daily life. Despite these limitations, they considered the population to be generally identifiable in clinical practice and a reasonable reflection of patients who might be considered for efgartigimod in the NHS.

Although the EAG considers the company's population to be reasonable, it has concerns about how this group is represented in the key trial of interest (ADHERE) (**Key issue 1**). Some of the key inclusion criteria relating to prior treatment in ADHERE were:

- Patients who received treatment with pulsed corticosteroids, oral corticosteroids and/or IVIg or SCIg within the previous 6 months and were willing to discontinue the treatment; or
- Patients who were treatment-naïve (including those who had not previously received treatment for CIDP or those who had not been treated with monthly or daily corticosteroids, IVIg or SCIg in the previous 6 months).

The patients in ADHERE who are most likely to be an accurate reflection of those included in the company's population are those who received treatment with pulsed corticosteroids, oral corticosteroids and/or IVIg or SCIg within the previous 6 months (51.2% of all patients in Stage A of the ADHERE trial and 43.4% in Stage B received prior IVIg or SCIg). However, unlike the company's definition, ADHERE did not require patients to have had Ig treatment for a full 6 months prior to the start of the trial, and with insufficient information collected to determine how many of these patients met the criteria for unsatisfactory treatment, it is unclear how many patients in this group are relevant to the proposed population (discussed further in Sections 3.2.1 and 3.2.3).

The EAG notes that patients in the treatment-naïve group (29.2% of all patients in Stage A of the ADHERE trial; 33.9% in Stage B) would not meet the company's criteria for experiencing a high burden of Ig treatment. While some of these patients could be refractory or intolerant to Ig, this information was not recorded as part of the ADHERE trial. Furthermore, 34 patients within the treatment-naïve group (10.6% of all patients in Stage A of the ADHERE trial), had no prior treatment for CIDP. These patients do not meet the criteria for the company's optimised population or for the anticipated marketing authorisation.

Given the issues outlined above, further clarification was requested about how the evidence from ADHERE is generalisable to the company's proposed population. The company considered that

participants choosing to volunteer for the trial despite the risk of treatment withdrawal in the run-in phase reflected their status as patients who were experiencing a high burden of Ig treatment. Without supporting information for this assumption, the EAG considers the company's view to be speculation, as many people participate in clinical trials to contribute to the advancement of medical science. While it is possible that some patients may have volunteered for the trial based on the potential to reduce their treatment burden, it remains unclear what proportion meet the criteria for a high burden of treatment.

Overall, the EAG has concerns about the applicability of the evidence to the patient groups defined in the company's proposed population. Some, but not all, of the patients in ADHERE may meet the definition for a high burden of treatment. However, it is not possible to determine which patients met this criterion. The greatest discrepancy between the proposed population and the current evidence base is for patients who are intolerant or refractory to Ig. These patients were not specifically included in ADHERE, preventing the assessment of the effects of efgartigimod for this group. The EAG also notes that in the economic evaluation, the company modelled patients who were intolerant or refractory to Ig separately to patients who were on Ig maintenance before starting treatment with efgartigimod (albeit assuming the same treatment effectiveness inputs for all three populations). The EAG considers that the economic modelling for the Ig-intolerant and Ig-refractory patients is subject to considerably more unresolvable uncertainty than for the Ig maintenance population.

2.3.2 Intervention

The intervention matched that specified in the NICE final scope (efgartigimod with recombinant human hyaluronidase PH20). Efgartigimod (brand name Vyvgart®) is a coformulation of efgartigimod and recombinant human hyaluronidase (rHuPH20), which binds to the neonatal Fc (FcRn) receptor that would normally protect IgG antibodies from degradation. By blocking the FcRn receptor, efgartigimod reduces the level of circulating IgG, which would otherwise result in damage to the nerves for people with CIDP. This reduction in levels of IgG is reversible, with levels typically returning to baseline values once treatment with efgartigimod is stopped.

Efgartigimod is delivered subcutaneously using a pre-filled syringe, with a recommended dose of 1000 mg administered over 20-30 seconds in a total volume of 5 ml. Although the initial four doses must be administered by, or under the supervision of, a healthcare professional, subsequent doses

can be self-administered at home. Efgartigimod is initially administered on a weekly basis, but this can be adjusted to every two weeks if a patient shows an adequate response to treatment.

The ADHERE trial initially assessed a patient's response to efgartigimod (1000 mg once per week) for up to 12 weeks (Stage A), at which point only those patients who showed a response to treatment were included in the RCT phase (Stage B) of the trial. The EAG's clinical experts considered this to be an acceptable time over which to assess someone's initial response to treatment. During Stage B, patients received efgartigimod or placebo for up to 48 weeks or until relapse. The EAG's clinical experts also considered this to be reasonable and noted that patients would likely remain on treatment beyond 48 weeks if they did show a response, with most patients remaining on treatment for 12 to 18 months before a phased withdrawal would be considered. The longer-term treatment effects of efgartigimod were considered in the ADHERE+ trial, which was an open-label extension trial, with treatment continuing for up to two years. Given that the dose, method of administration and assessment time points reflect what the clinical experts would expect in practice, the intervention used in the trials appears suitable to address the decision problem.

While the intervention is appropriate, the EAG notes that there appear to be two potential approaches for the timing of efgartigimod administration relative to prior Ig treatment. These are:

1. Following a wash-out period to remove the effects of prior Ig; or
2. Immediately following the cessation of prior Ig treatment.

The inclusion of a wash-out period reflects the design of the ADHERE trial, which included a 12-week window between the cessation of Ig treatment and the start of treatment with efgartigimod. A wash-out period between treatment with Ig and efgartigimod is already recommended for patients with myasthenia gravis, with a 2025 update to the Association of British Neurologists autoimmune myasthenia gravis management guidelines stating that, "*As both IVIg and FcRn monoclonal antibodies bind to the FcRn receptor, they cannot be given concurrently; a washout period of 4 weeks is required before starting an anti-FcRn following IVIg treatment*".⁷ The alternative option, where patients receive efgartigimod immediately after ending Ig treatment, reflects the company's approach in the economic analysis. It also reflects wording in the draft SmPC, which recommends that treatment is initiated before the clinical effect of any prior therapies starts to decrease. There is currently no evidence for the effectiveness of efgartigimod in patients who switch immediately from Ig to efgartigimod, due to the wash-out period that was included at the start of the ADHERE trial.

2.3.3 Comparators

2.3.3.1 Immunoglobulin (Ig)

The comparators matched those stated in the NICE final scope, including corticosteroids, Igs (IVIg or SCIg), PLEX and immunosuppressive therapies. The CS presents Ig as the primary comparator, reporting that this most closely reflects the point in the treatment pathway where patients are likely to be eligible for efgartigimod in NHS clinical practice. As discussed in Section 2.2, the company's clinical experts reported that Ig is the most commonly used maintenance treatment for CIDP, with other treatments generally reserved for patients with more severe or refractory disease.

As discussed in Section 2.3.2, Ig and efgartigimod both bind to the FcRn receptor, with guidelines for the management of autoimmune myasthenia gravis recommending a washout period of 4 weeks if the two treatments are used in succession.⁷ Given that Ig and efgartigimod both bind to the same receptor, the EAG requested a clinical rationale from the company to explain why patients who are refractory to Ig might instead be expected to respond to efgartigimod. The company's response highlighted how the mechanism of action differs between Ig and efgartigimod. While both treatments should bind to the FcRn receptor, some patients may not respond to the broader mechanism of action of Ig but will instead respond to the more targeted action of efgartigimod. The company therefore believe that the recommendation in the autoimmune myasthenia gravis management guidelines is aimed at avoiding competition for the FcRn receptor, rather than reflecting a similar mechanism of action of the two treatments. As such, the company consider the inclusion of Ig as the primary comparator to be justified.

There are two forms of Ig administration, both considered by the company to be relevant comparators to efgartigimod:

- IVIg: Used for both induction and maintenance treatment. Induction regimens use a dose of 2 g/kg divided over two to five days. The company reported that maintenance treatment is typically 1 g/kg every three weeks, while the EAG's clinical experts noted that it can be 0.8 g/kg every four weeks. Most treatment is delivered in hospital or day units, with home administration sometimes used under monitoring. All forms of Ig have marketing authorisation for the treatment of CIDP;
- SCIg: Only used for maintenance treatment, and most beneficial for patients who experience venous access difficulties, systemic side effects with IVIg, or a wearing off phenomenon with IVIg. It can also be used for patients who experience a high treatment burden as a result of

intensive hospital visits, which disrupt their work and daily activities. The company reported that only patients who have controlled disease while on a low dose of IVIg are considered for SCIg. However, the EAG's clinical experts noted that the reasons for choosing SCIg can vary between centres, with some using SCIg for patients who have concerns about IVIg impacting on their quality of life. HyQvia® is the only form of SCIg to currently have marketing authorisation for CIDP maintenance treatment.

As discussed in Section 2.2, the company reported that IVIg and SCIg are generally considered to have similar treatment effects. In their response to the EAG's clarification questions for supporting evidence, the company highlighted that SCIg (Hizentra®) is approved for maintenance treatment in CIDP following stabilisation treatment with IVIg, which demonstrates that regulators consider SCIg to be effective. The company supported their response with evidence from Markvardsen *et al.* (2016) who reported non-significant differences in improvements in isokinetic muscle strength between the two methods of administration, although the EAG notes that improvements were seen earlier with IVIg than SCIg.⁸ The company also included the PATH study as evidence of SCIg reducing the risk of relapse to a greater extent than placebo. However, the EAG notes that PATH aimed to compare placebo against different doses of SCIg in patients who were previously stable on IVIg, rather than providing a direct comparison between the effects of IVIg and SCIg. Although there appears to be limited evidence providing direct comparisons between the two methods of administration, the EAG's clinical experts also expected them to have similar treatment effects, suggesting that the choice of both IVIg and SCIg as comparators for most patients is reasonable.

2.3.3.2 *Alternative treatment options*

As discussed in Section 2.2, PLEX is rarely used for maintenance therapy, with the company reporting that less than 5% of all patients on maintenance therapy currently receive PLEX in the NHS.⁶ The EAG's clinical experts also highlighted how many centres in the UK do not currently have access to PLEX treatment, supporting the use of Ig as the primary comparator for efgartigimod for most patients. However, the EAG considers that some of the patients who are included in the company's population may not be adequately represented by comparisons between efgartigimod and Ig. For instance, PLEX may be a more appropriate comparator for patients who are intolerant or refractory to Ig. However, as discussed in Section 2.3.1, these patients were not identifiable in the ADHERE trial (**Key issue 1**). Therefore, based on the current evidence, the EAG does not consider it possible to

assess whether efgartigimod is an effective alternative treatment option for patients who are intolerant to Ig.

The company reported that corticosteroids are commonly used as induction therapy but are rarely used as maintenance treatment, due to their limited long-term effectiveness, and the risk of adverse effects and iatrogenic conditions. The CS reported that approximately 3% of CIDP patients currently use corticosteroids as maintenance treatment. The EAG's clinical experts agreed with the company's statements and did not consider corticosteroids to be a relevant comparator for efgartigimod.

Immunosuppressants or immunomodulatory agents were also included in the NICE final scope and the CS. The company discussed how azathioprine, mycophenolate mofetil or ciclosporin can be used, but highlighted that these options do not have marketing authorisation for CIDP, and evidence of their effectiveness is limited. The company's chart review indicates that azathioprine accounts for 36% of other treatments used for CIDP, while other immunosuppressants and immunomodulatory agents each account for 7% (Figure 6 of company's CIDP UK chart review study). The chart review provides no further explanation of what these proportions represent but appears to demonstrate that the use of most of these treatments is relatively infrequent. The EAG notes that recent research has demonstrated that mycophenolate can improve clinical outcomes when used as an adjunct treatment in patients who require high doses of IVIg (>2 g/kg/month).⁹ It therefore considers it important to acknowledge that there are other effective options when a patient demonstrates a poor response on a high dose of IVIg. However, given that these treatments do not currently have marketing authorisation and their use in NHS clinical practice is limited, the EAG considers their exclusion as comparators in the assessment of clinical effectiveness to be reasonable.

Although PLEX, corticosteroids and immunosuppressants were not included in the company's evaluation of clinical effectiveness, they were incorporated into the economic model. These were grouped into a basket of alternative treatments designed to reflect the treatment options available to patients in the Ig intolerant and Ig refractory cohorts. The inclusion of these treatments in the economic model is discussed in more detail in Section 4.2.2.

2.3.4 Outcomes

The outcomes in the CS match those in the NICE final scope (Table 22). A range of outcomes were reported to assess change in physical function and disease progression. These included the Inflammatory Neuropathy Cause and Treatment scores (INCAT/aINCAT), Inflammatory Rasch-built

Overall Disability Scale (I-RODS), Medical Research Council (MRC) muscle strength testing, grip strength testing and the Timed Up and Go (TUG) test. The EAG's clinical experts considered these to be appropriate and validated measures of disease severity and response to treatment, although they noted that the most commonly used measures vary between centres.

While the EAG considers the outcomes in the CS to be appropriate to address the decision problem, it has concerns about the assessment of clinical deterioration in the ADHERE trial (**Key issue 3**). A range of outcomes (change in aINCAT score, I-RODS or mean grip strength) were used to assess disease progression, improvement or relapse in the early stages of the ADHERE trial (see Section 3.2.1). The EAG's clinical experts agreed with this approach, noting that these measures are often used in combination, rather than decisions being made on the outcome of a single measure. In contrast, the RCT phase (Stage B) of ADHERE relied solely on change in aINCAT score to assess whether a patient experienced clinical deterioration. The EAG has concerns that this approach may have underestimated the number of patients who experienced clinical deterioration, particularly as both the EAG's clinical experts and results from the company's advisory board highlighted how some clinicians prefer to use I-RODS due to concerns over aINCAT lacking sensitivity when assessing disease burden and treatment response. These concerns are discussed in more detail in Section 3.2.3.

Health-related quality of life (HRQoL) was assessed using EQ-5D-5L. The EAG's clinical experts discussed how HRQoL is an important consideration for patients with CIDP, although they noted that in clinical practice this is often assessed informally during discussions with a patient, rather than with a specific tool. The EAG notes that while the ADHERE trial assessed HRQoL, this was not considered in the open-label extension phase of ADHERE+. Assessment of the effects of efgartigimod on HRQoL is therefore limited to the first 60 weeks of treatment (up to 12 weeks during Stage A of ADHERE and up to 48 weeks during Stage B).

For safety outcomes, the company provided information from ADHERE on adverse events (AEs), treatment emergent adverse events (TEAEs), serious AEs, Grade 3 AEs, AEs of special interest and injection site reactions. The most common TEAEs were reported in the CS (Section 2.11) and, in response to the EAG's clarification questions, the company provided the same information for serious or Grade 3 or higher TEAEs. In the open-label extension phase reported in ADHERE+, the company reported similar outcomes, although information on AEs of special interest and injection site reactions was not provided.

The timing of outcome assessment appears reasonable, with patients' response to efgartigimod initially assessed for up to 12 weeks, which the EAG's clinical experts considered reflective of clinical practice. In Stage B of ADHERE, outcomes were assessed every four weeks. This aligns with the frequency reported by some of the EAG's clinical experts, who reported monthly assessments for the first four months of CIDP treatment, although it was noted that assessments become less frequent (between every six and twelve months) once a patient is stable on treatment.

3 Clinical effectiveness

This section presents a summary and critique of the clinical effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical effectiveness analyses. Sections 3.4 and 3.5 critiques the subgroup and safety analysis, while Section 3.6 critiques the indirect comparisons presented by the company. Conclusions are presented in Section 3.7.

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify clinical evidence from randomised clinical trials (RCTs) for efgartigimod and comparator treatments for the management of CIDP (the global SLR). The EAG notes that the separate report that was provided as a reference for the indirect treatment comparisons (ITCs) stated that an additional SLR (ITC SLR) was conducted to identify studies relevant to the ITC, with a combination of both SLRs used to inform the ITC. The EAG notes from the ITC report that the company considered the global SLR to include a broader evidence base as it did not include a time restriction and it included a wider range of comparators (e.g. PLEX and neuromodulatory drugs). The ITC SLR is discussed further in Section 3.6.1, while the critique below focuses on the global SLR reported in the CS.

A total of 159 publications reporting on 123 studies were included (from the original and updated searches) with the included studies summarised in CS Appendix B Table 9. Of the 123 included studies, only two studies of efgartigimod for the treatment of CIDP are discussed in detail (ADHERE¹⁰ and ADHERE+¹¹). However, the EAG notes that additional comparator studies from this SLR may also have been considered for inclusion in the ITCs. It is unclear why the remaining 121 studies included from the SLR were not discussed further in the CS, alongside any reasons for exclusion. The EAG therefore considers it unclear whether any potentially relevant studies may have been excluded from the company's SLR, although it is noted that some of these studies may also have been the five studies considered in the feasibility assessment for the ITC, which is reported in more detail in the company's ITC report and discussed in Section 3.6.1.

Table 23. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix B1.1.1	The EAG considers the sources and dates searched to be comprehensive and appropriate. Databases searched (n=3): - Embase, MEDLINE (PubMed), and Cochrane. Congresses (n=7): - EAN, AAN, WCN, ANA, PNS, ISPOR and ABN. Regulatory agencies, HTA agencies and other healthcare agencies (n=28; 2 UK, 8 Europe, 13 Nordics and 5 other regions): - AEMPS, AETS, AGENAS, AIFA, C2H, CADTH, DHMA, DHTC, DMA, DMC, Fimea, Finland specific HTA publications, FinCCHTA, G-BA, HAS, ICER, IMA, INAHTA, IQWiG, JNHB, NICE, NIPH, NoMA, PBS, SBU, SMC, Spanish Regional HTA and Agencies and Units in the Spanish HTA Network, TLV. The search dates for each of the different searches varied slightly with the original searches conducted between September and November 2024 and update searches performed between July and August 2025.
Search strategies	Appendix B1.1.1	The EAG considers the search strategies used to be reasonable The search strategies for the literature review used free-text keywords and MeSH and Emtree terms for the population with further free-text keywords included for the interventions and outcomes of interest. It is unclear whether the inclusion of MeSH and Emtree headings were explored for the interventions and outcomes.
Inclusion criteria	Appendix B1.2	The EAG considers the inclusion criteria for the SLR to be reasonable Inclusion criteria for extraction in the SLR were broad and the exclusion criteria applied at this stage are deemed reasonable by the EAG. The EAG notes that non-English language publications were excluded and clinical studies with <10 patients.
Screening	Appendix B1.2	The EAG considers the methods for screening to be robust The company reported that the references identified through the electronic searches as well as from the congress searches were subjected to a multi-step selection process using pre-defined inclusion and exclusion criteria. The company reported that all of the record screening steps were performed using two independent reviewers with any discrepancies resolved by a third senior reviewer. Results of the literature screening processes were summarised in a PRISMA diagram.

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data extraction	Not Applicable	Unclear as the methods for data extraction in the clinical SLR are not described in the CS or CS appendices. The EAG notes that a description of the process for extracting studies is not described in the CS Appendix B with regards to the clinical SLR.
Tool for quality assessment of included study or studies	Appendix B3 and B3.1	The EAG considers the quality assessment tools used to assess ADHERE to be appropriate but notes that no quality assessment was reported in the CS for ADHERE+ For the randomised stage of ADHERE (Stage B), the company used the Cochrane risk of bias (RoB) 2 for parallel-group randomised controlled trials (RCTs) for quality assessment.¹² The company used the Institute of Health Economics (IHE) Quality Appraisal Checklist¹³ to assess study quality for the single-arm, non-comparative stage of ADHERE (Stage A). The EAG notes that the company reported that the risk-of-bias judgements were completed by a single reviewer and no quality assessment was provided for ADHERE+ in the CS.

Abbreviations: ABN, Association of British Neurologists; AEMPS, Spanish Agency of Medicines and Medical Devices; AETS, Health Technology Assessment Agency; AGENAS, Italian National Agency for Regional Healthcare Services; AIFA, Italian Medicines Agency; C2H, Centre for Outcomes Research and Economic Evaluation for Health; CADTH, Canadian Agency for Drugs and Technologies in Health; CS, company submission; DHMA, Danish Health and Medicines Authority; DHTC, The Danish Health Technology Council; DMA, Danish Medicines Agency; DMC, Danish Medical Council (Medicinrådet); EAG, External Assessment Group; Fimea, Finnish medicines agency; FinCCHTA, Finnish Coordinating Centre for Health Technology Assessment; G-BA, Federal Joint Committee (Gemeinsamer Bundesausschuss); HAS, French National Authority for Health (Haute Autorité De Santé); HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; IMA, Icelandic Medicines Agency; INAHTA, International HTA database; IQWiG, Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen); ISPOR, International Society for Pharmacoeconomics and Outcomes Research; JNHB, Joint Nordic HTA-bodies; MEDLINE, Medical literature analysis and retrieval system online; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NIPH, Norwegian Institute of Public Health

3.2 Critique of trials of the technology of interest

Two studies of efgartigimod were included in the CS; ADHERE and the ongoing long-term extension study, ADHERE+. The CS describes the ADHERE study as a “multistage phase 2, open-label, randomised-withdrawal, double-blind, placebo-controlled trial”. The ADHERE+ study is a single-arm, open-label phase 2 extension study for patients from the ADHERE study. Further details on the study design for ADHERE and ADHERE+, along with the EAG’s critique of ADHERE and ADHERE+ is provided below and in Appendix 7.3, Figure 23.

3.2.1 ADHERE study design

ADHERE was a phase 2 study designed to determine the safety and efficacy of efgartigimod in the management of CIDP in adults. It used a randomised withdrawal method and was comprised of two

parts, Stage A which was an open-label single-arm treatment phase with efgartigimod and Stage B which comprised a randomised, placebo-controlled treatment phase. An overview of the study design is presented in Appendix 7.3 (Figure 23) and described in further detail below.

Prior to entry to ADHERE patients underwent a screening period for up to 4 weeks, resulting in the exclusion of 28% of screened individuals (179/629) whose disease was judged as not definite or probable CIDP. Following the screening period, eligible patients underwent a treatment-free run-in (washout) period of up to 12 weeks. The company reported that this was to verify active disease and avoid exposing stable patients to the study drug. During the run-in phase, patients were required to stop their prior treatment for CIDP and those who experienced a clinically meaningful deterioration (defined as aINCAT score increase ≥ 1 point, I-RODS decrease ≥ 4 points, or mean grip strength decrease ≥ 8 kPa) progressed to Stage A of the study. The EAG notes from the Allen *et al.* 2024 publication of ADHERE⁵⁵ that participants who were off treatment with documented evidence for worsening on the aINCAT scale within 3 months before screening (when compared with a previous aINCAT score within 6 months before screening) were allowed to enter stage A without completing the run-in period.

Following screening and the run-in period, eligible participants entered Stage A and received subcutaneous efgartigimod 1,000 mg once weekly for up to 12 Weeks. Participants were required to receive at least four doses of efgartigimod and have evidence of clinical improvement (ECI) at two subsequent consecutive weekly visits in Stage A to be eligible for Stage B. If the ECI first appeared at the last scheduled Stage A visit, then an optional additional Week 12 visit with an injection was permitted to confirm ECI.

The ECI was determined using the same scale on which evidence of clinically meaningful deterioration (ECMD) was documented during the run-in period and was defined as follows:

- For participants who skipped run-in or deteriorated during the run-in period, ECI was ≥ 1 -point aINCAT improvement from the Stage A baseline.
- For participants with no aINCAT change during run-in but deterioration on I-RODS and/or mean grip strength (MGS), ECI was ≥ 4 -point I-RODS increase and/or ≥ 8 kPa mean grip-strength increase, respectively (ECI could also be met by ≥ 1 -point aINCAT improvement).

Only participants with confirmed ECI in Stage A of ADHERE were eligible to progress to Stage B (**Key issue 2**) where they were randomised 1:1 to receive double-blind weekly subcutaneous efgartigimod

1,000 mg or placebo (withdrawal phase) for up to 48 weeks or until relapse. Unlike the run-in phase and Stage A of the trial, which assessed change in disease status using a range of outcomes, relapse in Stage B was assessed solely based on change in aINCAT score (**Key issue 3**). The ADHERE study was stopped after 88 relapses had occurred, and eligible participants could enter the open-label extension ADHERE+ study (99% of those eligible entered ADHERE+). Participants who did not enter ADHERE+ received follow-up at 28 days after their final treatment dose in ADHERE.

3.2.2 *ADHERE+ study design*

ADHERE+ (NCT04280718) was designed to evaluate the safety, tolerability, and efficacy of open-label efgartigimod in adults (≥ 18 years) with CIDP. The trial is ongoing with results reported in the CS from an interim analysis at week 36 (data cut-off 6 February 2024). Participants were eligible to enrol in ADHERE+ if:

- they were still in the run-in phase or Stage A of ADHERE at the time the trial was stopped due to reaching 88 relapse events in Stage B;
- they had completed week 48 of the double-blind Stage B of ADHERE, or experienced a relapse (clinical deterioration) during Stage B of ADHERE; or
- they were still ongoing in Stage B of ADHERE at the time the trial was stopped.

Participants in ADHERE+ received weekly injections of 1,000 mg efgartigimod, with those who completed at least 24 weeks of treatment in ADHERE+ and had stable disease considered eligible for inclusion in an optional dosing substudy to evaluate the efficacy of maintenance with bi-weekly (q2w) efgartigimod. The substudy required a patient to be stable between the last two scheduled visits (i.e., approximately 12 weeks) and fulfil prespecified stability criteria (no deterioration on aINCAT, I-RODS or grip strength across consecutive assessments) prior to enrolment. After starting the q2w efgartigimod substudy, patients were allowed to return to the weekly dosing schedule if they showed signs of clinical deterioration on aINCAT, I-RODS or MGS.

3.2.3 *Summary and critique of ADHERE and ADHERE+ methods*

The ADHERE and ADHERE+ trials are summarised in Table 24. The EAG notes that the randomised Stage B part of ADHERE provides the key clinical efficacy data for efgartigimod in CIDP that is used in the company's ITCs. A detailed critique of Stage B is therefore provided in Table 25 below. In summary, and as discussed in Section 2.3.1, the EAG's key concerns about ADHERE are that much of

the population differs from the company's proposed positioning of efgartigimod (**Key issue 1**) and that relapse rates may have been underestimated in Stage B of the trial (**Key issue 3**).

As noted in Section 3.2.1, CIDP treatment was initially withdrawn during the run-in phase, and any patients who demonstrated clinical deterioration were able to continue to Stage A of the trial, where all patients received efgartigimod. The company reported this to be the most ethical approach as it avoided patients being assigned to placebo immediately after their deterioration during the run-in period. However, only patients with confirmed ECI in Stage A then progressed to Stage B of the trial, where they were randomised to efgartigimod or placebo. The exclusion of patients who did not achieve ECI with efgartigimod raises concerns for the EAG that the evidence from ADHERE reflects only those patients who respond to efgartigimod, rather than the wider CIDP population (**Key issue 2**). It may also have resulted in an overestimation of treatment effects and an underestimation of adverse events with efgartigimod. The potential effects of these biases imposed by the trial design should therefore be considered when interpreting the results of ADHERE.

As discussed in Section 2.3.1, the EAG has concerns that many of the patients included in the ADHERE trial do not reflect the company's proposed population (patients with a high treatment burden or who are intolerant or refractory to Ig) (**Key issue 1**). The EAG's main concerns about the relevance of the population in ADHERE include:

Patients with a high burden of Ig treatment (Ig maintenance population):

- Only 165 (51%) of patients in Stage A and 96 (43%) of patients in Stage B had received prior treatment with IVIg or SCIg in the 6 months prior to their enrolment in ADHERE;
- Information about how many patients met the company's definition of a high burden of treatment was not collected as part of the ADHERE trial. It is therefore unclear how many of the patients who had Ig in the 6 months prior to ADHERE are relevant to the company's proposed population.

Patients who are intolerant or refractory to Ig (Ig intolerant or refractory cohort):

- Patients who had been off treatment for 6 months (29% of patients in Stage A, 35% of patients in Stage B) were included in ADHERE. 36% of this group had no prior IVIg or SCIg treatment;

- 20% of patients in Stage A and 21% of patients in Stage B had received previous treatment with corticosteroids and had not previous treatment with IVIg or SClg during the 6 months prior to ADHERE;
- The EAG considers it unlikely that either of these groups were refractory or intolerant to Ig, although this cannot be confirmed as this information was not collected as part of the ADHERE trial.

Based on the concerns outlined above, the EAG considers there to be substantial uncertainty associated with the applicability of the clinical evidence from ADHERE to the proposed population in England who would be eligible for efgartigimod based on the company's proposed positioning in the current treatment pathway.

In addition to uncertainties regarding the relevance of the population, the EAG has concerns about the different methods of outcome assessment used in ADHERE (**Key issue 3**). As discussed in Sections 2.3.4 and 3.2.1, clinical deterioration in the run-in phase and clinical improvement during Stage A of the trial were assessed based on a range of outcomes (change in aINCAT score, I-RODS or MGS). However, once participants entered Stage B of the trial, relapse was assessed solely based on change in aINCAT score. This approach appears likely to have underestimated the number of patients who experienced relapse during Stage B, as patients will not have been considered to have relapsed if they showed a decline in I-RODS or MGS, but no accompanying decline in aINCAT.

In response to the EAG's concerns, the company acknowledged that the reliance on aINCAT in Stage B could have resulted in an underestimation of relapse rates, although they noted that I-RODS and MGS were secondary outcomes, with similar results to those reported for relapse. They also stated that consistency in the visit schedules and definition of aINCAT-based relapse throughout Stage B meant that any underestimation should be equal across trial arms. It is unclear to the EAG why the use of a consistent aINCAT definition would be sufficient to avoid differences in relapse rates between trial arms, particularly as randomisation for Stage B of ADHERE was not stratified by the measure on which a patient had shown a response in Stage A. The company also reported that any underestimation of relapse would be expected to reduce the relative treatment effect between efgartigimod and placebo. However, with no information about the number of patients in each arm who responded based on aINCAT, I-RODS or MGS, the EAG does not consider it possible to determine the impact of choosing to assess deterioration solely based on aINCAT score in Stage B.

Overall, while the EAG considers ADHERE to be relevant to clinical practice in terms of the intervention and outcomes used, it has some concerns about the potential for the underestimation of relapse and the applicability of the trial population to the company's proposed population in the NHS. These concerns are discussed in more detail in the EAG's critique of the results (Section 3.3).

Table 24. Summary of the clinical effectiveness studies of efgartigimod (adapted from Table 6 of the CS)

	ADHERE (ARGX-113-1802; NCT04281472)	ADHERE+ (ARGX-113-1902; NCT04280718)
Trial design	Multistage phase 2, open-label, randomised-withdrawal, double-blind, placebo-controlled trial.	Single-arm, open-label phase 2 extension study with no randomisation.
Duration of trial	The total study duration for each participant was up to 80 Weeks, with a maximum cumulative treatment period of 61 Weeks: - maximum 12-week run-in during which participants were required to have ECMD to enter Stage A. - Stage A consisted of a treatment period of up to 12 weeks subcutaneous efgartigimod once weekly until confirmed ECI (an optional additional week for ECI confirmation was allowed in participants who showed ECI only at the last visit in stage A). - Stage B (for participants with confirmed ECI) lasted up to 48 Weeks until a total of 88 events (relapses) occurred. Study participation ended when a participant relapsed or completed Week 48 of Stage B.	The ADHERE+ trial commenced in September 2020 and is ongoing with expected completion in April 2027. The trial was structured in repeating 48-Week cycles, with participants monitored throughout each cycle and continuing cycles until study completion. The actual duration for individual participants may vary depending on when they enter the study relative to the original ARGX-113-1802 (ADHERE) trial completion or early termination.
Settings and locations where data were collected	146 participating clinical sites (academic centres or centres of excellence, hospitals, or smaller private neurology clinics) across 22 countries from different regions in Asia-Pacific, Europe, and North America.	147 sites in 24 countries, including multiple locations in North America, Europe, and Asia. The study locations include China (18 sites), Japan (16 sites), and several European countries (including 7 UK sites).
Patient eligibility criteria	Key inclusion criteria Adults (≥18 years) with definite or probable CIDP*, who had: a CDAS score of ≥2 at screening, and an INCAT score of ≥2 (a score of 2 had to be exclusively from leg disability) at the first run-in visit or at Stage.	Key inclusion criteria Adults (≥18 years) who completed Week 48 of Stage B in the ARGX-113-1802 (ADHERE) trial, deteriorated during Stage B of ADHERE, been offered participation due to early termination in ADHERE, or completed a previous open-label extension trial cycle in ADHERE+.

	Had never received CIDP treatment or had not received it within 6 months of study entry ("off treatment") OR receiving CIDP treatment (i.e., corticosteroids, intravenous or subcutaneous immunoglobulin, or both) but willing to discontinue that treatment. Participants who received CIDP treatment within 6 months before study entry or who discontinued treatment were required to have evidence of ECMD[†] in the run-in period, and participants who were off treatment who had documented evidence of recent active disease could directly enter Stage A.	
	Key exclusion criteria The pure sensory CIDP variant Polyneuropathies of other causes A total IgG concentration less than 6 g/L at screening Pregnant, lactating, or planning pregnancy during the trial Significant comorbid disease, recent or planned major surgery, use of prohibited medications/therapies, or any condition that could confound results or pose undue risk	Key exclusion criteria Week-48/end-of-study visit in ADHERE or prior OLE >14 days before OLE start, or >21 days since last IMP dose Pregnant, lactating, or planning pregnancy during the trial Significant comorbid disease, recent or planned major surgery, use of prohibited medications/therapies, or any condition that could confound results or pose undue risk
Trial drugs	Subcutaneously administered. Efgartigimod 1,000 mg once weekly (Stage A and Stage B). Matched placebo containing 2,000 U/ml of PH20 (Stage B only).	Subcutaneously administered. Efgartigimod 1,000 mg once weekly.
Concomitant medication	Efgartigimod is indicated as monotherapy, with no concomitant CIDP therapy permitted during the trial.	Efgartigimod is approved as a monotherapy and as such no concomitant CIDP therapy was allowed during the trial.
Primary endpoints	Run-in: ECMD to demonstrate active disease before treatment initiation. Stage A: Percentage of participants with confirmed ECI (responders). Stage B: Time to first aINCAT deterioration during Stage B, defined as an increase of ≥ 1 point on the aINCAT score compared with Stage B baseline. Increases of 1 point in aINCAT required confirmation at a second study visit 3-7 days after the original change was documented. Changes of 2 points or more did not require confirmation at a consecutive study visit.	Incidence of TEAEs and serious TEAEs by standard of care and PT and incidence of clinically significant laboratory abnormalities.

	Primary endpoints in both Stages A and B were assessed by the site investigator and monitored centrally.	
Other endpoints used in the model/specified in scope	Run-in: No secondary endpoints. Stage A secondary endpoints: Time to initial confirmed ECI during Stage A Time to first improvement (in aINCAT, I-RODS, or grip strength) during Stage A Change from Stage A baseline in aINCAT, I-RODS, MGS, MRC sum and TUG test scores EQ-5D-5L Stage B secondary endpoints: Time to CIDP disease progression in Stage B (from stage B baseline to the first I-RODS score decrease of ≥ 4 points) Proportion of participants with functional improvement compared with Stage B baseline (improvement of ≥ 4 point in I-RODS score) Changes from Stage B baseline in aINCAT, I-RODS, MGS, MRC sum and TUG test scores EQ-5D-5L Safety and tolerability endpoints: Incidence of treatment-emergent adverse events (TEAEs), discontinuations due to TEAEs, and serious TEAEs in Stages A and B	Secondary endpoints: Change from baseline over time in aINCAT score, MRC sum score, I-RODS score, MGS, and TUG score Percentage of participants without clinical deterioration over time, defined by aINCAT increase ≥ 1 point compared to baseline Percentage of participants with titres of antidrug antibodies against efgartigimod and the presence of neutralising antibodies against efgartigimod Efgartigimod serum concentrations over time Changes from baseline over time in serum IgG levels (total) Change from baseline over time in EQ-5D-5L, BPI-SF, TSQM-9, RT-FSS, and HADS Percentage of participants with self- or caregiver-administered treatment over time
Other outcomes of interest	Changes in serum IgG concentrations (total IgG) over time (Stage A and Stage B). Exploratory endpoints evaluated the following additional patient-reported outcome measures: BPI-SF, TSQM-9, RT-FSS, HADS, and PCIG.	Infections by IgG level over time.

Source: Allen et al (2024)⁵⁵; Clinical Study Report ARGX-113-1802¹⁴; ADHERE+ PNS publication and clinicaltrials.gov entry^{11, 15}

*A baseline CIDP diagnosis for each participant was confirmed by an independent expert adjudication CIDP confirmation committee of neurologists with extensive clinical and research experience in CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society guidelines (EFNS/PNS) 2010.¹⁶

† ECMD was defined as an at least 1-point increase in aINCAT score, at least a 4 point (centile metric) decrease in the I-RODS, or at least an 8 kPa decrease in grip strength.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; BPI-SF: Brief Pain Inventory Short Form; CDAS: CIDP disease activity score; CIDP: Chronic inflammatory demyelinating polyneuropathy; ECI: Evidence of clinical improvement; ECMD: Evidence of clinically meaningful deterioration; EQ-5D-5L: EuroQol 5-Dimension 5-Level Questionnaire; HADS: Hospital Anxiety and Depression Scale; IgG: Immunoglobulin G; INCAT: Inflammatory Neuropathy Cause and Treatment; I-RODS: (24-item) Inflammatory Rasch-built Overall Disability Scale; MGS: Mean grip strength; MRC: Medical Research Council; OLE: Open-label extension; PGIC: Patient Global Impression of Change; PT, Preferred term; RT-

Table 25. EAG's summary of the design, conduct and analysis of ADHERE Stage B

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Appendix B3.1	Appropriate Patients were randomised 1:1 to efgartigimod or placebo using interactive response technology with stratification by aINCAT score change in Stage A (i.e., no change in aINCAT score or aINCAT score decrease of ≥ 1 point) and previous CIDP medication within 6 months before screening (i.e., off treatment, corticosteroid treatment, or intravenous or subcutaneous immunoglobulin treatment).
Concealment of treatment allocation	Appendix B3.1 and ADHERE clinical study report	Appears appropriate Participants were centrally assigned to randomised treatment using an interactive response technology system.
Eligibility criteria	2.3	Some concerns regarding prior treatments The key inclusion and exclusion criteria of ADHERE allowed the inclusion of patients with no prior treatment with Igs and patients with no history of prior treatment with Igs in the 6 months prior to the study. The EAG is therefore concerned that the prior treatments in ADHERE may not fully align with the company's proposed positioning of efgartigimod for patients with unsatisfactory treatment with Igs (IVIg or SCIg).
Blinding	3.1	Likely to be appropriate Double-blind with the investigator, investigational site staff, participant, funder, and funder's designated contract research organisation masked to treatment during Stage B until the final database lock. The study drugs in Stage B were provided in identical blinded vials.
Baseline characteristics	2.6.1.1	Trial population may not fully align with the company's proposed population for efgartigimod in the treatment pathway The EAG's clinical experts generally considered the baseline characteristics of patients in ADHERE to be reasonable although one expert noted a possible slight under-representation of black or African American patients. The EAG is also concerned with regards the prior treatments of patients in ADHERE and that they may not fully align with the company's proposed positioning of efgartigimod for patients with unsatisfactory treatment with Ig (IVIg or SCIg) as not all patients in the trial had a prior history of treatment with Ig and it is unclear if patients on Ig met the company's definition of unsatisfactory treatment (high burden of Ig, or refractory or intolerant to Ig).

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Dropouts	2.4.1.2 and Appendix B2	Appears reasonable In Stage B, most discontinuations in both arms reflected the event-driven study stop (participants still on study when the 88th relapse was reached [n=61]). Total discontinuations for other reasons were similar between trial arms. One death occurred in the placebo arm due to pneumonia.
Statistical analysis		
Sample size and power	2.4	Appears reasonable ADHERE was an event-driven trial, which finished when 88 relapses (events) were reached in stage B. Based on a relapse rate of efgartigimod versus placebo for the Stage B primary endpoint of 0.50 (hazard ratio [HR] 0.50), 88 relapses were required to provide 90% power at a one-sided α level of 0.025 with a log-rank test. To obtain a sufficient number of patients randomly assigned into Stage B, up to 360 patients were required to be enrolled into Stage A. Patients continued to be randomly assigned into Stage B until 88 events were observed. The EAG notes that a total of 322 participants entered Stage A (36 directly and 286 after the run-in period) and 221 of these were randomised and treated in Stage B (n=111 with efgartigimod; n=110 with placebo) prior to study completion (88 relapse events).
Handling of missing data	Not reported	Appears reasonable Patients who discontinued the study during Stage B or were lost to follow-up without experiencing relapse were censored at the time of their last aINCAT assessment. Right censoring was used with no additional imputation.
Outcome assessment	2.4	Appears reasonable The Stage B primary endpoint was analysed via Cox regression modelling in the modified intention-to-treat (mITT) population. Participants who completed the study at Week 48 without relapse or withdrew early for any other reason (including completion of the trial) were censored at the last aINCAT assessment. The Cox model was stratified for randomisation stratification factors (previous CIDP medication and aINCAT score during Stage A), with a fixed-effect term included as a covariate for randomised treatment. Secondary endpoints in Stage B were analysed as follows: • The time to CIDP disease progression during Stage B was analysed in the same way as the primary endpoint. • The percentage of participants with improved functional level, measured by the I-RODS score during Stage B, was analysed by exact logistic regression, with a fixed effect term for randomised treatment and I-RODS score at the end of Stage A included as a covariate. The odds ratio (OR) was obtained from an exact logistic regression model with treatment as a fixed effect along with the associated 95% CI

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
		and two-sided p value; this analysis was done overall and also stratified by previous CIDP therapy and aINCAT score during stage A. Exact Clopper–Pearson two-sided 95% CI limits were calculated for the proportion of participants with disease progression in each arm. Changes from Stage B baseline in aINCAT score, I-RODS score, MGS, and other secondary endpoints in Stage B were analysed descriptively.
Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; CI, confidence interval; CIDP, chronic inflammatory demyelinating polyneuropathy; EAG, External Assessment Group; ECI, evidence of clinical improvement; I-RODS, (24-item) Inflammatory Rasch-built Overall Disability Scale; Igs, immunoglobulins; IVIg, intravenous immunoglobulin; MGS, mean grip strength; mITT, modified intent-to-treat; OR, odds ratio; SCIg, subcutaneous immunoglobulin.		

3.3 Critique of the clinical effectiveness analysis and interpretation

The EAG provides a summary of the key clinical effectiveness results of relevance to the NICE final scope from Stage A and Stage B of ADHERE and from ADHERE+, with a focus on adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) score as this is the key measure of clinical effectiveness used in the company's economic model.

3.3.1 ADHERE Stage A efficacy results

Following successful completion of the run-in phase, 322 patients entered Stage A of ADHERE. As discussed in Section 3.2.3, when interpreting the results it is important to note that all patients were treatment-free at baseline of Stage A due to the wash-out period during the run-in phase.

3.3.1.1 Stage A primary endpoint: ECI response

A total of 66% (n=214, 95% CI: 61.0-71.6) of patients in stage A of ADHERE had evidence of clinical improvement (ECI) with efgartigimod by the completion of Stage A (Table 26). A pre-specified sensitivity analysis excluding the 18 participants who were ongoing in Stage A at study completion (after the 88th relapse in Stage B) resulted in a higher percentage (70% (n=214/304) [95% CI: 64.9% to 75.5%]) of all participants in Stage A with confirmed ECI (CS Table 11). A smaller proportion of patients (61%) demonstrated confirmed ECI with efgartigimod when only the subgroup of patients with prior IVIg or SCIg treatment was considered.

Based on the results in Table 26, the EAG considers it important to note that a substantial proportion of patients in the pre-specified sensitivity analysis (30% of all patients and 39% those who received IVIg or SCIg prior to enrolment in ADHERE) showed clinical deterioration when treatment was

withdrawn in the run-in phase, but did not achieve ECI with efgartigimod (**Key issue 4**). This appears to be a crucial consideration when interpreting the results, as it suggests that many patients who switch to efgartigimod may have poorer outcomes than on prior treatments, particularly those who were previously treated with Ig.

Table 26. ADHERE Stage A – confirmed ECI responders (primary endpoint) by prior CIDP therapy in the sensitivity analysis (Stage A safety analysis set excluding participants ongoing in Stage A at the 88th relapse event in Stage B) (reproduced from Table 11 of the CS)

	Any prior therapy N=304 n (%)	Corticosteroids n=59 n (%)	IVIg or SCIg n=158 n (%)	Off treatment n=87 n (%)
Number of participants with confirmed ECI	214 (70)	49 (83)	97 (61)	68 (78)
95% CI	64.9-75.5	71.0-91.6	53.3-69.0	68.0-86.3
Number of participants without confirmed ECI	90 (30)	10 (17)	61 (39)	19 (22)
Completed Stage A treatment without confirmed ECI	21 (7)	2 (3.4)	8 (5)	11 (13)
Discontinued treatment in Stage A	69 (23)	8 (14)	53 (34)	8 (9)
Discontinued early for other reasons	69 (23)	8 (14)	53 (34)	8 (9)
Source: Clinical Study Report ARGX-113-1802 ¹³¹ Abbreviations: CI, confidence interval; ECI, evidence of clinical improvement; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.				

3.3.1.2 Stage A secondary and other endpoint efficacy results

The median time to initial confirmed ECI with efgartigimod in Stage A was 43.0 (95% CI: 31.0 to 51.0) days and 40% of patients had ECI by week 4 (n=128). Treatment with efgartigimod in Stage A resulted in improvements in baseline for mean aINCAT score, mean grip strength (MGS), mean 24-item Inflammatory Rasch-built Overall Disability Scale (I-RODS) score and mean scores for the EuroQol 5-Dimension 5-Level Visual Analogue Scale (EQ-5D-5L-VAS) (Table 27). The EAG notes that aINCAT measures a patient's level of impairment in their arms and legs, with each part being scored between 0 and 5 points, resulting in an aINCAT total score between 0 and 10. An aINCAT score of 0 represents no functional impairment and 10 represents the inability to make any purposeful movement with either arms or legs, therefore, lower aINCAT scores represent better outcomes. In contrast, higher MGS and I-RODS scores represent improvements in function.

Table 27. ADHERE Stage A change from Stage A baseline in aINCAT score, I-RODS score, MGS score, MRC sum score, TUG test score and EQ-5D-5L VAS at Stage A last assessment (Stage A safety analysis set; reproduced from Table 12 of the CS)

Secondary endpoint	Efgartigimod (N=322)
aINCAT	
N	■
Mean change from baseline (SD)	-0.9 (1.71)
Median change from baseline (min, max)	■
I-RODS score	
N	■
Mean change from baseline (SD)	7.7 (15.48)
Median change from baseline (min, max)	■
MGS (dominant hand), kPa	
N	■
Mean change from baseline (SD)	12.3 (18.68)
Median change from baseline (min, max)	■
MGS (non-dominant hand), kPa	
N	■
Mean change from baseline (SD)	11.2 (21.12)
Median change from baseline (min, max)	■
MRC sum score mean change from baseline (SD)	■
TUG test score mean change from baseline (SD)	■
EQ-5D-5L VAS	
n	■
Change from baseline (SE)	10.7 (22.3)
Source: Clinical Study Report ARGX-113-1802 ¹³¹ Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; EQ-5D-5L VAS, 5-Level European Quality of Life 5 Dimensions Visual Analogue Scale; I-RODS, (24-item) Inflammatory Rasch-built Overall Disability Scale; MGS, mean grip strength; MRC, Medical Research Council; SD, standard deviation; SE, standard error; TUG, Timed Up and Go.	

In response to clarification questions, the company provided a breakdown of the results for patients who achieved ECI on aINCAT during Stage A by the ECMD measure used during the run-in phase (Table 28). The EAG notes that while ■ of patients who completed the run-in were assessed using aINCAT, a relatively high percentage were assessed using I-RODS or MGS.

Table 28. Stage A clinical improvement based on aINCAT, by measure of clinically meaningful deterioration during run-in (Stage A safety analysis set) (adapted from clarification response Table 1)

Way of confirmed ECI during Stage A	Way of ECMD during run-in						Total n (%)
	ECMD on aINCAT only n (%)	ECMD on I-RODS only n (%)	ECMD on MGS only n (%)	ECMD on I-RODS and MGS n (%)	No ECMD on any parameter n (%)	Did not enter run-in n (%)	
ECI on adjusted INCAT	████	████	████	████	-	████	████

Source: argenx data on file - tables, figures and listings table 14.2.4.1.³

Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause And Treatment score; ECI, evidence of clinical improvement; ECMD, evidence of clinically meaningful deterioration; INCAT, Inflammatory Neuropathy Cause And Treatment score; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; MGS, mean grip strength.

A range of exploratory efficacy endpoints were reported from Stage A in the CS including additional measures of health-related quality of life. Results for pain severity and intensity (Brief Pain Inventory–Short Form [BPI-SF]), fatigue (the Rasch-transformed Fatigue Severity Scale [RT-FSS]), and anxiety and depression (Hospital Anxiety and Depression Scale [HADS]) all showed reductions following treatment with efgartigimod (CS Table 14). In addition, improvements were noted in the global satisfaction with CIDP treatment (9-item Treatment Satisfaction Questionnaire for Medication [TSQM-9]) and the Patient’s Global Impression of Change [PGIC] score (CS Table 14).

3.3.2 ADHERE Stage B efficacy results (double-blinded, randomised)

A total of 221 (69%) patients out of the 322 who started Stage A of ADHERE were deemed to have ECI and were randomised in Stage B. The EAG notes that all patients entering Stage B had demonstrated ECI with efgartigimod in Stage A and were then randomised to treatment with either efgartigimod (N=111) or placebo (N=110). The EAG is therefore concerned that the results from Stage B are confounded by prior efgartigimod treatment and notes that the efgartigimod arm represents continued treatment with efgartigimod, while the placebo arm reflects discontinuation/withdrawal of efgartigimod (**Key issue 2**).

3.3.2.1 Stage B primary endpoint: Time to first relapse

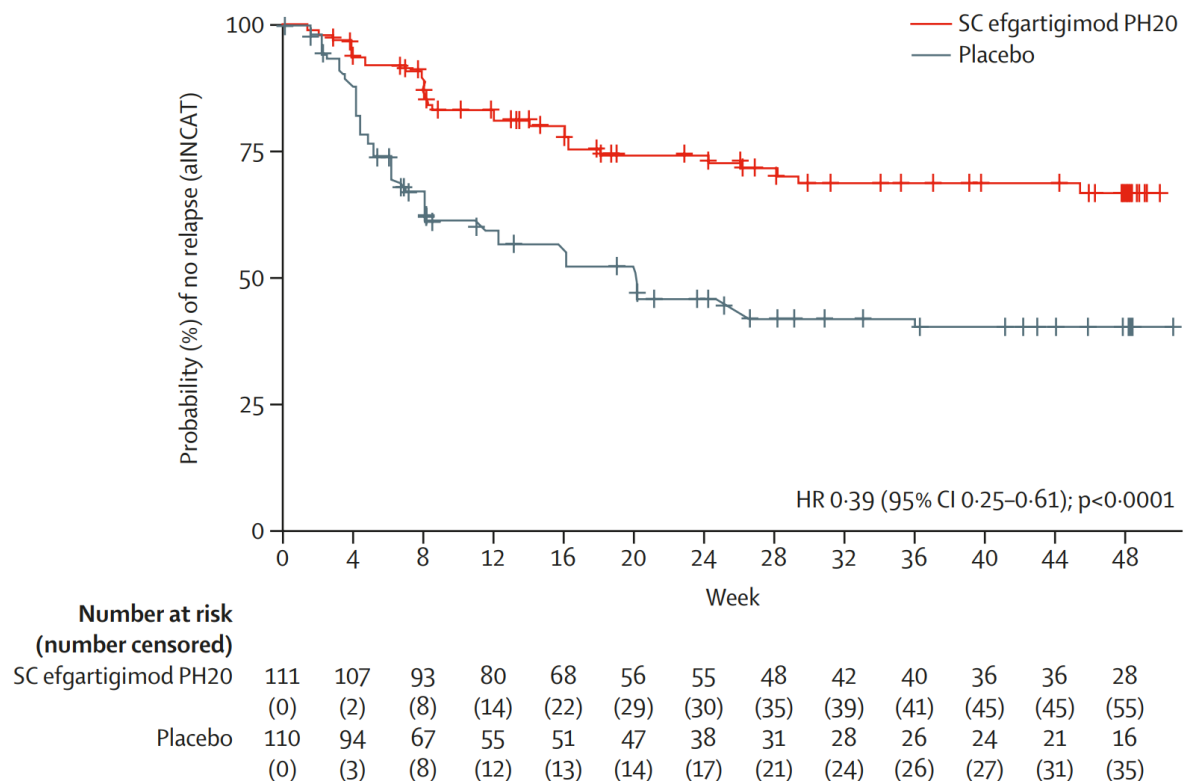
Relapse rate, based on time to first aINCAT score deterioration of ≥ 1 point, was assessed as part of the primary endpoint in ADHERE Stage B. There was a statistically significant difference in time to first relapse with efgartigimod compared with placebo at Week 48 in the modified intention-to-treat population (HR 0.39, 95% CI: 0.25 to 0.61, $p < 0.0001$ [estimated from a Cox proportional hazard model stratified by prior CIDP therapy and aINCAT score during Stage A]; Figure 3). The EAG notes

that a consistent effect was seen in the prior treatment with IVIg or SCIg (HR 0.30 [95% CI: 0.15 to 0.57] and corticosteroid subgroups (HR 0.29 [95% CI: 0.11 to 0.81])). The difference in the baseline off-treatment subgroup was substantially smaller, with a non-statistically significant difference between efgartigimod and placebo (HR 0.72 [95% CI: 0.34 to 1.53])).

The median time to clinical deterioration could not be calculated for the efgartigimod treatment arm because fewer than 50% of patients had clinically deteriorated. The median time to deterioration in the placebo arm was 140.0 days (95% CI: 75.0 to not calculated [NC]) days (Figure 3). At the point of study completion, there were fewer relapses in participants in the efgartigimod arm (n=31 [27.9%]) than the placebo arm (n=59 [53.6%]) with a risk difference for efgartigimod versus placebo of -25.7 (95% CI: -38.0 to -11.4; nominal p=0.0001).

Although the results indicate reduced relapse rates with efgartigimod compared to placebo, the EAG has concerns about the reliance on aINCAT to measure relapse in Stage B, as discussed in Section 3.2.3 (**Key issue 3**). The EAG considers there to be uncertainty surrounding the extent to which relapse rates in both arms may have been underestimated by excluding the use of I-RODS or MGS as indicators of relapse, despite their use in Stage A. This potential source of bias should be noted when considering the magnitude of benefit of efgartigimod over placebo in regard to relapse rates.

Figure 3. ADHERE Stage B – Kaplan–Meier analysis of the relative risk of CIDP relapse based on time to first aINCAT deterioration in participants treated with efgartigimod or placebo (mITT analysis set) (reproduced from Figure 6 of the CS)



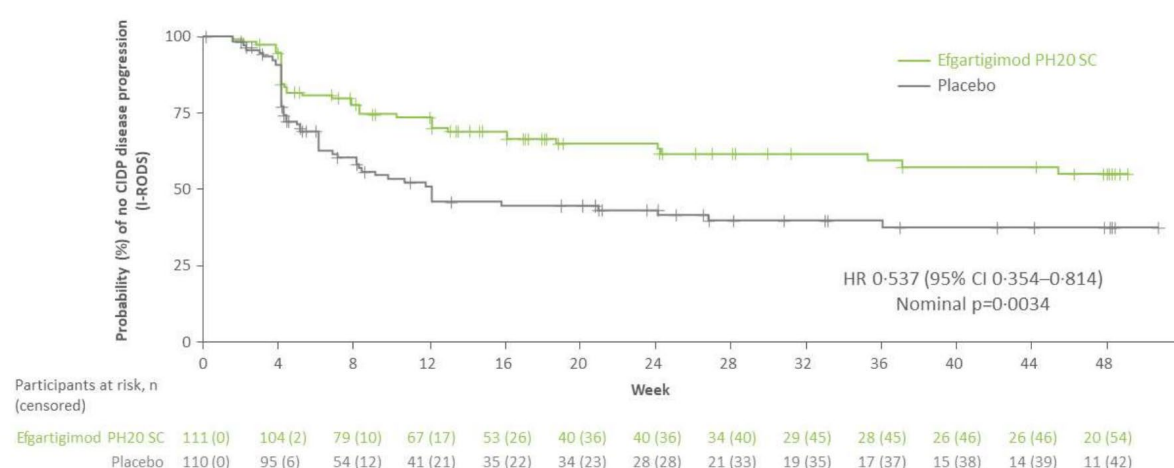
Source: Allen *et al.* 2024⁵⁵

Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CI, confidence interval; CIDP, chronic inflammatory demyelinating neuropathy; HR, hazard ratio; mITT, modified intent-to-treat; SC, subcutaneous.

3.3.2.2 Stage B secondary endpoint efficacy results

Results for the analysis of time to I-RODS deterioration supported the results of the analysis for time to aINCAT deterioration (Figure 4) and demonstrated that patients in the efgartigimod arm had a lower probability of I-RODS deterioration than patients in the placebo arm (HR 0.54, 95% CI: 0.35 to 0.81; nominal p value=0.003). The median time to I-RODS deterioration could not be calculated for participants in the efgartigimod arm (95% CI: 247.0 to not calculated [NC]) and was 85 days (95% CI: 50.0 to 253.0) in the placebo arm (Figure 4).

Figure 4. ADHERE Stage B Kaplan–Meier analysis of time to I-RODS deterioration in participants treated with efgartigimod or placebo (mITT analysis set, reproduced from figure 8 of the CS)



Source: Allen *et al.* 2024⁵⁵

Note: The HR was obtained from a Cox proportional hazard model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and aINCAT during Stage A.

Abbreviations: aINCAT: Adjusted Inflammatory Neuropathy Cause and Treatment; CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyneuropathy; HR: Hazard ratio; I-RODS: Inflammatory Rasch-built Overall Disability Scale; mITT: Modified intent-to-treat; SC: Subcutaneous.

A summary of the results for the secondary endpoints from Stage B is presented in Table 29. The secondary endpoint results showed that patients in the efgartigimod arm of Stage B generally maintained or showed improvements during Stage B across the secondary endpoints, whereas those in the placebo arm generally deteriorated (Table 29). For quality of life, EuroQoL 5-Dimension 5-Level (EQ-5D-5L) visual analogue scale (VAS) scores were reasonably stable over Stage B for patients in the efgartigimod arm (mean change from Stage B baseline of 0.5, SD 17.4), whereas the placebo group experienced a deterioration of -10.2 (SD 23.5) (Table 29).

Table 29. ADHERE Stage B – summary of secondary endpoint results of participants treated with efgartigimod or placebo (reproduced from Table 15 of the CS)

Secondary Endpoint	Measure	Efgartigimod, n (%)	Placebo, n (%)	HR/OR (95% CI)	Nominal p-value
Time to CIDP progression	Time to first I-RODS deterioration, n ≥4 points, n (%)	40 (36)	57 (52)	HR 0.54 (0.35 to 0.81)	0.0034
Improved functional level	I-RODS improvement of ≥4 points from Stage B baseline, n (%)	50 (45)	40 (36)	OR 1.44 (0.81 to 2.57)	0.23

aINCAT score	Mean (SE) change from Stage B baseline to last assessment	0.1 (0.1)	0.9 (0.19)	-	-
I-RODS score	Mean (SE) change from Stage B baseline to last assessment	0.8 (1.17)	-7.0 (1.84)	-	-
MGS (dominant hand), kPa	Mean (SE) change from Stage B baseline to last assessment	2.1 (1.26)	-8.2 (1.98)	-	-
MGS (non-dominant hand), kPa	Mean (SE) change from Stage B baseline to last assessment	2.0 (1.64)	-6.9 (2.04)	-	-
MRC sum score	Mean (SE) change from Stage B baseline to last assessment	-0.3 (0.43)	-3.0 (0.86)	-	-
TUG test, seconds	Mean (SE) change from Stage B baseline to last assessment	0.8 (0.36)	1.9 (0.60)	-	-
EQ-5D-5L VAS	Mean (SD) change from Stage B baseline to last assessment	0.5 (17.4)	-10.2 (23.5)	-	-

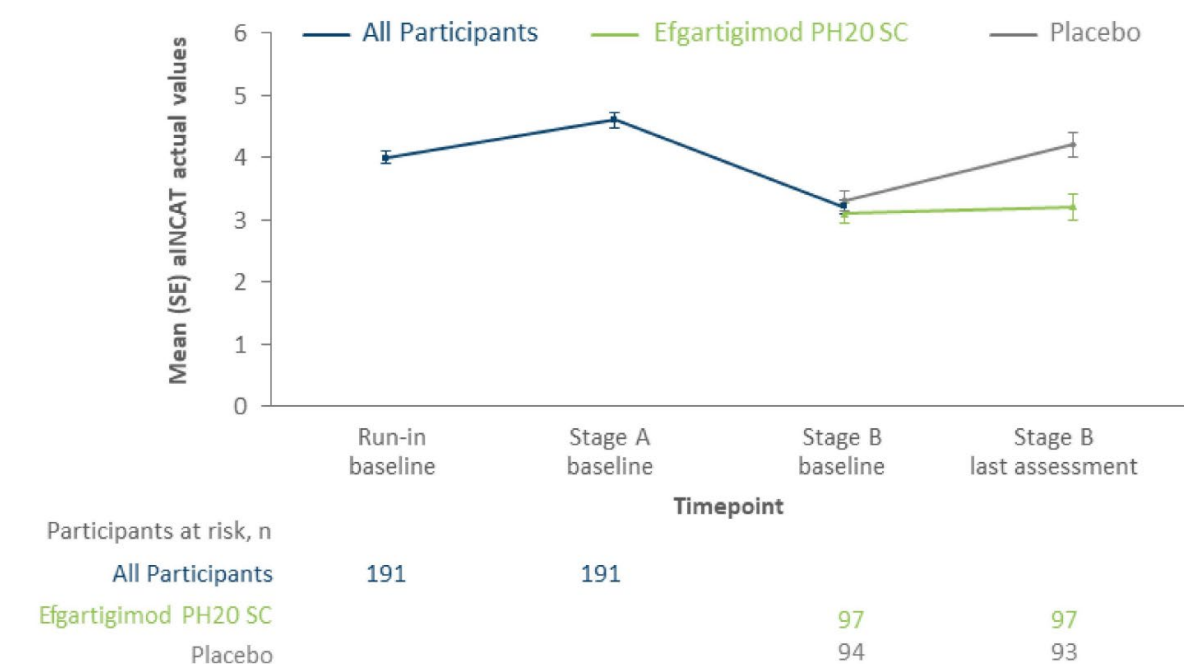
Source: Allen *et al.* 2024⁵⁵

Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CI, confidence interval; ECI, evidence of clinical improvement; HR, hazard ratio; I-RODS, (24-item) Inflammatory Rasch-built Overall Disability Scale; MGS, mean grip strength; MRC, Medical Research Council; OR, odds ratio; SD, standard deviation; SE, standard error; TUG, Timed Up and Go.

3.3.2.3 Stage B post-hoc endpoint efficacy results for longitudinal mean aINCAT scores of Stage A responders

The CS also included results from a *post-hoc* analysis of longitudinal mean aINCAT score between the baseline prior to the run-in phase, up to the last assessment in Stage B (Figure 5). The EAG notes that an aINCAT score of 0 represents no functional impairment and a score of 10 represents the highest possible level of functional impairment. The results of the longitudinal mean aINCAT score analysis, therefore, suggest a benefit with treatment with efgartigimod in Stage A of ADHERE that is maintained during Stage B. In contrast, patients randomised to placebo during Stage B returned to a similar functional level as the beginning of the run-in period. However, the EAG notes that this analysis only included 191 of the 221 patients randomised in Stage B and not the full mITT Stage B population (possibly due to the exclusion of the Stage A direct entry patients). It also comprises a *post-hoc* analysis, and so the EAG recommends the results are interpreted with caution.

Figure 5. ADHERE longitudinal mean aINCAT scores of Stage A responders from run-in baseline to last assessment in Stage B (post-hoc analysis; run-in and mITT analysis sets [reproduced from Figure 9 of the CS])



Source: Allen *et al.* 2024⁵⁵

Note: Stages A and B baseline were defined as the last available value before the first administration of the investigational medicinal product in Stages A and B, respectively, and Stage B last assessment as the last non-missing post-baseline value in Stage B.

Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; mITT, modified intent-to-treat; SC, subcutaneous.

3.3.3 ADHERE+ efficacy results

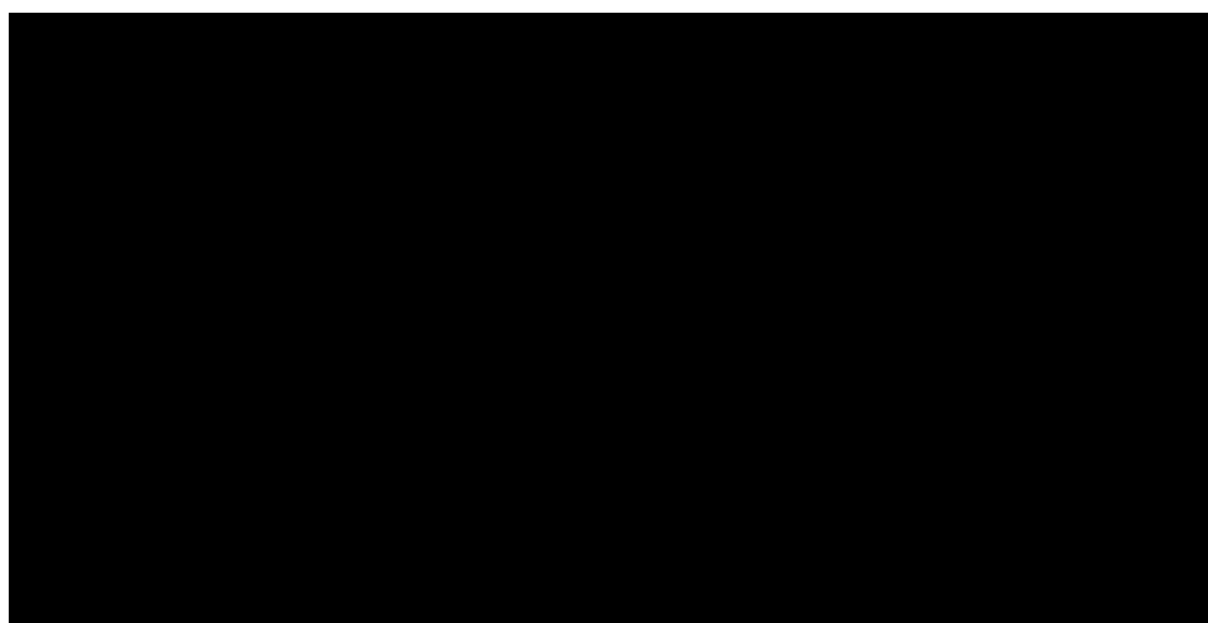
As noted in Section 3.2.2, ADHERE+ is ongoing and the results reported in the CS were from an interim data cut-off at Week 36 (February 2024) with limited numerical data presented. The EAG notes that 229 patients were enrolled in ADHERE+, but only 228 patients received treatment with efgartigimod and were included in the analyses. In response to clarification, the company reported that 200 patients enrolled in ADHERE+ from Stage B (although 1 of these did not receive treatment in ADHERE+), and the remaining patients came directly from the run-in phase (n=7) or Stage A (n=22) as they were still ongoing in these earlier phases when the 88th relapse event occurred in Stage B leading to termination of ADHERE+. The CS initially reported pooled results for all patients irrespective of how they entered ADHERE+. However, the EAG had concerns that each group was at a different point in the treatment pathway or had shown different levels of response to efgartigimod or placebo. In addition, patients who were randomised to placebo in Stage B had a break in treatment prior to entry into ADHERE+, which the EAG does not consider to be reflective of expected

treatment in clinical practice in England. The company therefore provided the results separated by patient's entry routes into ADHERE+, which are included in the EAG's critique below.

3.3.3.1 ADHERE+ results

The company reported that patients showed [REDACTED] in functional disability, daily activity and muscle strength between baseline at the start of the ADHERE run-in phase and Week 36 of ADHERE+. Figure 6 shows the mean (SE) change in aINCAT score from the baseline of ADHERE+ by prior treatment group. The company highlighted that the later timepoints in the analysis are subject to uncertainty due to the small patient numbers and the interim nature of the analysis.

Figure 6. aINCAT Score: Mean (SE) changes From OLE Baseline (mITT Analysis Set; reproduced from Figure 3 of company response to clarification questions)



Notes: ADHERE+ baseline corresponds to the last available value before the first EFG PH20 SC administration in ADHERE+. Week 4 was the first time point at which efficacy assessments were measured.

Abbreviations: aINCAT: Adjusted INCAT disability score; EFG PH20 SC: Efgartigimod for subcutaneous administration coformulated with recombinant human hyaluronidase PH20; INCAT: Inflammatory Neuropathy Cause and Treatment; mITT: Modified intent-to-treat; OLE: Open-label extension; PBO PH20 SC: Placebo for subcutaneous administration coformulated with recombinant human hyaluronidase PH20; RI: Run-in during ADHERE.

Figure 6 suggests a [REDACTED] in aINCAT from baseline in ADHERE+ with efgartigimod treatment (Figure 6), although the difference between groups declines over time, with a [REDACTED] from Week 84 onwards. This is not unexpected, as patients who were in the placebo group in ADHERE were gaining benefits from the switch to active treatment in ADHERE+. However, the EAG considers these results to be highly uncertain, due to the small patient numbers, particularly from Week 108 onwards, and

concerns about the variety of entry routes into ADHERE. To address some of these concerns, the results of ADHERE+ based on patients' entry routes from ADHERE are considered in Table 30. The EAG considers the results for the patients randomised to efgartigimod in ADHERE and who either completed ADHERE without relapse, or deteriorated during Stage B, to be the most relevant when considering the longer-term effects of efgartigimod. As highlighted above, the EAG does not consider the patients who were randomised to placebo in Stage B and therefore had a break in treatment, to be reflective of expected clinical practice in England.

Patients who received efgartigimod in ADHERE and who completed Week 48 without relapse showed [REDACTED] aINCAT scores and MGS during ADHERE+ and [REDACTED] in I-RODS (Table 30). This may indicate sustained longer-term benefits for patients who respond well to efgartigimod. The EAG notes that patients who experienced clinical deterioration in ADHERE demonstrated [REDACTED] in aINCAT, MGS and I-RODS in ADHERE+. The EAG's clinical experts considered that this could reflect a lag period in some patients, where it takes time to respond to improvements with cumulative dosing. However, it is unclear how long this lag period may last with efgartigimod.

While the results of ADHERE+ indicate there may be longer-term benefits of efgartigimod beyond the 48 weeks assessed in ADHERE, concerns about the relevance of the trial population to the company's proposed population (**Key issue 1**) (discussed in Sections 2.3.1, 3.2.3 and 3.3), the different entry routes into ADHERE+, the small patient numbers at later timepoints and the interim analysis methods, mean that the EAG considers the longer-term effects of efgartigimod to be associated with substantial uncertainty.

Table 30. Outcomes of ADHERE+ separated by patient entry route from Stage B of ADHERE

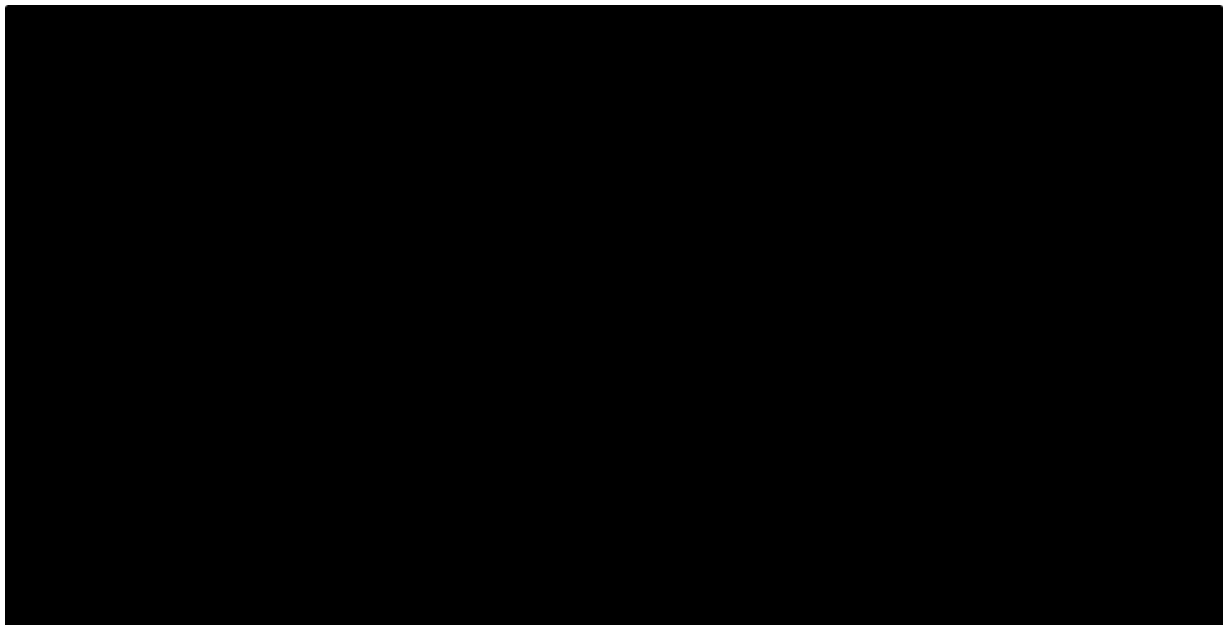
ADHERE+ entry	Efgartigimod		Placebo		All patients	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Change in aINCAT score from ADHERE+ baseline						
Patients who completed Week 48 of ADHERE	██████	██████	██████	██████	██████	██████
Patients who experienced clinical deterioration during ADHERE	██████	██████	██████	██████	██████	██████
Patients ongoing in ADHERE at the stopping point in the trial	██████	██████	██████	██████	██████	██████
Change in I-RODS score from ADHERE+ baseline						
Patients who completed Week 48 of ADHERE	██████	██████	██████	██████	██████	██████
Patients who experienced clinical deterioration during ADHERE	██████	██████	██████	██████	██████	██████
Patients ongoing in ADHERE at the stopping point in the trial	██████	██████	██████	██████	██████	██████
Change in MGS (dominant hand, kPa) from ADHERE+ baseline						
Patients who completed Week 48 of ADHERE	██████	██████	██████	██████	██████	██████
Patients who experienced clinical deterioration during ADHERE	██████	██████	██████	██████	██████	██████
Patients ongoing in ADHERE at the stopping point in the trial	██████	██████	██████	██████	██████	██████
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; kPa, kilo Pascals; MGS, mean grip strength; n, number; SE, standard error						

3.3.3.2 Efficacy results from the ADHERE+ substudy of patients treated with q2w dosing schedule

A total of [REDACTED] patients were enrolled in the ADHERE+ substudy and had received the q2w dosing schedule of efgartigimod as of the latest data cut-off (04 April 2025). The company reported that patient demographics and baseline characteristics at Stage A baseline were similar for the substudy and overall ADHERE population.

Results for median time to clinical deterioration (primary endpoint, defined as worsening of adjusted INCAT [≥ 1 point increase] or I-RODS [≥ 4 points decrease] or MGS [≥ 8 kPa decrease]) compared to q2w baseline was [REDACTED]; Figure 7). The company reported that at week 12 and 24, the proportion (95% CI) of patients without clinical deterioration was [REDACTED] and [REDACTED] respectively. With over [REDACTED] of patients deteriorating at week 24 of the q2w schedule, the EAG's clinical experts reported that they would be unlikely to consider switching to less frequent dosing with efgartigimod if a patient was already responding on a weekly dose. They noted that there might be specific subgroups who would benefit more than others from q2w dosing, but without further evidence they would not be able to identify which patient groups these were likely to be.

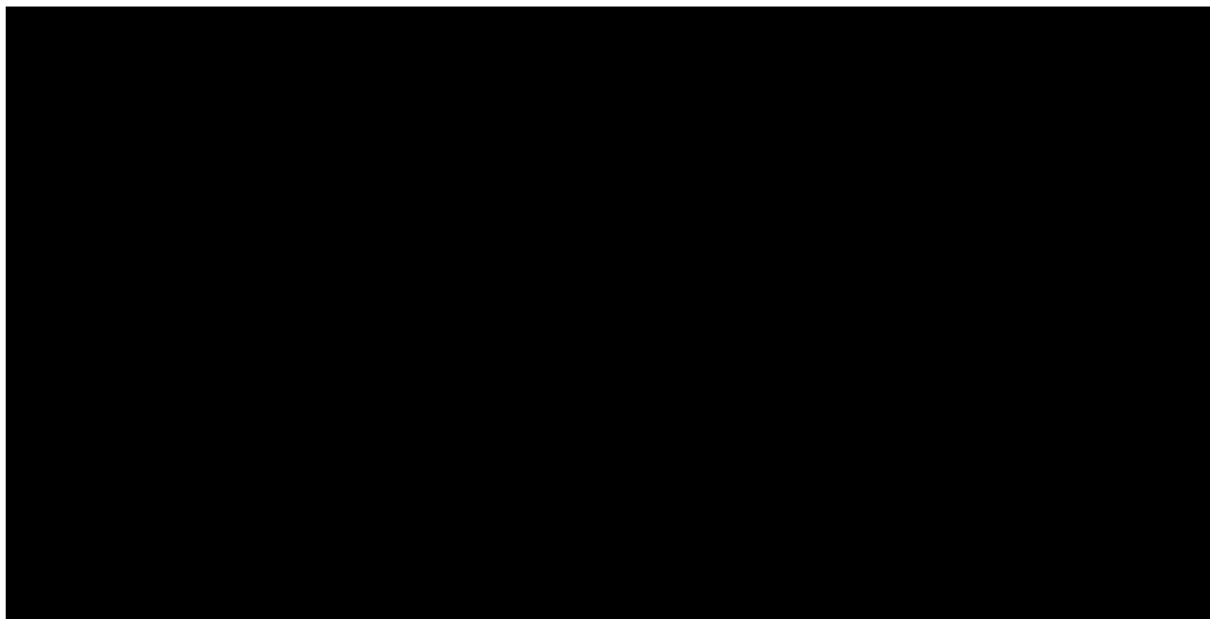
Figure 7. ADHERE+ substudy – Kaplan–Meier analysis of time to clinical deterioration during q2w dosing regimen (efficacy analysis set, reproduced from Figure 10 of the CS)



Note: Clinical deterioration (protocol V6) was defined as worsening of adjusted INCAT (≥ 1 point increase) or I-RODS (≥ 4 points decrease) or MGS (≥ 8 kPa decrease) compared to Q2W-1 baseline.

Of the patients who deteriorated on q2w dosing, [REDACTED] restabilised on weekly dosing, with [REDACTED] having restabilised by the first post-q1w baseline visit (week 6) (Figure 8). While this indicates that any negative effects of q2w dosing can be reversed for many patients, the EAG is concerned that [REDACTED] of patients who were previously stable on weekly dosing did not return to stable levels of disease following the switch to q2w dosing.

Figure 8. ADHERE+ substudy – Kaplan-Meier time to restabilisation on q1w after clinical deterioration during q2w dosing (reproduced from Figure 11 of the CS)



Note: Restabilisation (protocol V6) was defined as improvement on at least one of the parameters on which the participant deteriorated in Q2W-1 compared to the Q1W-1 baseline: adjusted INCAT (≥ 1 point decrease), I-RODS (≥ 4 points increase), or MGS (≥ 8 kPa increase).

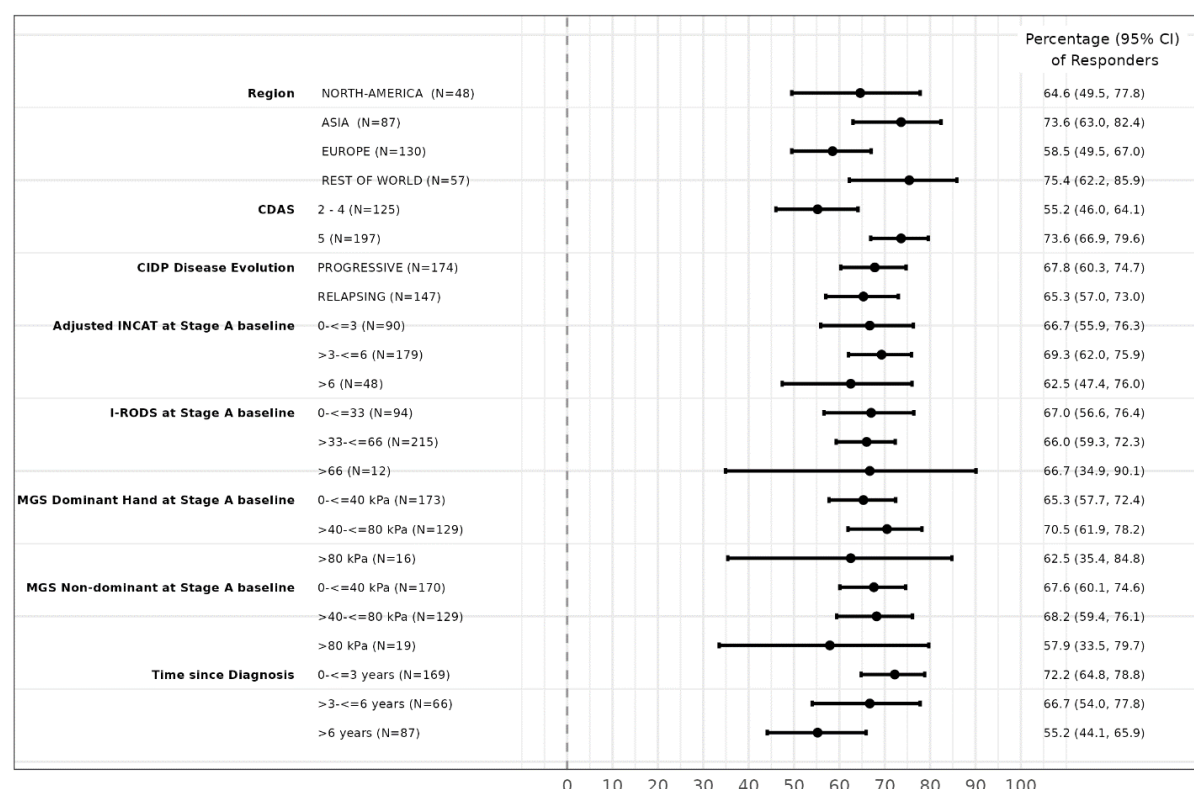
3.4 Subgroup results

3.4.1 ADHERE Stage A subgroup analyses

The company conducted *post-hoc* subgroup analyses by baseline characteristics for ECI response in Stage A of ADHERE (Figure 9). The EAG notes that there was a higher percentage of ECI responders with efgartigimod in the subgroup of patients with unstable disease activity (CDAS score of 5) than those with stable disease activity (CDAS score of 2 to 4) (73.6% vs 55.2%, respectively). In addition, the EAG notes that there was a trend suggesting a decrease in the percentage of ECI responders with

increasing time since first diagnosis of CIDP (subgroup with time since diagnosis of 0 to ≤ 3 years [72.2% responded]_compared to those with >6 years since first diagnosis [55.2% responded]).

Figure 9. ADHERE Stage A forest plot of a post-hoc analysis of confirmed ECI responders (primary endpoint) by subpopulation of participants treated with open-label efgartigimod (reproduced from Figure 12 of the CS)



Source: Clinical Study Report ARGX-113-18021

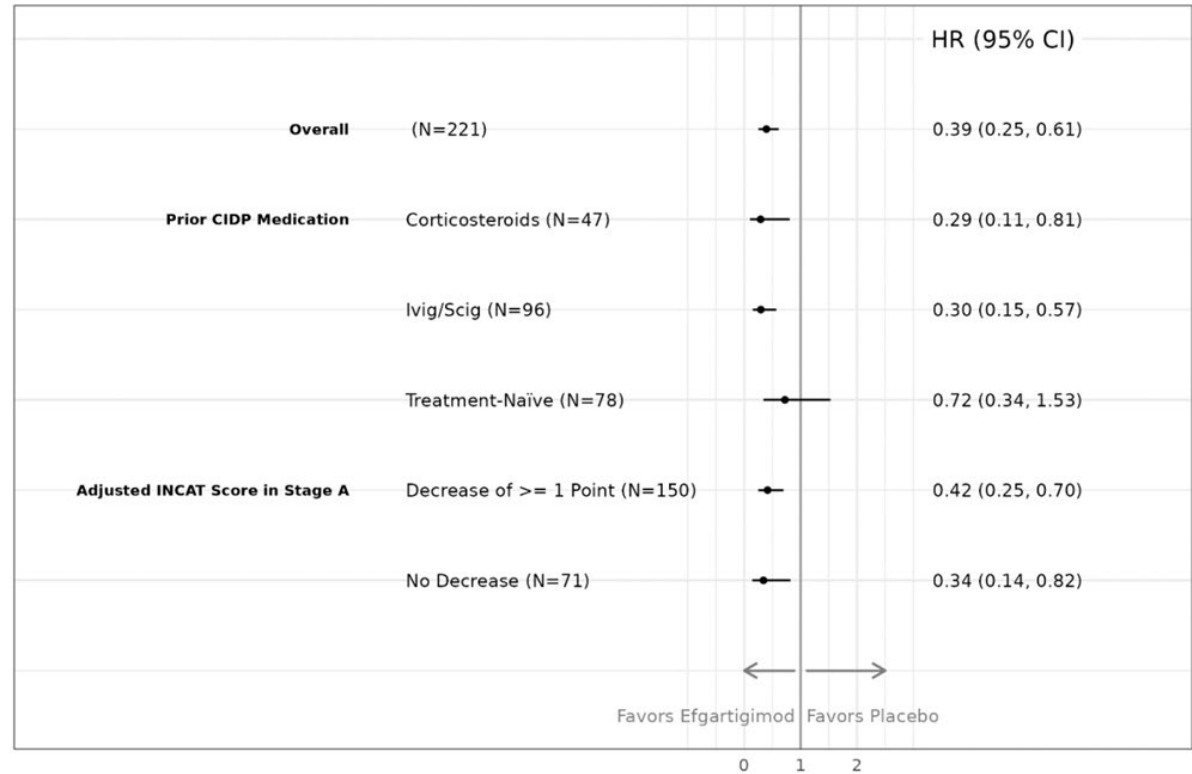
Abbreviations: CDAS: Chronic inflammatory demyelinating polyneuropathy disease activity status; CI: Confidence interval; CIDP: Chronic inflammatory demyelinating polyneuropathy; ECI: Evidence of clinical improvement; INCAT: Inflammatory Neuropathy Cause and Treatment score; I-RODS: (24 item) Inflammatory Rasch-built overall disability scale; MGS: Mean grip strength.

3.4.2 ADHERE Stage B subgroup analyses

Subgroup analyses for ADHERE Stage B were performed by the stratification factors used during randomisation. Results were reported for the primary efficacy outcome of time to first occurrence of clinical deterioration (Figure 10). As discussed in Section 3.3.2.1, the results in the subgroup of patients off treatment for the 6 months prior to screening do not reach statistical significance and suggest a lower probability of response to efgartigimod compared with the other prior treatment

subgroups. The CS notes that this may be due to the withdrawal stage of ADHERE, where prior Ig patients had already shown deterioration on aINCAT. The change in aINCAT score during Stage A (no change in aINCAT score vs decrease in aINCAT score of ≥ 1 point) did not appear to have a major effect on time to clinical deterioration during Stage B.

Figure 10. Time to first occurrence of clinical deterioration in Stage B of ADHERE - overall and by stratification factors for randomisation (mITT analysis set, reproduced from Figure 13 of the CS)



Source: Clinical Study Report ARGX-113-18021
 Note: Treatment-naïve participants were defined as participants with no history of prior CIDP therapy or having discontinued their CIDP therapy (corticosteroids, IVIg, or SCIg therapy) for ≥ 6 months before screening. The HRs were obtained from a Cox proportional hazards model.
 Abbreviations: CI: Confidence interval; INCAT: Inflammatory neuropathy cause and treatment; CIDP: Chronic inflammatory demyelinating polyneuropathy; HR: Hazard ratio; IVIg: Intravenous immunoglobulin; mITT: Modified intent-to-treat; SCIg: Subcutaneous immunoglobulin.

3.5 Safety

3.5.1 ADHERE

The CS presented information on treatment-emergent adverse events (TEAEs), serious AEs (SAEs), Grade 3 AEs, AEs of special interest (AESI) and injection site reactions in both Stage A (Table 31) and Stage B of ADHERE (Table 32).

Although [REDACTED] of patients had an AE in Stage A of the trial, only a relatively small percentage of these were classed as serious [REDACTED] or Grade 3 or higher [REDACTED]). Few TEAEs occurred in 5% or more

of patients, with injection site erythema (10%), CIDP worsening (5%), headache (5%) and injection site pain (5%) the most commonly reported.

Table 31. Safety outcomes from Stage A of ADHERE. Reproduced from Table 20 of the CS

Type of AE	Efgartigimod (n=322) n (%)
≥1 TEAE	██████████
≥1 SAE	██████
≥1 Grade 3 or higher AE	██████
≥1 AESI	██████████
≥1 Injection-related reaction	██████████
≥1 Injection site reaction	██████████
Fatal AEs	██████

Abbreviations: AE, adverse event; AESI, adverse event of special interest; n, number; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Stage B resulted in a similar percentage of TEAEs to Stage A (64% in the efgartigimod arm, 56% in the placebo arm) (Table 32). Although efgartigimod resulted in a higher percentage of TEAEs than placebo, the percentage of SAEs and Grade 3 or higher TEAEs were similar between the two arms, and no fatal AEs were reported with efgartigimod. The most common TEAEs differed to those in Stage A, with COVID-19 (efgartigimod 17%, placebo 13%), injection site bruising (efgartigimod 5%, placebo 1%), injection site erythema (efgartigimod 5%, placebo 0%) and nasopharyngitis (efgartigimod 5%, placebo 3%) occurring in 5% or more of efgartigimod patients. Other TEAEs were low in both arms, with the exception of upper respiratory tract infection which occurred in 10% of placebo patients but only 2% of efgartigimod patients.

In response to the EAG's clarification questions, the company reported information on serious or Grade 3 or higher TEAEs in Stage B (Table 30 of clarification responses). The frequency of Grade 3 or higher TEAEs was low, and [REDACTED] between the efgartigimod and placebo arms. Only [REDACTED] Grade 3 or higher TEAE was reported in more than one patient in the efgartigimod arm, with [REDACTED]

Table 32. Safety outcomes from Stage B of ADHERE. Reproduced from Table 22 of the CS

Type of AE	Efgartigimod (n=111) n (%)	Placebo (n=110) n (%)
≥1 TEAE	71 (64.0)	62 (56.4)
≥1 SAE	6 (5.4)	6 (5.5)

Searches for the ITC SLR were last updated in September 2023, two years prior to the date of the company's submission. The searched included RCTs or observational studies, including cross-sectional, case-control, cohort or retrospective cohort studies, which assessed the effectiveness of efgartigimod, corticosteroids (oral or IV) or Ig (IVIg or SCIg). PLEX was not included as one of the treatments of interest, although the EAG considers this a potentially relevant comparator for the subgroup of patients who are intolerant or refractory to Ig (Section 2.3.3). However, searches for the global SLR included PLEX and were updated in July and August 2025. As such, any more recent evidence, including evidence for PLEX, should still have been identified for consideration in the ITCs. Both SLRs used similar inclusion criteria, although a minimum of 5 patients were needed for inclusion in the ITC SLR compared to 10 patients in the global SLR. Some, very small, studies published after September 2023 could therefore have been excluded.

The CS reports that 78 relevant publications were identified in the ITC SLR. After pooling with the 123 includes in the clinical SLR, a total of 183 publications were considered for inclusion in the ITCs. Of the 183 publications, there were 167 full-text studies, one study report, and 15 congress abstracts, from which five (four RCTs and one pilot study) were considered for inclusion in the ITC.

The company selected change in aINCAT score as the outcome of interest for the ITC to align with the health states in the company's cost-effectiveness model. Following a feasibility assessment which assessed study design, methods of randomisation, concomitant therapies, eligibility criteria and discontinuation criteria, only one of the studies identified in the SLRs (Epoch 1 of ADVANCE-CIDP-1) was considered suitable for the aINCAT ITC.

Assessment of the quality of the evidence for Epoch 1 of ADVANCE-CIDP-1 is presented in Table 33. The EAG considers ADVANCE-CIDP-1 to provide high-quality evidence on the use of SCIg for CIDP, although it has concerns about the applicability of the results to the company's proposed population (**Key issue 5**). Key concerns are similar to those highlighted for the ADHERE trial, including uncertainty over how many patients would have met the company's definition of a high burden of treatment and the exclusion of patients who were intolerant or refractory to Ig (Table 33).

In addition to concerns about the relevance of the population, the EAG has concerns about the different trial designs used in the ADHERE and ADVANCE-CIDP-1 trials (**Key issue 5**). Prior to randomisation to efgartigimod or placebo in Stage B of the ADHERE, all patients underwent a wash-out period, followed by 12 weeks of treatment with efgartigimod (Stage A). In contrast, all patients

in ADVANCE-CIDP-1 were already receiving IVIg and were randomised directly to SCIg or placebo with no washout period between treatments. These differences lead to the following potential issues:

- Patients in the two trials were at a different stage in the clinical pathway. The company's response to clarification questions highlights how treatment with efgartigimod in Stage A of ADHERE effectively reflects induction treatment, while the RCT phase of the trial (Stage B) reflects maintenance treatment. Patients in ADVANCE-CIDP-1 were all receiving IVIg as maintenance treatment prior to the trial and were therefore switching to a different type of maintenance treatment if they were randomised to SCIg.
- ADHERE only compared efgartigimod to placebo in those patients who had already shown a response to efgartigimod (Section 3.2.1). Patients in ADVANCE-CIDP-1 were required to have previously responded to IgG treatment and were receiving a stable dose of IVIg treatment for ≥ 12 weeks before screening, but enrolment in the RCT was not based on how well they responded to SCIg. The exclusion of non-responders in ADHERE could therefore bias the comparison in favour of efgartigimod.
- ADVANCE-CIDP-1 assessed the effects of switching from one active treatment (IVIg) to either another active treatment (SCIg) or placebo. ADHERE assessed the effects of remaining on a treatment which a patient had already responded to (efgartigimod) or being withdrawn from a treatment which they had already shown a response to (placebo) (Section 3.2.1).

The EAG considers that the potential issues outlined above may limit the validity of the ITC and the applicability of the results to the company's proposed population. This is discussed in more detail in the EAG's critique of the ITC (Sections 3.6.2 and 3.6.3)

Table 33. EAG's summary of the design, conduct and analysis of ADVANCE-CIDP-1 (Epoch 1)

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	ADVANCE-CIDP-1 supplementary appendix	Appropriate Patients were randomised 1:1 to fSCIG or placebo using an Interactive Web Response System. No information was provided about stratification factors at randomisation.
Concealment of treatment allocation	ADVANCE-CIDP-1 supplementary appendix	Appropriate Participants were centrally assigned to randomised treatment using an Interactive Web Response System. Treatment allocation was not revealed to patients, carers or the investigator.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Eligibility criteria	2.10.3.1 and ADVANCE-CIDP-1 report	Some concerns regarding how prior Ig dose reflects the company's proposed population Patients were included if they had previously responded to Ig and were receiving a stable dose of IVIg (cumulative monthly dose of 0.4-2.4 g/kg for at least 12 weeks prior to screening). The wide range of doses mean that many patients will not meet the company's criteria for a high dose of Ig. Results are not separated by patients who received high or low doses of IVIg. No information is available to determine whether any patients would meet the company's definition of a high treatment burden. As patients had to be on a stable dose of IVIg and have responded to treatment, they do not meet the criteria for patients who are refractory or intolerant to Ig.
Blinding	ADVANCE-CIDP-1 supplementary appendix	Appropriate The trial was double-blind. The only unblinded study personnel were those who maintained any unblinded records in a secure, access-controlled location.
Baseline characteristics	ITC report, Table 16.1 and ADVANCE-CIDP-1 report	Concerns about differences in prior treatments and relevance to the company's proposed positioning of efgartigimod All patients in ADVANCE-CIDP-1 received prior Ig, compared to 44.1% of patients in the efgartigimod arm and 42.7% of patients in the placebo arm of ADHERE. Fewer patients in ADVANCE-CIDP-1 had received prior corticosteroids (11.3% for SCIg and 10.0% for placebo compared to 23.4% for efgartigimod and 21.8% for placebo in ADHERE) No patients were treatment-naïve in ADVANCE-CIDP-1, compared to 32.4% for efgartigimod and 35.5% for placebo in ADHERE. Therefore, the EAG has concerns that the population may not align with that proposed by the company. It also has concerns that there are considerable differences between the prior treatment history of patients in the two trials which introduces heterogeneity into the ITCs.
Dropouts	ADVANCE-CIDP-1 report	Appears reasonable Few discontinuations and the number of discontinuations were similar between trial arms.
Statistical analysis		
Sample size and power	ADVANCE-CIDP-1 report and supplementary appendix	Appears reasonable Trial recruitment was ended early due to the COVID-19 pandemic, prior to achieving the target sample size (138 patients randomised compared to the target of 174). The original target sample size was chosen to detect a difference in relapse rates of 18% with a power of 80% ($p < 0.05$). The target sample size was revised based on new evidence for relapse rates with fSCiG and placebo, resulting in a target sample size of 120 (60 per trial arm with 15% drop-out

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
		rate) to detect at treatment difference of 29% with a power of 90% (p<0.05).
Handling of missing data	ADVANCE-CIDP-1 report	Some concerns Missing information for relapse outcomes was imputed as no relapse. Sensitivity analyses indicate that the choice of imputation could result in an overestimation of the treatment effect.
Outcome assessment	2.4	Appears reasonable ADHERE-CIDP 1 reported change in aINCAT score from baseline as a tertiary endpoint. The outcome was reported separately for each arm and so the mean difference was calculated by the company as part of the ITCs, using statistical formulas (not described) to estimate the SE of the mean difference. Other tertiary outcomes (change in MGS and change in MRC sum score) were also reported but not included in the company's ITC. ITCs were conducted for these additional outcomes in response to clarification questions.
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; EAG, External Assessment Group; fSCIG, facilitated subcutaneous immunoglobulin; Ig, immunoglobulins; ITC, indirect treatment comparison; IVIg, intravenous immunoglobulin; MGS, mean grip strength; MRC, Medical Research Council; SCIG, subcutaneous immunoglobulin; SE, standard error		

Given the EAG's concerns about the relevance of the ADVANCE-CIDP-1 population to the company's proposed population, and differences in the design of the ADVANCE-CIDP-1 and ADHERE trials, it considered whether other trials identified in the company's SLR would be more appropriate for comparisons with efgartigimod. The company's reasons for exclusion of the other trials from the aINCAT ITC were:

- ADVANCE-CIDP-1 [Epoch 2] (SCIG vs placebo): Only included patients who relapsed in Epoch 1;
- PATH (high- or low-dose SCIG vs placebo): Mean value of aINCAT not reported;
- PIMPA (SCIG pump vs manual push technique): Small sample size, different discontinuation criteria to ADHERE and outcome was measured using INCAT rather than aINCAT;
- Katzberg 2013 (IVIg): Small sample size and outcome was measured using INCAT rather than aINCAT.

While a small sample size does not necessarily prevent the inclusion of a trial in an ITC, the use of a different outcome measure in the PIMPA and Katzberg trials justifies the exclusion of these trials. The exclusion of Epoch 2 of ADVANCE-CIDP-1 also appears appropriate, as only patients who

relapsed on SCIg in the first Epoch of the trial were included, thereby overlooking all patients who showed a positive response to treatment.

Although the PATH trial, which randomised patients to low dose SCIg (0.2g/kg), high dose SCIg (0.4g/kg) or placebo did not report the mean change in aINCAT, the company reported an ITC between ADHERE and PATH as part of its sensitivity analyses (Appendix 9 of the ITC report). Mean change in aINCAT and SD were estimated using methods reported by Wan *et al.* 2014 based on median, minimum and maximum values reported in the trial.¹⁷ The EAG notes that this approach assumes that data are normally distributed, which could not be verified from the data available in PATH. As such, there is a risk that, if the PATH data are skewed, the derived estimates may not accurately reflect the data (**Key issue 5**). In addition, the EAG has similar concerns about the population to those noted for ADVANCE-CIDP-1, including a lack of information to determine how many patients met the company's definition of a high treatment burden and the exclusion of patients who were intolerant to Ig (Table 88, Appendix 7.1). However, there are fewer concerns about differences in trial design than with ADVANCE-CIDP-1. Many aspects of the ADHERE trial design were based on the PATH trial, with both studies including a wash-out period, an active treatment phase for all patients, and an RCT phase. The EAG has included the results of comparisons between the ADHERE and PATH trials in its critique of the ITC results, alongside a discussion of these limitations.

An additional study (ICE), comparing IVIg (Gamunex) against placebo was identified in the searches and included in the sensitivity analyses for the ITC (Appendix 9 of the ITC report) but not reported in detail in the ITC report. The ICE trial randomised patients to IVIg (1 g/kg every three weeks) or placebo for 24 weeks, with non-responders crossing over to the alternative trial arm for an additional 24 weeks. Following the crossover period, any patients who responded to IVIg treatment were included in an extension phase where they were re-randomised to IVIg or placebo for a further 24 weeks. Given that comparisons with IVIg are relevant to the decision problem, the EAG requested clarification for the reasons behind the exclusion of ICE from the ITC. The company reported that:

- Patients in the ICE trial were different to those in ADHERE and the company's proposed population. ICE included patients who did not have prior treatment with IVIg, corticosteroids or PLEX in the three months prior to study entry. This does not align with the company's proposed population of Ig pre-treated patients;

- The IVIg loading dose in the first phase of the ICE trial represented an induction regimen, rather than the maintenance dose of efgartigimod which was received by patients in Stage B of ADHERE;
- The populations and reasons for leaving the first period of each trial differed. In ICE, patients were randomised to IVIg or placebo for 24 weeks. Non-responders were required to switch to the alternative treatment if they did not show any response by Week 6 or if they had deteriorated at any time point during the 24-week period. In contrast, patients in ADHERE were only able to progress to the RCT phase of the trial if they showed a response to efgartigimod.

Given these concerns, the company concluded that it was not feasible to conduct an ITC between ADHERE and the first period or crossover period of the ICE trial. Although the baseline characteristics were similar between the two trials, the EAG notes the company's concerns that, at the point the ADHERE trial would be compared with the first phase of the ICE trial, patients in ADHERE would have had up to 12 weeks treatment with efgartigimod, while patients in ICE would have been starting IVIg treatment following 3 months with no treatment for CIDP. This, in addition to the differences in trial design and the exclusion of non-responders from ADHERE mean that comparisons with the early stages of the ICE trial would be associated with substantial uncertainty.

Despite the company's concerns about comparisons between ADHERE and ICE, an ITC was included as part of the sensitivity analyses using results from the extension phase of the ICE trial. The EAG considers this to be an appropriate comparison since, at this point in the ICE trial, patients had received 24 weeks of prior IVIg treatment and were then re-randomised to IVIg or placebo. This is similar to ADHERE, where patients had 12 weeks of treatment with efgartigimod prior to randomisation to efgartigimod or placebo. However, this analysis is associated with similar limitations to those identified for ADVANCE-CIDP-1 and PATH, with uncertainty over how many patients in the ICE trial would have met the company's criteria for unsatisfactory treatment (**Key issue 5**). Comparisons were also based on a small number of patients from the ICE trial (31 in the IVIg arm, 26 in the placebo arm) and most baseline characteristics were only available for the first period of the trial and not for the extension phase which has implications for adjustments in the ITC (discussed in Section 3.6.2.1). These concerns are discussed in more detail in Section 3.6.3.1 and a quality assessment of ICE is reported in Table 89 (Appendix 7.2).

The EAG also had concerns about the company's decision to only report one outcome (change in aINCAT score) in its ITC given that there are multiple tools used to assess the symptoms of CIDP, and treatment decisions are often made using a combination of these measures (Section 2.3.4). In response to clarification questions, the company therefore provided additional ITCs for change in I-RODS score and MGS, using results from ADVANCE-CIDP-1, ICE (IVIg) and PATH (high- and low-dose SCIg).

3.6.2 Statistical methods

3.6.2.1 Primary ITC analysis (Change in aINCAT score)

As discussed in Section 3.6.1, the company's ITC feasibility assessment identified one study (ADVANCE-CIDP-1) which it considered appropriate for comparisons with ADHERE. Given the difference in trial design between the two studies as well as the substantial heterogeneity between baseline characteristics, an anchored MAIC was considered the most appropriate method to address these issues. The EAG considers this to be an appropriate decision but has concerns about some of the methods reported in the CS, including a lack of clear differentiation between prognostic factors and treatment effect modifiers, and uncertainty over the effectiveness of the weighting adjustments applied to the ADHERE population (**Key issue 5**).

As discussed in Section 3.2.1, only efgartigimod responders were included in the RCT phase of ADHERE, which may have resulted in an overestimation of the treatment effect compared to the standard RCT methodology used in ADVANCE-CIDP-1. While an anchored MAIC cannot control for these differences in trial design, the company attempted to reduce the heterogeneity between the trials by restricting the population of the ADHERE trial to better match the inclusion criteria of ADVANCE-CIDP-1. Only those patients from ADHERE who received IVIg or SCIg in the six months prior to screening were included in the ITC, and those who had an aINCAT score of ≥ 8 at baseline of Stage B were excluded. The population restrictions reduced the population available for comparison from the original 221 in Stage B of ADHERE to 96 patients. The EAG considers that restricting the ADHERE trial based on prior treatment may be reasonable, as it removed the treatment-naïve patients from the analysis, who do not appear to reflect the company's proposed population. Randomisation of ADHERE was also stratified by prior CIDP therapy. The removal of patients who had an aINCAT score of ≥ 8 is more of a concern as these patients had more severe symptoms and are therefore likely to have represented some of the company's subgroup of patients who have unsatisfactory treatment.

Following the population restrictions, the company reweighted the individual patient data (IPD) from ADHERE to better align the baseline characteristics with those of ADVANCE-CIDP-1. The company identified a number of potential treatment effect modifiers and prognostic factors based on feedback from two clinicians (Table 34). These broadly aligned with the views of the EAG's clinical experts, except for sex, which they did not expect to have a major impact on treatment effectiveness.

Table 34. Prognostic factors and treatment effect modifiers identified by the company's clinical experts. Reproduced from Table 12 of CS (Appendix 1.3)

Prognostic factors and/or treatment effect modifiers adjusted for in the ITC analysis	Prognostic factors and/or treatment effect modifiers that were not adjusted for in the ITC analysis
• Age • Sex • Disease duration / time from diagnosis • % prior treatment with corticosteroids • I-RODS • MRC sum score	• CIDP type (typical vs atypical) • Symmetrical vs asymmetrical symptoms • CIDP Disease Activity Status score • % prior treatment with Ig • % treatment naïve • MGS
Abbreviations: CIDP, Chronic inflammatory demyelinating polyneuropathy; Ig, Immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; ITC, indirect treatment comparison; MGS, mean grip strength; MRC, Medical Research Council	

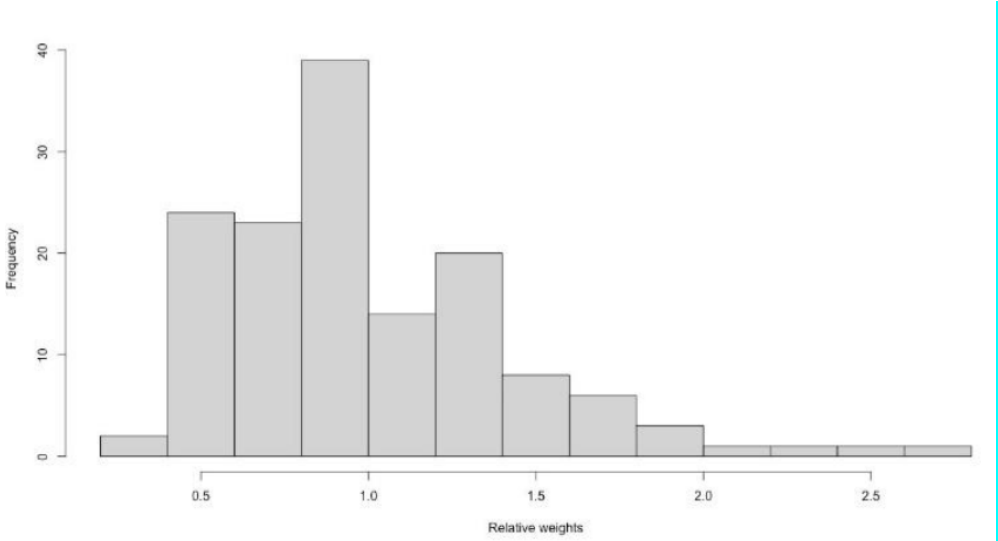
Although the EAG's clinical experts broadly agreed with the factors identified for adjustment, the EAG has concerns about the lack of differentiation between treatment effect modifiers and prognostic factors. NICE DSU TSD 18 recommends that only treatment effect modifiers are adjusted for when performing an anchored MAIC, as prognostic factors should be accounted for by individual trial randomisation, and further adjustments can result in over-matching.¹⁸ The company's ITC report states that, following a validation process with clinicians, all variables were identified as both prognostic factors and treatment effect modifiers, but no further information was provided about this validation process.

In addition to the lack of differentiation between treatment effect modifiers and prognostic factors, the EAG has concerns about the number of potential treatment effect modifiers identified which could not be adjusted for in the analysis (Table 34) (**Key issue 5**). Although the percentage of patients receiving prior Ig treatment and the percentage of treatment-naïve patients were addressed by the company's population restrictions, a number of other factors were not reported in ADVANCE-CIDP-1. This included the percentage of patients in each trial who had typical or atypical CIDP, which the EAG's clinical experts identified as an important treatment effect modifier. It is

unclear what impact this lack of adjustment may have had on the results of the ITC, leading to uncertainty when comparing the effectiveness of efgartigimod and SCIg.

Following the weighting adjustments, the effective sample size (ESS) was 84, and this, combined with the histogram of relative weight distributions (Figure 11), led the company to conclude that the analysis was based on a sufficiently large sample size with no major outliers driving the results. However, the EAG notes that uncertainty remains over how many of the patients in this re-weighted analysis met the company’s criteria for unsatisfactory prior treatment with Ig.

Figure 11. Relative weight distributions of the ADHERE population following weighting adjustments. Reproduced from Appendix 8 of the ITC report



Re-weighting of the IPD for ADHERE resulted in identical baseline characteristics between the two trials (Table 35). However, as discussed above, not every treatment effect modifier or prognostic factor outlined in Table 34 was reported in ADVANCE-CIDP-1 and so it is not possible to assess the similarity of other key patient characteristics between the two trials. This limitation should be considered when interpreting the results of the ITC, as there is the potential for these unmeasured (and unadjusted) factors to impact a patient’s response to treatment.

Table 35. Comparison between baseline characteristics of ADHERE and ADVANCE-CIDP-1 before and after population weighting adjustments in ADHERE. Reproduced from Table 20-3 of the ITC report

Baseline characteristics	ADVANCE-CIDP-1	ADHERE Stage B	
		Unweighted*	Weighted†
Number/ESS	132	96	84 (87.5%)
% female	43.9	40.6	43.9
Mean age (years)	54.4	54.3	54.4
Mean disease duration (years)	4.10	4.52	4.10
Mean aINCAT score	3.00	2.74	3.00
Mean I-RODS score	58.2	56.9	58.2
Mean MRC Sum Score	55.3	55.2	55.3
% receiving corticosteroids as prior treatment	10.6	7.3	10.6
* After selection of patients to meet inclusion/exclusion criteria in comparator study			
† Adjusted for baseline characteristics listed in the table			
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; ESS, effective sample size; I-RODS, Inflammatory Rasch-built Overall Disability Scale; MGS, mean grip strength			

In response to clarification questions, the company provided results for the change from baseline for the placebo arms of ADVANCE-CIDP-1 and the adjusted ADHERE population. Typically, following adjustments for treatment effect modifiers in an anchored MAIC, some differences in placebo response between trials may remain because of unadjusted prognostic factors. However, as the company considered the characteristics in Table 34 to be both treatment effect modifiers and prognostic factors, the population restrictions and weighting adjustments should have resulted in similar placebo responses between the trials.¹⁸ However, the EAG notes that even following the weighting adjustments, change from baseline in aINCAT remained much greater in the placebo arm of ADHERE than ADVANCE-CIDP-1 (Table 36).

The company attributed the limited impact of the weighting adjustments to differences in trial design, populations and unmeasured prognostic factors. The EAG agrees with this conclusion and considers that the treatment effect modifiers that could not be adjusted for due to limited reporting in ADVANCE-CIDP-1 are also likely to have had an impact on the differences between the trials. The company did not consider the differences in placebo response to be a major concern for the validity of the ITC. Instead, it was reported to demonstrate the limitations of comparing absolute changes across trials and support the use of the anchored MAIC, which estimates relative treatment effects in comparison to placebo. The EAG does not agree with this conclusion, instead considering that the issues discussed above (differences in trial design and limited adjustment of treatment effect modifiers) are likely to have affected patients' response to treatment. The impact of these underlying differences on relative treatment effects is unclear. The EAG considers this to be a major

limitation of the ITC, resulting in considerable uncertainty when interpreting the results of the anchored MAIC (**Key issue 5**).

In addition to the differences in placebo response between the two trials, the EAG notes that reweighting had a minimal impact on the change from baseline in the placebo arm of ADHERE (a reduction in aINCAT score of 0.21) (Table 36). This implies that the two studies have similar characteristics which, given the issues outlined above, does not appear to be a plausible assumption.

Table 36. Change from baseline in aINCAT in the unweighted and weighted placebo arm of ADHERE and ADVANCE-CIDP-1

Comparator trial		Placebo arm in comparator trial	Placebo in ADHERE Stage B	
			Unweighted*	Weighted
Change in aINCAT from baseline, mean (SE)				
ADVANCE-CIDP-1 (SCIg)	0.2 (0.155) [†]		1.53 (0.331)	1.32 (0.328)
* After selection of patients to meet inclusion/exclusion criteria in comparator study				
[†] Calculated from published SD=1.3 and n=70				
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; SCIg, subcutaneous immunoglobulin; SE, standard error				

The company used the same methodology for the sensitivity analyses for the PATH and ICE trials, including restricting the ADHERE population and applying weighting adjustments. For comparisons with PATH, ESS for the ADHERE placebo arm was relatively small (47.7 patients [52.4%] for high dose SCIg and 49.4 [54.3%] for low dose SCIg). ESS was higher for comparisons with ICE (77.1 patients [62.7% of patients in the placebo arm]).

The weighting adjustments resulted in matching baseline characteristics between ADHERE and both PATH and ICE (Tables 20-1, 20-2 and 20-4 of the ITC report) but had a minimal impact on the change from baseline in the ADHERE placebo arm (Table 37). Differences in placebo response were considerably smaller than those reported for comparisons with ADVANCE-CIDP-1. However, as with ADVANCE-CIDP-1, not all potential effect modifiers could be adjusted for due to lack of reporting in the comparator trials (**Key issue 5**). This was most apparent for comparisons with ICE, where information was only available for mean aINCAT score at the start of the extension phase. Other baseline characteristics were only reported for the first period of the trial, leaving a high number of unknown treatment effect modifiers and prognostic factors which may differ between ICE and ADHERE. The PATH trial did not report the percentage of patients with either typical or atypical CIDP, or the percentage with prior corticosteroid treatment.

Table 37. Change from baseline in aINCAT in the unweighted and weighted placebo arm of ADHERE and comparator trials

Comparator trial		Placebo arm in comparator trial	Placebo in ADHERE Stage B	
			Unweighted*	Weighted
Change in aINCAT from baseline, mean (SE)				
PATH (low dose SCIg)	1.3 (0.144) [†]	1.46 (0.338)	1.49 (0.363)	
PATH (high dose SCIg)	1.3 (0.144) [†]	1.46 (0.338)	1.42 (0.359)	
ICE (IVIg)	0.4 (1.7)	0.56 (1.423)	0.93 (1.932)	
* After selection of patients to meet inclusion/exclusion criteria in comparator study				
† Mean and SE are not reported in the PATH published data. These were calculated based on the sample number, the median and min/max using the approach published by Wan et al. (2014)				
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin; SE, standard error				

The EAG requested that the company provide a simulated treatment comparison (STC) as validation of the anchored MAIC. In response the company provided the results of an STC which included baseline aINCAT score and disease duration, as the two covariates identified by the unadjusted regression model to have a statistically significant interaction with treatment. Other covariates included in the MAIC, but not included in the regression model, were baseline age, percentage male, I-RODS, MRC sum score and proportion on prior corticosteroids. However, the EAG notes similar concerns to those reported for the anchored MAIC, as limited reporting in ADVANCE-CIDP-1 meant that many treatment effect modifiers (CIDP type, symmetry of symptoms, CIDP Disease Activity Status Score, percentage on prior Ig, percentage treatment-naïve and MGS) could not be assessed for inclusion in the STC. The NICE DSU TSD 18 notes that without the inclusion of all treatment effect modifiers which are imbalanced between two trials, the results of an STC are considered to be biased.¹⁸ As such, results of the company's STC are subject to similar concerns over uncertainty as those reported for the anchored MAIC, based on the inability to assess for potential imbalances between each of the factors which were unreported in ADVANCE-CIDP-1. Therefore, while the EAG considers the results of the STC in its discussion of the results (Section 3.6.3.1), concerns about the underlying heterogeneity between the two trials means that the EAG considers the results of the ITC likely to be biased, although the direction of bias is unclear (**Key issue 5**).

3.6.2.2 Additional ITC outcomes requested by the EAG

In response to clarification questions, the company performed additional ITCs for change in I-RODS and MGS from baseline. As with the ITCs for aINCAT, the adjustments resulted in identical baseline characteristics between ADHERE and each of the comparator trials (Tables 18-20, 22-23 and 25-26 of

the clarification response). However, the EAG notes that for some of the outcomes, particularly MGS, reweighting of the ADHERE population actually increased, rather than decreased, the difference in change from baseline between the placebo arms of ADHERE and the comparator trials (Table 38); i.e. making the placebo arms more dissimilar rather than more similar. Consequently, the EAG notes the same concerns as those outlined for the aINCAT ITCs (Section 3.6.2.1) about differences in treatment effect modifiers and prognostic factors which may have impacted the relative treatment effects in each trial (**Key issue 5**). The same concerns about the uncertainties associated with the comparisons with ADVANCE-CIDP-1, PATH and ICE in Section 3.6.2.1 therefore apply to each of the comparisons for I-RODS and MGS.

Table 38. Change from baseline in the unweighted and weighted placebo arm of ADHERE and the comparator trials

Comparator trial	Placebo arm in comparator trial	Placebo in ADHERE Stage B	
		Unweighted*	Weighted
Change in I-RODS score from baseline, mean (SE)			
ADVANCE-CIDP-1	-6.1 (1.640)	-13.61 (3.328)	-14.33 (3.673)
PATH (low dose SCIg)	-6.3 (1.612) [†]	-11.88 (3.206)	-11.09 (3.123)
PATH (high dose SCIg)	-6.3 (1.612) [†]	-11.88 (3.206)	-11.96 (3.310)
Change in MGS (dominant hand) from baseline, mean (SE)			
PATH (low dose SCIg)	-9.3 (2.206) [†]	-12.55 (2.847)	-15.80 (2.912)
PATH (high dose SCIg)	-9.3 (2.206) [†]	-12.55 (2.847)	-15.96 (3.447)
ICE (IVIg)	NR	NR	NR
Change in MGS (non-dominant hand) from baseline, mean (SE)			
PATH (low dose SCIg)	-10.4 (2.659) [†]	-10.00 (2.913)	-13.73 (2.614)
PATH (high dose SCIg)	-10.4 (2.659) [†]	-10.00 (2.913)	-13.50 (3.266)
ICE (IVIg)	NR	NR	NR
* After selection of patients to meet inclusion/exclusion criteria in comparator study			
† The mean and SE are not reported in the PATH published data. These were therefore calculated based on the sample number, the median and inter-quartile range using the approach published by Wan <i>et al.</i> 2014.			
Abbreviations: ESS, effective sample size; I-RODS, Inflammatory Rasch-built Overall Disability Scale; MGS, mean grip strength; NR, not reported; SCIg, subcutaneous immunoglobulin; SE, standard error			

3.6.3 Clinical effectiveness results

3.6.3.1 Primary ITC analysis (Change in aINCAT score)

Comparisons with ADVANCE-CIDP-1 indicated statistically significant benefits of efgartigimod over SCIg for change in aINCAT score, reflecting reduced levels of impairment (Table 39). The company considered these results to demonstrate the benefits of efgartigimod over established maintenance therapy.

However, the EAG notes that the differences between trials was not clinically meaningful (improvement of ≥ 1 point). Additionally, as discussed in Section 3.6.2.1, the EAG considers these results to be associated with considerable uncertainty, with notable differences in the placebo responses between ADHERE and ADVANCE-CIDP-1 (**Key issue 5**). The EAG therefore considers that much of the difference in treatment effectiveness may reflect the different trial designs and treatment effect modifiers that could not be adjusted for in the analyses.

Table 39. Results of the anchored MAIC for change from baseline in aINCAT. Values below 0 favour efgartigimod

Comparator trial	Comparator treatment	Follow-up time*	Difference in means (95% CI)	p value
ADVANCE-CIDP-1 † (n=132)	SCIg	32 weeks	-0.88 (-1.72 to -0.04)	0.040
ICE§ (n=57)	IVIg	24 weeks	-0.53 (-1.53 to 0.47)	0.297
PATH‡ (n=113)	SCIg (low dose)	25 weeks	-1.13 (-2.05 to -0.21)	0.015
PATH‡ (n=114)	SCIg (high dose)	25 weeks	-0.58 (-1.45 to 0.29)	0.194

* Follow-up data for ADHERE Stage B were available up to 48 Weeks. Data were analysed up to the same timepoint as that in the comparator study to more closely align the study designs

† Patients in ADVANCE-CIDP-1 were pre-treated with Ig

‡ The mean and SE are not reported in the PATH published data. These were therefore calculated based on the sample number, the median and min/max using the approach published by Wan et al. (2014). Patients in PATH were responders to Ig

§ Patients in the extension phase of ICE were IVIg responders from the first period of the ICE trial

Notes: all p values are nominal

Abbreviations: aINCAT; adjusted Inflammatory Neuropathy Cause and Treatment; CI, confidence interval; IVIg, intravenous immunoglobulin; MAIC, matched adjusted indirect comparison; SCIg, subcutaneous immunoglobulin

Results from the STC between ADHERE and ADVANCE-CIDP-1 were similar to those reported for the anchored MAIC:

- Difference in means (95% CI): -0.744 (-1.478 to -0.010), p=0.0468

However, as discussed in Section 3.6.2.1, the unmeasured treatment effect modifiers in ADVANCE-CIDP-1 leads to concerns about underlying heterogeneity between the two trials, leaving the results of the STC at risk of bias. As such, while the results of the STC provide some reassurance about the

methods used in the anchored MAIC, uncertainty remains over the comparative effectiveness of efgartigimod and SCIg.

Effect estimates also favoured efgartigimod over SCIg when ITCs were performed with the PATH trial, but results were only statistically significant in comparison to low dose SCIg. Comparisons with low dose SCIg were also the only effect estimate to exceed the value for a clinically meaningful difference (improvement of ≥ 1 point). The EAG notes that these comparisons are associated with fewer concerns about trial design than the comparisons with ADVANCE-CIDP-1 (Section 3.6.2.1). However, there are concerns about the robustness of this comparison due to potential differences in treatment effect modifiers and the uncertainty arising from the estimation of the mean and SE in the PATH trial (**Key issue 5**). The EAG is also uncertain whether many of those patients who required a low dose of SCIg would meet the company's criteria for unsatisfactory treatment.

The ICE trial is the only source of evidence for IVIg, and while the effect estimate numerically favours efgartigimod, results are not statistically significant and the difference between trials is not clinically meaningful. As discussed in Section 3.6.2.1, the EAG considers that this comparison may be more relevant to the decision problem than ADVANCE-CIDP-1, with similar inclusion criteria to ADHERE and fewer concerns about the differences in trial design. However, the EAG acknowledges that the lack of reporting of patient baseline characteristics for the extension phase of ICE is a major limitation, with weighting adjustments for the ADHERE population only possible for mean aINCAT score (**Key issue 5**). As such, there are an unknown number of treatment effect modifiers which may differ between the two studies.

Overall, the results indicate benefits, albeit not all statistically significant, of efgartigimod over both SCIg and IVIg. However, due to the wide range of limitations associated with each comparison, the EAG has concerns about the robustness of the results from each of the ITCs. All three ITCs are associated with uncertainty about the relevance of the trial populations to the company's proposed population and unreported treatment effect modifiers and prognostic factors. Comparisons with ADVANCE-CIDP-1 are further limited by differences in trial design to ADHERE and concerns about differences in placebo response, while there are concerns about the estimation of the mean and SE with the PATH trial, and about the lack of relevant baseline characteristics in the ICE trial. The EAG therefore considers there to be substantial uncertainty associated with each of the comparisons, making it difficult to draw any strong conclusions on the effectiveness of efgartigimod relative to Ig.

3.6.3.2 Additional ITC outcomes requested by the EAG

Comparisons of change in I-RODS score demonstrate statistically significant benefits of efgartigimod over both low doses and high doses of SCIg (Table 40), reflecting improvements in a patient's ability to perform daily activities. Effect estimates for MGS numerically favoured efgartigimod over SCIg and IVIg but only comparisons with high-dose SCIg in the dominant hand were statistically significant. The EAG notes the very wide 95% CIs associated with these comparisons, reflecting the high levels of heterogeneity in the analyses.

These comparisons indicate potential benefits of efgartigimod over current treatment options, particularly in relation to improvements in I-RODS. However, the EAG notes that the limitations discussed in Section 3.6.3.1 also apply to these additional outcomes (**Key issue 5**). The EAG again highlights the substantial uncertainty in the results. As a result, the EAG is unable to draw strong conclusions about the potential benefits of efgartigimod over SCIg or IVIg.

Table 40. Results of the anchored MAICs for change from baseline in I-RODS and MGS. Values greater than 0 favour efgartigimod

Number of patients		Difference in means change from baseline for efgartigimod vs comparator treatment	
Comparator trial	Comparator treatment	Difference in means (95% CI)	p value
Change in I-RODS score from baseline			
PATH [†]	SCIg (low dose)	██████	██████
PATH [†]	SCIg (high dose)	██████	██████
ADVANCE-CIDP-1 [‡]	SCIg	██████	██████
Change in MGS from baseline (dominant hand)			
PATH [†]	SCIg (low dose)	██████	██████
PATH [†]	SCIg (high dose)	██████	██████
ICE [*]	IVIg	██████	██████
Change in MGS from baseline (non-dominant hand)			
PATH [†]	SCIg (low dose)	██████	██████
PATH [†]	SCIg (high dose)	██████	██████
ICE [*]	IVIg	██████	██████

* Up to 24 weeks. Patients in the extension phase of ICE were IVIg responders from the first period of ICE

[†] Up to 25 weeks in PATH. The mean and SE are not reported in the PATH published data. These were therefore calculated based on the sample number, the median and min/max using the approach published by Wan et al. (2014). Patients in PATH were responders to Ig.

[‡] Up to 32 weeks in ADVANCE-CIDP-1. Patients in ADVANCE-CIDP-1 were pre-treated with Ig.

Abbreviations: CI, confidence interval; I-RODS, Inflammatory Rasch-built overall disability scale; IVIg, intravenous immunoglobulin; MAIC, matched adjusted indirect comparison; MGS, mean grip strength; SCIg, subcutaneous immunoglobulin

3.7 Conclusions of the clinical effectiveness section

The EAG considers the decision problem presented in the CS to be appropriate to address the NICE scope. The population is identifiable in clinical practice and the choice of Ig as a comparator appears justified for most patients, although the EAG considers that PLEX would have been a more appropriate comparator for patients who are refractory or intolerant to Ig.

While the decision problem appears appropriate, the EAG considers there to be substantial uncertainty in the current evidence base. The ADHERE trial indicated a reduction in physical impairment with efgartigimod in comparison to placebo, alongside improvements in mean grip strength (MGS) and the ability to perform daily activities. However, the EAG has concerns that the inclusion criteria of ADHERE does not align with the company's proposed population (patients with a high burden of treatment or who are intolerant or refractory to Ig), thereby limiting the applicability of the evidence (Sections 2.3.1, 3.2.1 and 3.2.3). Concerns relating to each subgroup in the company's proposed population include:

- Patients who were intolerant or refractory to Ig (intolerant or refractory cohort): These patients were not identifiable in ADHERE and so there is no evidence for this subgroup;
- Patients with a high burden of treatment (Ig maintenance cohort):
 - Patients who had no prior CIDP treatment were included in ADHERE but do not meet the company's population criteria or the marketing authorisation for treatment with efgartigimod;
 - There is insufficient information from ADHERE to determine which patients met the company's definition of a high burden of treatment. Results in the CS therefore reflect a wider population than those expected to be eligible for efgartigimod in NHS clinical practice.

The EAG also has concerns about aspects of the ADHERE trial design which made it difficult to draw strong conclusions of the magnitude of any benefit of efgartigimod over placebo (Sections 3.2.1, 3.2.3 and 3.3.2):

- By excluding non-responders from the RCT stage of ADHERE, comparisons between efgartigimod and placebo overlooked the high percentage of patients who did not respond to efgartigimod (Section 3.3.1.1);

- The randomised withdrawal design provides a comparison between patients with ongoing efgartigimod treatment and patients who discontinued efgartigimod, rather than assessing the effects of a switch from Ig to efgartigimod;
- The assessment of relapse in the RCT phase of the trial was based on a single outcome (change in aINCAT) rather than the combination of measures used in previous stages of the trial (aINCAT, I-RODS and MGS). This may have underestimated the number of patients who relapsed in each arm.

The company's ITC between efgartigimod and SCIg (ADVANCE-CIDP-1 trial) was also associated with uncertainty. While comparisons indicated potential benefits of efgartigimod (Section 3.6.2.1), there was uncertainty about the applicability of the population in both trials and differences in trial design led to concerns about an overestimation of the treatment effect with efgartigimod. The ITC was further confounded by limited reporting of treatment effect modifiers in ADVANCE-CIDP-1, with differences in placebo response indicating underlying differences between the trial populations which could not be accounted for. Each of these issues are likely to have impacted on the relative effectiveness of efgartigimod and SCIg, limiting the conclusions that can be drawn about the effects of efgartigimod.

ITCs between other comparator trials (PATH and ICE) were subject to fewer concerns over trial design and indicated potential benefits of efgartigimod over SCIg and IVIg (Sections 3.6.1 to 3.6.3). However, these comparisons were subject to many of the same concerns as ADVANCE-CIDP-1 in addition to further methodological limitations. The EAG therefore considers there to be major limitations associated with the ITCs for all three trials. Given the issues outlined above for both ADHERE and the ITCs, the EAG has two main concerns: uncertainty over the relative treatment effects of efgartigimod and placebo or Ig, and a lack of clarity over how the evidence from ADHERE and each of the comparator trials reflects the population proposed by the company.

Given the exclusion of non-responders from Stage B of the ADHERE trial and the high percentage of patients who had prior Ig but did not respond to efgartigimod, the EAG considers that any conclusions drawn from the current evidence base are most applicable to efgartigimod responders. While the ITCs indicate potential benefits of efgartigimod over Ig, the substantial uncertainty associated with each comparison limits confidence in this conclusion. Instead, the EAG considers that it may be more reasonable to assume that the two treatments have broadly similar effectiveness in patients known to respond to efgartigimod.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and section 4.2 covers the company's economic evaluation.

Table 41 presents the company's revised base case result post clarification. The company considers a disease severity modifier of 1.0 is appropriate and the EAG agrees.

Table 41. Company's base case results

Interventions	Total Costs	Total LY	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Established clinical management*	██████	17.17	1.65	-	-	-	-
Efgartigimod	██████	17.17	5.91	██████	-	4.26	██████
Probabilistic results							
Established clinical management*	██████	17.17	0.35	-	-	-	-
Efgartigimod	██████	17.17	4.31	██████	-	3.96	██████
Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intravenous; LY, life year; PLEX, plasma exchange; QALY, quality-adjusted life-year; SC, subcutaneous.							
* Established clinical management includes treatment with immunoglobulins (IV or SC), PLEX, corticosteroids and immunosuppressants.							

4.1 Critique of the review of cost effectiveness evidence

The company conducted separate systematic literature reviews (SLRs) to identify published cost-effectiveness and health-related quality of life (HRQoL) studies. A costs and resource use SLR was not conducted, with the company instead preferring to identify health care resource use (HCRU) through clinical expert interviews. The cost-effectiveness and HRQoL SLRs were originally conducted in September 2024 and updated in July 2025. For HCRU, separate qualitative and expert elicitation workshops were conducted with five experts each in the spring of 2025.

The SLRs drew studies from electronic databases (Embase, MEDLINE and Cochrane), congresses (i.e. ISPOR) and regulatory agencies (i.e. NICE). The company stated that records identified through electronic database and congress searches were subjected to a multi-step selection process using pre-defined inclusion and exclusion criteria. Two reviewers were double-blinded during screening,

with discrepancies resolved by a third reviewer. The methods used for data extraction and quality assessments were not explicitly outlined by the company in the relevant Appendices.

A summary of the External Assessment Group's (EAG's) critique of the company's methods to identify relevant evidence is presented in Table 42.

Table 42. EAG critique of company SLR methods

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix E 1.1.2	Appendix F 3.1.1	Appendix E 1.1.2	Appropriate
Inclusion/ exclusion criteria	Appendix E 1.2	Appendix F 3.2	Response to clarification C3b	Appropriate
Screening	Appendix E 1.2	Appendix F 3.2	Appendix E 1.2	Appropriate
Data extraction	No relevant studies identified to extract data		Not reported	The EAG considers that the company's reporting of the SLRs were incomplete and so it was difficult to understand if data from studies were appropriate to be included in the cost-effectiveness analysis.
Quality assessment of included studies	No relevant studies identified to perform quality assessment		Not reported	

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life.

The cost-effectiveness SLR identified 54 relevant studies; however, the company considered that none provided robust cost-effectiveness data, with the most relevant studies being two budget impact analyses assessing the introduction of efgartigimod into the CIDP treatment pathway.

Of the 82 studies and reports captured in the HRQoL SLR, the company did not provide comment on the relevance of any of the studies, with no corresponding results section included in the CS. Overall, from the SLRs conducted and relevant studies identified, no information was extracted by the company for use in the company's cost-effectiveness or scenario analysis.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 43 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.

Table 43. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Aligns with the reference case; the company's base case includes HRQoL impacts on informal caregivers, although these are excluded in a scenario analysis.
Perspective on costs	NHS and PSS	Aligns with the reference case
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Aligns with the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with the reference case; a lifetime horizon was used.
Synthesis of evidence on health effects	Based on systematic review	Aligns with the reference case; The company's systematic reviews were appropriate.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Aligns with the reference case; health state utility values were informed by EQ-5D-5L values from the ADHERE trial, cross-walked to EQ-5D-3L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligns with the reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligns with the reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligns with the reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Aligns with the reference case

Element of health technology assessment	Reference case	EAG comment on company's submission
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with the reference case
Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY, quality adjusted life year		

4.2.2 Population, intervention and comparators

The company considered three distinct patient groups in the economic analysis, which were modelled as separate cohorts, as follows:

- Ig maintenance cohort: patients receiving a stable Ig maintenance dose at baseline, but who may wish to switch to efgartigimod due to the high burden of treatment;
- Ig-intolerant cohort: patients who may have responded to Ig in the past, but had to discontinue treatment with Ig due to safety concerns;
- Ig-refractory cohort: patients who did not show any response to Ig.

For all three cohorts, efgartigimod was considered to be the intervention. For the Ig maintenance cohort, Ig was considered to be the appropriate comparator. The company explicitly considered the separate Ig products available in the UK, in order to incorporate differences in cost, AE rates and administration methods. The distribution of patients between Ig products was informed by an interim analysis from a UK chart review study conducted by the company. This was a retrospective study collecting details of healthcare resource use of 69 adult CIDP patients across four NHS secondary care sites in England, all of which have established expertise in CIDP management. Data were extracted from patients' medical records dating from the period March 2016-March 2021. The company provided a report detailing the methodology and results of this study during clarification (response dated 16th December).¹⁹

The input values used for distribution across Ig products are given in Table 44.²⁰ However, the company also provided a scenario analysis in which proportions were informed by the final analysis from the chart review study.

Table 44. Distribution of patients across Ig products

Ig product	Proportion of patients (interim analysis)	Proportion of patients (final analysis)
Privigen (IVIg)	51.28%	■
Gamunex (IVIg)	38.46%	■
Hizentra (SCIg)	5.13%	■
Flebogamma DIF (IVIg)	5.13%	■

Abbreviations: IVIg: intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.

For the Ig-intolerant and Ig-refractory cohorts, a treatment ‘basket’ consisting of PLEX, corticosteroids and immunosuppressants was considered to be the appropriate comparator. In the absence of appropriate data from existing literature, the proportions of patients receiving each treatment in the comparator basket were informed by a structured expert elicitation (SEE) with UK clinicians, conducted by the company.²¹ This was conducted as part of a workshop with five clinicians, following the Sheffield Elicitation Framework (SHELF) approach.²² The EAG considers that this approach was reasonable, and that the SEE workshop was broadly conducted appropriately. Full details are given in a report provided as a reference for the original CS.²¹ The proportion of patients receiving each treatment in the comparator basket at any given time was assumed to be constant (i.e., the distribution of patients between treatments was assumed to be in steady state).

The proportions used in the economic analysis are given in Table 45.

Table 45. Distribution of patients across treatments in the comparator basket

Treatment	Proportion of patients
PLEX	22.9%
Corticosteroids	77.0%
Immunosuppressants	0.1%

Abbreviations: PLEX, plasma exchange.

In the company’s base case analysis, the populations were combined into a single ‘mixed’ population, with 95% of patients assumed to belong to the Ig maintenance cohort, 2.5% belonging to the Ig-intolerant cohort, and 2.5% belonging to the Ig-refractory cohorts. These values were based on estimates informally elicited from clinical experts. The EAG’s clinical experts agreed that these proportions were broadly appropriate.

The company presented subgroup analyses for the following populations:

- Patients receiving a stable Ig maintenance dose at baseline;

- Patients who were considered to be Ig-dependent at baseline (i.e., they deteriorate if they try to down-titrate their Ig dosage);
- Patients who are Ig-dependent at an ultra-high dosage at baseline (i.e., patients who are Ig-dependent at a dosage of 2.0 g/kg per treatment cycle).

At the EAG's request, the company also provided a subgroup analysis of the Ig-intolerant/refractory patient population.

4.2.2.1 EAG critique

Overall, the EAG considers that the population, intervention and comparators selected by the company are broadly appropriate. However, the EAG has several concerns around the approach taken to modelling the basket of 'alternative' comparator treatments other than Ig (i.e., PLEX, corticosteroids and immunosuppressants).

Firstly, the EAG considers that it is more appropriate to use the final data cut from the company's chart review study to inform the proportion of patients receiving each Ig product (see Table 44), as the company did not give any justification for why the interim analysis would be more appropriate. The EAG has included this in the EAG base case, outlined in Section 5.2.3; this issue also forms part of **Key Issue 6**, discussed in Section 1.3.

Regarding the proportion of patients receiving each treatment in the comparator basket, the EAG considers that the 'steady state' assumption is very strong. While in the clarification response, the company stated expert clinicians considered that the proportion of patients receiving each treatment in the basket would be approximately constant over time, the EAG would have liked to have seen stronger justification for this assumption, especially given the short-term nature of most treatments included in the basket. However, given the general heterogeneity of treatment pathways for patients after Ig treatment has failed, and the lack of available data from the literature on the proportion of patients receiving each treatment at each line, the EAG concedes that this may be a necessary simplification to facilitate modelling, and that this may be an unavoidable source of uncertainty in the economic analysis.

Nonetheless, the EAG considers that the company's model inputs for the proportions of patients receiving each treatment in the alternative basket are unlikely to be representative of UK clinical practice, for several reasons.

Firstly, the EAG considers that the framing of the questions used to elicit inputs for these proportions in the SEE does not sufficiently reflect the steady state assumption in the model. In particular, clinical experts were asked what proportion of patients at the relevant stage in the treatment pathway 'have started treatment' with one of the alternative basket treatments after discontinuing Ig.²¹ The EAG therefore considers that the model inputs are more likely to reflect the first subsequent line of treatment after a patient discontinues Ig for the first time, rather than giving an indication of a long-term steady state distribution.

In addition, the EAG notes that the proportion of patients assumed to receive PLEX and corticosteroids is very high. However, both the company's and the EAG's clinical experts stated that these treatments are generally not considered to be long-term treatment options; in particular, the company's clinical experts stated that the median duration of treatment for corticosteroids would be 3.5 months, and the EAG's clinical experts stated that PLEX would be administered for a limited course of treatment.²¹ The company's and the EAG's clinical experts also noted that access to PLEX varies between centres in England, with many patients having limited or no access.²¹ Therefore, the EAG considers that the proportion of patients modelled to receive PLEX or corticosteroids is likely to overrepresent the proportion of patients receiving these treatments in steady state.

At the EAG's request, the company provided several scenario analyses exploring different compositions of the alternative basket, as detailed in Table 46.

Table 46. Scenario analyses varying the proportion of patients receiving each treatment in the 'alternative' basket

Scenario	Details	Proportion receiving PLEX	Proportion receiving corticosteroids	Proportion receiving immunosuppressants
Company BC	Proportions from SEE ²¹	22.9%	77.0%	0.13%
Scenario 1	Proportions from company's chart review ²⁰	■	■	■
Scenario 2	25% treated with corticosteroids. Percentages for PLEX and immunosuppressants aligned with proportions from the SEE, reweighted to make up the remaining 75%. ²¹	■	■	■
Scenario 3	25% treated with corticosteroids. Remaining 75% divided equally between PLEX and immunosuppressants.	37.5%	25.0%	37.5%
Scenario 4	0% treated with corticosteroids. Percentages for PLEX and immunosuppressants aligned with proportions from the SEE, reweighted to make up 100%. ²¹	■	■	■
Scenario 5	0% treated with corticosteroids. 100% divided equally between PLEX and immunosuppressants.	50.0%	0.0%	50.0%

Abbreviations: BC, base case; PLEX, plasma exchange; SEE, structured expert elicitation.

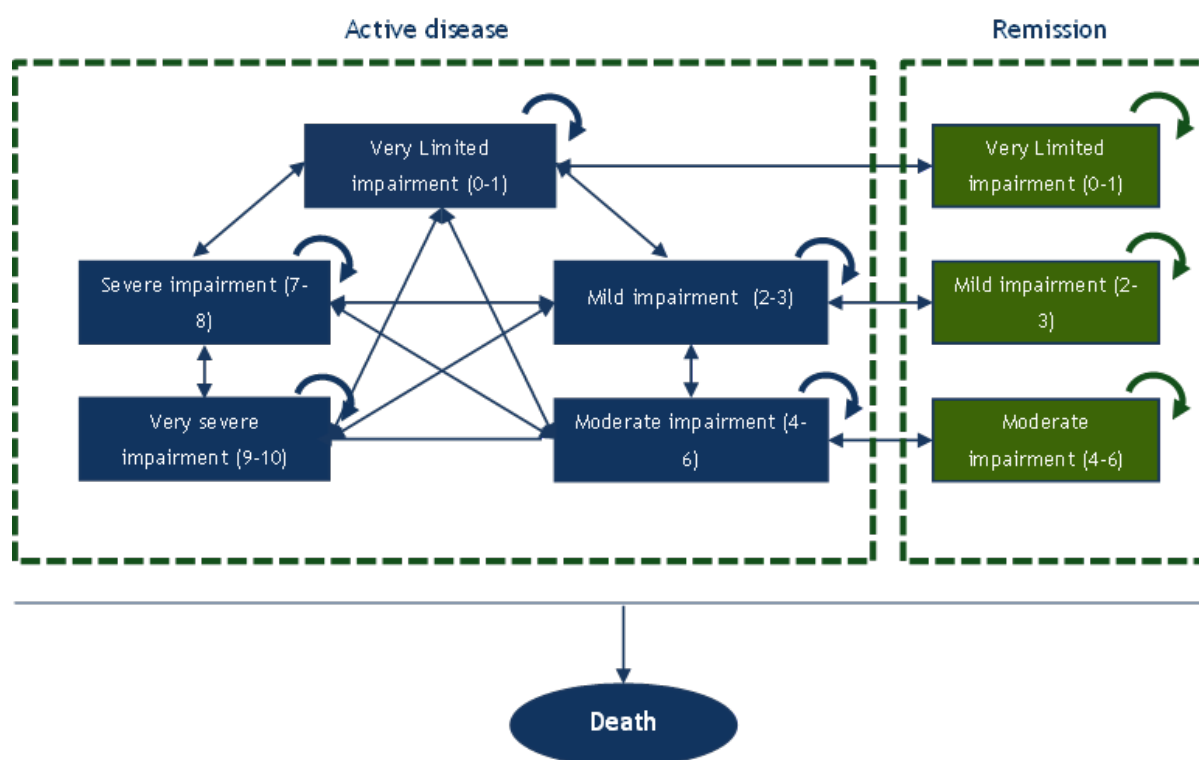
The scenarios detailed in Table 46 had a relatively small impact on the NHB. The EAG considers estimates of the proportion of patients receiving comparator treatments to be highly uncertain, and the EAG's clinical experts gave very different estimates of the proportion who would be receiving each treatment at any given time, based on their individual experience. Overall, the EAG considers that, of the available options, the proportions from the company's chart review are the most likely to be representative of UK clinical practice, and this is included in the EAG's preferred base case (see Section 5.2.3). However, the EAG has retained the company's base case approach and other scenarios as scenario analyses.

The EAG also considers that it is more transparent to present the results for the Ig maintenance population separately from the Ig-intolerant and Ig-refractory populations, since the comparators for these populations are different. Therefore, the EAG considers results for the separate cohorts to be primary results, although results for the company's 'mixed' patient population are also presented for the EAG's analyses.

4.2.3 Model structure

The model presented by the company was a Markov model with time-varying transition probabilities. The health states are illustrated in Figure 12.

Figure 12. Model structure diagram, reproduced from Figure 18 in the company submission



Health states were defined by patients' aINCAT score; the company stated that aINCAT was selected as the most appropriate outcome for defining health states as it was the primary endpoint in the ADHERE trial, is commonly used in clinical practice, is not purely based on patient-reported outcomes, and captures sensory as well as motor impairment. The company noted that although aINCAT is a compound score composed of an arm and leg component, the majority of patients in the ADHERE trial with the same overall score had roughly equal contributions from arm and leg components, rather than extreme scores in either the arm or leg component; for example, patients

with an overall aINCAT score of 5 generally had a score of 2 in one component, and a score of 3 in the other component.²³ In the company's model validation exercise, clinical experts considered that this was reflective of the UK patient population.²¹ Therefore, patients grouped by aINCAT score are likely to have similar overall levels of impairment, and therefore similar HRQoL and healthcare resource use needs.

The health states were defined by aggregating aINCAT scores into five categories: very limited impairment (aINCAT score 0-1), mild impairment (aINCAT score 2-3), moderate impairment (aINCAT score 4-6), severe impairment (aINCAT score 7-8), and very severe impairment (aINCAT score 9-10). These groupings were informed by grouping scores which were considered likely to represent a similar level of functional impairment, based on data from the ADHERE trial. The appropriateness of the health states was validated by UK clinical experts.

The company also presented details of a clustering analysis in which aINCAT observations from the ADHERE trial were clustered based on associated HRQoL data, in order to derive groupings of aINCAT scores with similar patient HRQoL. Details of this analysis are given in Section 3.2.3 of the CS and the company's cost-effectiveness model validation report.²³ This analysis appears to have been inconclusive, with several groupings of health states being classed as optimal in a similar percentage of simulations, and no grouping being classed as optimal in more than ■■■ of cases.²³ Furthermore, the grouping ultimately selected by the company does not align with any of the groupings resulting from the clustering analysis.

For all aINCAT groupings, a health state corresponding to 'active disease' was included; this refers to patients receiving ongoing active treatment. For the very limited, mild and moderate impairment aINCAT groupings, a 'remission' health state was also included; this refers to patients who have stable symptoms and have successfully undergone withdrawal from active treatments (note that in this case, 'remission' does not refer to reduced severity of symptoms, and only indicates that a patient has stable symptoms which can be managed without active treatment). Patients could move between any two active disease health states based on transition probabilities specific to the current treatment received, informed by clinical data (see Section 4.2.7 for further details). Patients were assumed to move between active disease and the corresponding remission health state at the same rate for very mild, mild and moderate impairment, and independently of the treatment received.

At baseline, all patients were assumed to be receiving active treatment (i.e., all patients were in the active disease health states rather than the remission health states). For the Ig maintenance and Ig-intolerant cohorts, the distribution of patients between health states was informed by the aINCAT scores of Ig-pretreated patients in the ADHERE trial at baseline for the run-in period (i.e., before withdrawal of prior treatment), while for the Ig-refractory cohort, the distribution at baseline was informed by the aINCAT scores of Ig-pretreated patients at the baseline of Stage A of the ADHERE trial (i.e., after withdrawal of treatment but before starting efgartigimod).¹⁴ The distributions of patients between health states are given in Table 47.

Table 47. Patient distributions at baseline

Health state	Distribution at baseline: Ig maintenance and Ig-intolerant	Distribution at baseline: Ig-refractory
Very limited impairment	0.0%	0.0%
Mild impairment	42.1%	27.4%
Moderate impairment	51.8%	58.5%
Severe impairment	5.5%	9.8%
Very severe impairment	0.6%	4.3%
Abbreviations: Ig, immunoglobulin.		

The model used a six-month cycle length, with a half-cycle correction applied. The company stated that this aligns with the standard interval for assessing dose adjustments for Ig, and that a six-month timeframe should be short enough to capture fluctuations in aINCAT score.

4.2.3.1 EAG critique

The EAG considers that the company's model structure was broadly appropriate.

The EAG considers that grouping aINCAT scores is appropriate for reducing the model complexity. Furthermore, the sample sizes of the trial data used for deriving transition probabilities were relatively small, so aggregating aINCAT scores leads to more robust transition probabilities. The EAG's clinical experts also considered that the groupings of aINCAT scores defining the model health states were appropriate, and also that the inclusion of health states corresponding to withdrawal of active treatment was appropriate.

The EAG considers that the clustering analysis performed by the company was generally superfluous. In general, it is sufficient to prioritise functional similarity and clinical expert input in determining model health states, rather than relying on unsupervised machine learning algorithms which do not

take clinical practice or underlying disease processes into consideration. Furthermore, applying a clustering approach to HRQoL trial data neglects other important considerations in determining model health states, such as healthcare resource use. However, this is not a major consideration, since ultimately the clustering analysis performed by the company does not appear to have played a major role in determining health states.

The EAG is unsure why the company chose to parametrise the distribution of patients between health states at baseline using data from the baseline of the ADHERE run-in period for the Ig maintenance and Ig-intolerant cohorts, but using data from the baseline of ADHERE Stage A for the Ig-refractory cohort. In particular, while it is potentially reasonable to assume that Ig-refractory patients are distributed between health states similarly to patients who had stopped treatment with Ig, the EAG would not expect to see a difference in baseline distribution between the Ig-intolerant and Ig-refractory cohorts, as both cohorts are modelled as receiving the same basket of treatments (further details are given in Section 4.2.4). In fact, this approach is in line with the company's response to clarification question B7a, which mistakenly claimed that the same baseline distribution was used for both the Ig-refractory and Ig-intolerant cohorts.

Overall, the EAG preferred to inform the baseline distribution for the Ig maintenance cohort using the baseline data from the run-in period of ADHERE for all treatments. This is more consistent with the company's assumption that patients who do not respond to efgartigimod, and patients on comparator treatments, would be distributed between health states in line with the baseline of the run-in period by the end of the first cycle (see Section 4.2.7.2 for further details).

However, the baseline data for Ig-refractory and Ig-intolerant cohorts is not known, as patients in these cohorts who had been pre-treated with Ig were not included in the ADHERE trial; therefore, the EAG also considered a scenario analysis in which baseline distributions were informed by baseline data from the run-in period of ADHERE Stage A for the Ig-refractory and Ig-intolerant cohorts. This assumption is included in the EAG base case (see Section 5.2.3). However, this approach had a relatively limited impact on results.

Finally, the EAG considers that the use of a six-month cycle length was not appropriate, since the EAG's clinical experts suggested that this may be insufficiently granular to capture rapid changes in disease severity after starting a new treatment. Furthermore, the use of a six-month cycle length is incompatible with much of the trial data used to inform the model, leading to a misalignment

between the model and the time of observation of clinical data informing model inputs (in particular, transition probabilities and the approach to modelling twice-weekly dosing). In order to address these issues, the EAG requested that the company update the model to include a scenario which used a cycle length of 12 weeks for the first two years, with a cycle length of six months used thereafter. The company instead updated the model to include an option to use a cycle length of three months for the first two years, but did not update their preferred base case to include this modelling approach, for the following reasons:

1. The company's approach to calculating transition probabilities when using the three-month cycle approach resulted in less robust transition probabilities, as fewer datapoints informed each transition probability matrix (see Section 4.2.7.1).
2. The company argued that the misalignment between clinical data and model timepoints had a minimal impact.
3. The company stated that it was not possible to model transition to the remission health state from baseline in the comparator arm when using the three-month cycle length, therefore underestimating the benefits in the comparator arm.
4. The company stated that patients tend to be reviewed by clinicians on a six-monthly basis, and therefore, this was the appropriate cycle length to use.

Overall, the EAG considers that a 12-week cycle length would still be the most appropriate approach; however, as a pragmatic approach, the EAG considers that it is reasonable to use the three-month cycle length implemented by the company, as the difference between 12 weeks and three months is unlikely to have a major impact on results, and implementing a 12-week cycle length would require large structural changes to the model. Therefore, the three-month cycle length is used in the EAG's base case (see Section 5.2.3). The EAG responds to the company's arguments around appropriate model cycle length as follows:

1. The EAG has proposed an alternative approach to modelling 12-week transition probabilities which avoids the issue described by the company (see Section 4.2.7.1 for further details).
2. The EAG considers that while adjusting the cycle length does not have a major impact on the company's base case, this is not the case when the EAG's corrections are applied, and the EAG's preferred assumptions are used.
3. The EAG does not agree with the company's assessment that it is not possible to model transition to the remission health state from baseline in the comparator arm when using the 12-week cycle length, and has subsequently incorporated this into the model.
4. While the EAG's clinical experts agreed that patients are generally reviewed on a six-monthly basis when they are stable on treatment, patients may be reviewed on a more regular basis if they are undergoing rapid changes (which may be true for some patients in the first two years of treatment), and would be likely to be assessed for response after around 12 weeks on treatment.

The choice of cycle length for the first two years is **Key Issue 7**, discussed in Section 1.3.

4.2.4 *Treatment pathway*

The transition probabilities between aINCAT health states were specific to the treatment received. Therefore, the modelled treatment pathways played a key role in modelling treatment effectiveness. Separate treatment pathways were modelled for the Ig maintenance cohort, and the Ig-refractory and Ig-intolerant cohorts; these are described in detail below.

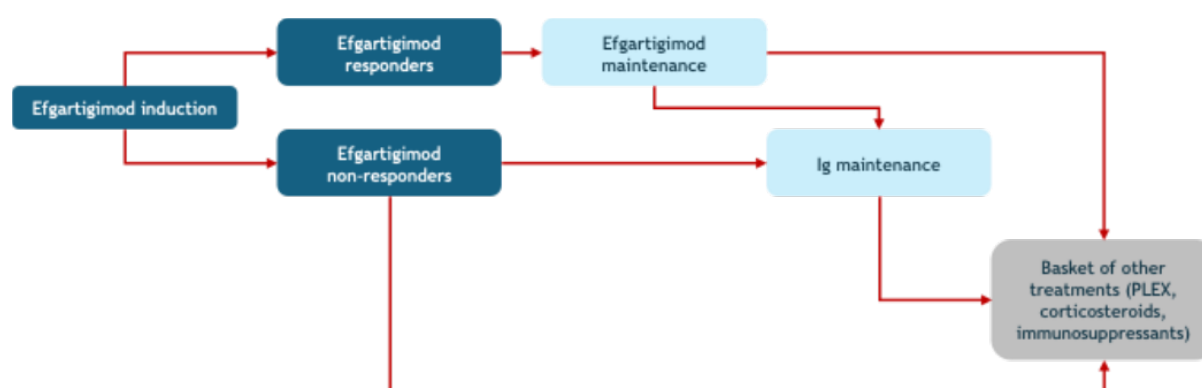
4.2.4.1 *Ig maintenance cohort*

In the efgartigimod arm, for patients in the Ig maintenance cohort, patients were assumed to initially undergo an efgartigimod induction period, after which response would be assessed. Patients who responded to efgartigimod were assumed to progress to efgartigimod maintenance. Patients who did not respond to efgartigimod, or who discontinued for another reason during the maintenance period, were assumed either to return to Ig maintenance, or to proceed to a basket of alternative treatments consisting of PLEX, corticosteroids and immunosuppressants; the proportions of patients receiving each treatment were informed by the SEE workshop.²¹ Discontinuation of efgartigimod for reasons other than non-response was only modelled for the first 18 months of treatment, as the company's clinical experts stated that discontinuation of an established treatment after this point would be unusual.²¹

Patients who discontinued efgartigimod and switched to Ig maintenance were also modelled to have a chance of discontinuing treatment for the first 18 months on treatment. These patients were then assumed to proceed to the basket of alternative treatments (PLEX, corticosteroids and immunosuppressants), in the same proportions as in the comparator basket for the Ig-refractory and Ig-intolerant cohorts. For patients receiving basket treatments, during clarification, the company stated that patients were not assumed to continue with the same treatment indefinitely, but that the proportion of patients receiving each treatment were assumed to be in steady state (i.e., individual patients may switch between treatments included in the basket, but the proportion of patients receiving a treatment in any given cycle is constant over time). After this, no further treatment options were modelled, as patients were assumed to be receiving one of the alternative basket treatments at any given time.

The treatment pathway for patients in the efgartigimod arm for the Ig maintenance cohort is illustrated in Figure 13; proportions of patients receiving each subsequent treatment are given in Table 48.

Figure 13. Treatment pathway for the efgartigimod arm, Ig maintenance cohort (reproduced from Figure 14 of the company submission)



Abbreviations: Ig, immunoglobulin; PLEX, plasma exchange.

Table 48. Proportion of patients receiving each subsequent treatment (efgartigimod arm, Ig maintenance cohort)

Subsequent treatment	Proportion of patients (first line, after efgartigimod discontinuation)	Proportion of patients (second line, after Ig discontinuation)
Ig	31.0%	0%
PLEX	14.5%	22.9%
Corticosteroids	49.9%	77.0%
Immunosuppressants	4.6%	0.1%

Abbreviations: Ig, immunoglobulin; PLEX, plasma exchange.

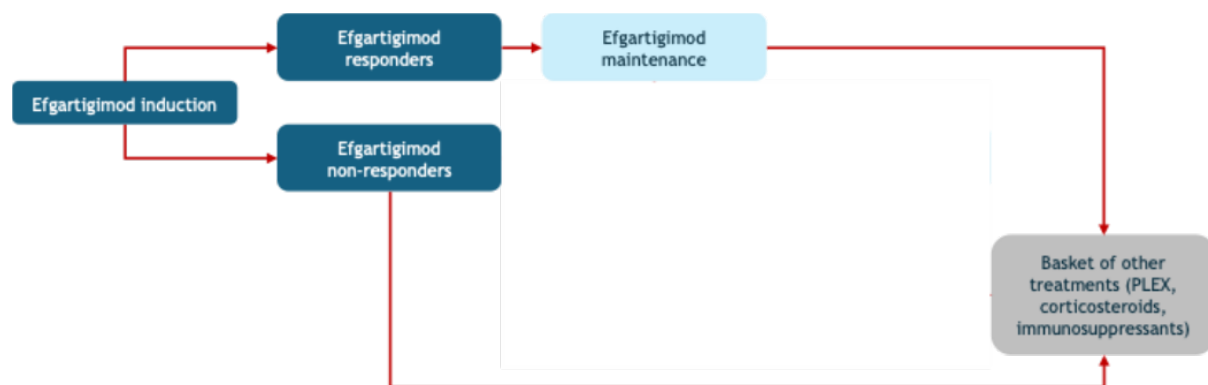
Patients in the Ig maintenance cohort in the comparator arm were assumed to begin on Ig maintenance treatment; if patients discontinued treatment, they were assumed to start a treatment in the basket of alternative treatments, in the same proportions as in the comparator basket for the Ig-refractory and Ig-intolerant cohorts, similarly to patients in the efgartigimod arm who had discontinued both Ig and efgartigimod (see Table 48 for relevant input values). As for the efgartigimod arm, rather than explicitly modelling switching between treatments in the alternative basket, it was assumed that the proportion of patients receiving each treatment was in steady state.

4.2.4.2 Ig-refractory and Ig-intolerant cohorts

The treatment pathways for the Ig-refractory and Ig-intolerant cohorts were similar to the treatment pathways for the Ig maintenance cohort, albeit with Ig removed as a potential treatment option. In the comparator arm, patients were assumed to remain on treatments in the alternative basket indefinitely, with the proportion of patients receiving each treatment assumed to be in steady state. In the efgartigimod arm, patients who discontinued efgartigimod either due to non-response or for

other reasons were assumed to proceed immediately to the basket of alternative treatments, in proportions aligned with the comparator arm (see Table 45 or Table 48 for relevant input values), assumed to be in steady state. As in the Ig maintenance cohort, discontinuation of efgartigimod was modelled for the first 18 months of treatment. The treatment pathway for the efgartigimod arm is illustrated in Figure 14.

Figure 14. Treatment pathway for the efgartigimod arm, Ig maintenance cohort (reproduced from Figure 15 of the company submission)



Abbreviations: PLEX, plasma exchange

4.2.4.3 EAG critique

The EAG does not consider the approach to modelling the treatment pathway to be appropriate, for several reasons. Firstly, the EAG considers that for the Ig maintenance cohort, the proportion of patients returning to treatment with Ig after discontinuing efgartigimod is implausibly low. The EAG's clinical experts suggested that they would expect almost all patients in this cohort to recommence treatment with Ig after discontinuing efgartigimod, since the patients were known to respond to treatment with Ig, even if the burden of treatment was high. According to the company's report on the SEE, the input for the proportion of patients returning to Ig treatment used in the model was settled on as a compromise between clinical experts who, similarly to the EAG's clinical experts, considered that the majority of patients would return to treatment with Ig, and clinical experts who considered that patients who had started efgartigimod would have had strong reasons not to wish to return to Ig, and that therefore the proportion of patients returning to Ig should be 'very, very low'.²¹ The EAG considers that the latter group of clinicians was potentially considering a narrower patient population than the positioning proposed by the company. The company also noted the disagreement between clinical experts, and conducted subsequent qualitative interviews

with clinical experts, which generally aligned with the view that the majority of patients would recommence treatment with Ig after discontinuing efgartigimod.

The company provided scenario analyses with alternative proportions of patients restarting Ig after efgartigimod in the Ig maintenance cohort, with proportions ranging from 0% to 100%. Increasing the proportion of patients restarting Ig considerably reduced the resulting incremental NHB. Overall, the EAG considers that it is more appropriate to model all patients receiving subsequent Ig after efgartigimod discontinuation, in the Ig maintenance cohort.

The uncertainty around the treatment pathway after discontinuing efgartigimod is **Key Issue 8**, discussed in Section 1.3.

The EAG's concerns around the modelling of the comparator treatment basket, as detailed in Section 4.2.2.1, also apply to the approach taken to the company's approach to modelling subsequent treatments for patients in the Ig maintenance cohort who discontinue Ig. In addition, the EAG's clinical experts stated that, for patients in the Ig maintenance cohort, PLEX or corticosteroids may be used as a short-term 'rescue' therapy to alleviate severe symptoms, but many patients may return to treatment with Ig in the long-term after their symptoms had stabilised. Therefore, the EAG considers that it is appropriate to include Ig in the treatment basket for the second line after Ig discontinuation.

The company also provided scenario analyses in which between 10% and 90% of patients who were treated with PLEX returned to treatment with Ig thereafter. The EAG notes that the company did not directly model patients returning to Ig after initially discontinuing treatment, but instead reduced the proportion of patients on PLEX by the given percentage, and assumed that this cohort of patients was receiving Ig rather than PLEX. Given that the proportion of patients returning to Ig is unknown, the EAG has conservatively assumed that Ig displaces 90% of the presumed share for PLEX in the alternative treatment basket in the EAG base case (see Section 5.2.3), but also presents a scenario analysis in which patients do not return to Ig after an alternative treatment. This scenario impact has a relatively small impact on the incremental NHB.

4.2.5 Patient baseline characteristics

The key patient baseline characteristics used in the model were mean age and sex, which were used to calculate adjusted general population utilities and mortality rates, as well as mean weight, which was used to calculate dosing for IVIg and SCIg. The input values used by the company were informed

by patient characteristics at screening for the ADHERE trial, and are detailed in Table 49; the same input values were used for the Ig maintenance, Ig-refractory and Ig-intolerant cohorts.¹⁴

Table 49. Patient baseline characteristics used in the economic model

Patient baseline characteristics	Input value
Mean age	55.1 years
Mean weight	80.6 kg
Proportion female	38.8%

4.2.5.1 EAG critique

The EAG's clinical experts confirmed that the input values for mean age and proportion female were relatively representative of the UK patient population. However, the mean weight from the ADHERE trial is likely to be slightly lower than that of the UK patient population. At the EAG's request, the company conducted a scenario analysis using UK-specific data. In particular, the company used UK Health Survey for England (HSE) data from 2021; a mean weight of 79.9kg was used, based on the mean adult weight in the UK, adjusted to align with the distribution of male and female patients in ADHERE.²⁴ This scenario has a minimal impact on the incremental NHB, as the input value for mean weight is very similar to the value used in the company's base case. However, the EAG notes that this analysis may still not be fully reflective of the UK patient population, as the input value was not adjusted for patient age. Since the EAG was unable to identify an appropriate alternative input, the value from the ADHERE trial was used in the EAG's base case, as detailed in Section 5.2.3.

4.2.6 Perspective, time horizon and discounting

The company's economic model had an NHS and PSS perspective, in line with the NICE reference case. A lifetime horizon was used, assumed to be 45 years, based on the assumed age of 55.1 years at baseline, and a maximum age of 100 years; the EAG considers that this appropriately captures the costs and benefits of efgartigimod, given the long-term nature of CIDP. However, at the EAG's request, the company presented a scenario analysis with a two-year time horizon, as the benefits of efgartigimod beyond this timepoint are highly uncertain (see Section 4.2.7 for further details); this led to a substantial decrease in the net health benefit (NHB). A discounting rate of 3.5% per year was used for both costs and benefits, also in line with the NICE reference case.

4.2.7 *Treatment effectiveness*

Treatment effectiveness is captured in the economic model via transition probabilities between health states based on aINCAT category. The company's and EAG's preferred approaches to parametrising these transition probabilities are described in the following sections. The probability of withdrawal of active treatment (i.e., entering a 'remission' health state) from the very limited impairment, mild impairment and moderate impairment health states was assumed to be the same for all treatments, and is discussed in Section 4.2.8.1.

4.2.7.1 *Patients receiving efgartigimod*

For patients who responded to efgartigimod, estimates of treatment effectiveness derived from data from ADHERE Stage B and the ADHERE+ open-label extension.¹⁴ At the end of the first cycle, the distribution of patients between health states was aligned with the baseline distribution for ADHERE Stage B. Thereafter, patients were assumed to move between health states based on transition probabilities. To derive transition probabilities, individual patient aINCAT data from ADHERE and ADHERE+ for efgartigimod responders randomised to the efgartigimod arm in ADHERE Stage B were combined into a single set of observations for each patient, i.e., time from baseline for each observation in ADHERE+ was shifted to account for time on treatment in ADHERE Stage B. This yielded a dataset with aINCAT observations up to 144 weeks from response assessment, although the company noted that observations from 96 weeks onwards were very sparse (data were available for fewer than 10 patients); therefore, only data for the first 96 weeks after response were used. The aINCAT score for missing observations was assumed to be equal to the last observed aINCAT score.

In the company's original approach, separate transition probabilities were derived for the time periods 0-24 weeks from response assessment, 24-48 weeks from response assessment, 48-72 weeks from response assessment, and 72-96 weeks from response assessment. For each of these time periods, the number of patients in each aINCAT category at the start and end of the time period was calculated, and these 'shift' data were rescaled to derive a matrix of transition probabilities between aINCAT categories. In the company's original approach, using a cycle length of six months, the transition matrices for 0-24 weeks, 24-48 weeks, 48-72 weeks and 72-96 weeks were applied for the first, second, third and fourth model cycles respectively, for patients who had not permanently discontinued efgartigimod. After two years, the company assumed that patients' aINCAT category would not change, although shifts between the remission and active disease health states for the very limited impairment, mild impairment and moderate impairment health states were still

permitted. The EAG's clinical experts stated that this assumption was reasonable, given that patients would be well-established on treatment, and that patients on stable treatment are unlikely to experience fluctuations in aINCAT in the long term. The company also explored a scenario analysis in which the transition probabilities for the fourth cycle were applied for the remainder of the time horizon, which slightly decreased the incremental NHB.

The transition probabilities for the company's original approach are given in Tables 37- 41 of the CS.

Following the clarification stage, the model was updated to include a scenario analysis which used a three-month model cycle for the first two years; in this analysis, separate transition probabilities were derived for 12-week cycles from 0 to 96 weeks from baseline, rather than 24-week cycles. The resulting transition probabilities are presented in Table 56 of the company's clarification response. This approach to a considerable reduction in the number of datapoints informing transition probabilities for each cycle, as very few patients in ADHERE and ADHERE+ had multiple visits within a 12-week timeframe.

The approaches for deriving transition probabilities for patients who initially do not respond to efgartigimod or who permanently discontinue efgartigimod are discussed in Section 4.2.7.2.

4.2.7.1.1 EAG critique

The EAG has several concerns around the company's approach to parametrising treatment effectiveness for efgartigimod.

The EAG notes that the induction phase for efgartigimod (i.e., after starting treatment with efgartigimod but prior to response assessment) was assumed to align with the first model cycle. In the company's base case, this is a time period of six months, whereas the EAG's clinical experts stated that response assessment after three months on treatment would be more appropriate. This further justifies the EAG's preferred approach of using a three-month cycle length for the first two years of treatment. The EAG also notes that at some points in the CS, the company states that the induction phase was not explicitly modelled, and that therefore a one-off cost for efgartigimod treatment during the induction phase was applied at baseline. For efgartigimod responders, this is redundant, as the treatment costs for efgartigimod in the induction phase are already accounted for in the treatment cost for the first cycle. Therefore, the EAG has removed this cost in a model correction. The EAG has also removed the cost for treatment with Ig for efgartigimod non-

responders for the first three months, as during this period, patients would be treated with efgartigimod.

The EAG also notes that, as discussed in Section 4.2.3.1, the timepoints for which transition probabilities are derived from the pooled ADHERE/ADHERE+ data are fundamentally misaligned with the timepoints used in the company’s base case approach in the model, since the model uses a cycle length of six months, which is considerably different to the 24-week windows over which the transition probabilities are derived. This supports the EAG’s preferred approach of using a three-month cycle length for the first two years.

The EAG also notes that the number of datapoints informing even the 24-week transition probabilities is relatively low (see Sections 3.3.2.3 and 3.3.3.1 for discussion of changes in aINCAT scores over time from a clinical perspective); the total number of patients starting in each health state for each time period over which the transition probabilities were calculated is given in Table 50. In particular, the EAG notes that there are no data informing transitions out of the very severe impairment health state, and very limited data for transitions out of the severe impairment health state. Given the severe lack of data, the EAG’s preferred approach is to assume that all patients in the severe and very severe impairment health states remain in these health states indefinitely, regardless of whether the patients are receiving efgartigimod or a comparator treatment. At the EAG’s request, the company provided a scenario analysis implementing this approach, which led to a large decrease in incremental NHB. The lack of treatment effectiveness data for patients with severe disease is **Key Issue 9**, discussed in Section 1.3.

Table 50. Patient numbers in each health state informing 24-week transition probabilities for efgartigimod

Health state at start of time period	0-24 Weeks	24-48 Weeks	48-72 Weeks	72-96 Weeks
Very limited impairment	■	■	■	■
Mild impairment	■	■	■	■
Moderate impairment	■	■	■	■
Severe impairment	■	■	■	■
Very severe impairment	■	■	■	■

The EAG agrees with the company’s assessment that the transition probabilities derived for the 12-week model cycles are less robust than the 24-week transition probabilities; therefore, the EAG’s

preferred approach for implementing the three-month cycle length approach is to rescale the 24-week transition probabilities, assuming that the time to transition out of the very limited impairment, mild impairment and moderate impairment health states is exponentially distributed, and assuming no transition out of the severe and very severe impairment health states. The resulting transition probabilities are presented in Appendix 7.4. This approach is included in the EAG's base case, as outlined in Section 5.2.3.

The EAG also notes that the assumption that patients will remain in the same aINCAT category indefinitely after being stable on treatment for two years is very strong. Both the company's and the EAG's clinical experts considered that this assumption was reasonable, but the EAG notes that given the lifetime horizon of the model, the results are very sensitive to the transition probabilities used for the first two years, and in particular, the transition probabilities used from 72-96 weeks of response assessment. The scenario analysis presented by the company in which the 72-96-week transition probabilities are reused indefinitely for the remainder of the time horizon gives some reassurance, but this remains an unresolvable source of uncertainty in the economic analysis.

4.2.7.2 Patients receiving comparator/subsequent treatments

The company assumed equal treatment efficacy for Ig and for the 'basket' of alternative treatments, since no appropriate efficacy data could be identified for the treatments included in the basket. Therefore, the same transition probabilities were used for patients on each of these treatments. The company stated that this approach was in line with European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guidelines.⁵ The EAG's clinical experts considered that this assumption was reasonable (see also Section 2.3.3) .

Similar to the approach for the first cycle on efgartigimod, both patients who did not respond to efgartigimod and patients in the comparator arm, the distribution of patients between health states at the end of the first cycle was aligned with the distribution of patients at the baseline of the ADHERE trial, pre-run in period. Thereafter, movement between health states was parametrised based on transition probabilities.

The transition probabilities for comparator treatments were derived by combining the shift data for efgartigimod with the outcomes of the company's ITC comparing efgartigimod and Ig based on the ADHERE and ADVANCE-CIDP-1 trials (see Section 3.6). The ITC suggested that the mean change in aINCAT from baseline to the end of study visit was 0.88 points greater for patients receiving

efgartigimod than patients receiving Ig; since aINCAT is a discrete scale, the company assumed that this would be equivalent to 88% of patients achieving a one point greater change in aINCAT change from baseline (CfB) if they were hypothetically treated with Ig rather than efgartigimod, with the remainder of patients assumed to have the same response to efgartigimod and Ig. The transition probabilities for Ig (and by extension, the basket comparators) were therefore calculated as follows:

1. A new set of shift data was generated for patients who would experience a one-point greater change in aINCAT CfB if they were treated with Ig rather than efgartigimod; the efgartigimod shift data from ADHERE and ADHERE+ described in Section 4.2.7.1 were offset so that the 'end' aINCAT score for each patient shift was increased by 1. For example, patients in the original dataset who shifted from aINCAT 3 to aINCAT 1 would shift from aINCAT 3 to aINCAT 2 in the new dataset.
2. A new set of transition probabilities was generated from the new shift data derived in Step 1.
3. The transition probabilities used for patients receiving comparator treatments in the model were calculated by taking a weighted average of the transition probabilities derived in Step 2, and the original transition probabilities for efgartigimod, with a weight of 88% given to the transition probabilities derived in Step 2.

Similar to patients receiving efgartigimod, transition probabilities with movement between aINCAT categories were applied for approximately the first two years of treatment (four six-month cycles or eight 3-month cycles, depending on the selected cycle length), with different transition probabilities calculated for each cycle. Thereafter, patients were assumed to remain in the same aINCAT category indefinitely. The calculated transition probabilities are given in Tables 44-48 of the CS.

Patients in the efgartigimod arm who did not respond to efgartigimod were modelled using the comparator transition probabilities from baseline, as the induction phase was not explicitly modelled. For patients who initially responded to efgartigimod but subsequently permanently discontinued, the company assumed that within one cycle the patients discontinuing treatment would be redistributed between health states to align with the long-term distribution of patients between health states for patients on stable comparator treatment (i.e., after cycle 4 in the six-month cycle approach, or cycle 8 in the three-month cycle approach).

4.2.7.2.1 EAG critique

The EAG considers that the company's approach to modelling treatment effectiveness for comparator treatments is inappropriate.

The EAG notes that the assumption of equal efficacy for all comparator treatments is strong, and it is unclear whether this is reflective of clinical practice. However, the EAG considers that this assumption is reasonable, given the lack of available data to parametrise alternative efficacies for the treatments included in the alternative basket, and that this may be an unresolvable area of uncertainty. However, the EAG's key area of concern is that the methodology used to calculate transition probabilities relies on uncertain input data and flawed assumptions.

In general, the EAG's concerns about the robustness of the company's ITC, as described in Section 3.6, suggest that the ITC is not an appropriate source for model inputs for the economic analysis, and that no other appropriate ITC is feasible. The small number of data points included in the shift data used to derive the transition probabilities also contributes to the uncertainty of this approach.

Even if the input data were more robust, the EAG considers that the company's approach is flawed, since the ITC estimated the difference in aINCAT CfB for efgartigimod compared to Ig over the trial period (approximately six months), but the company's approach effectively applied the entire difference in CfB for each six-month cycle for the first two years. In their response to clarification question B13, the company stated that this was reasonable, as some patients in the ADHERE+ open-label extension, who were in the efgartigimod arm for ADHERE, continued to show a clinical response, with 'some domains showing continued improvement over time'. The EAG considers that there is insufficient evidence to justify extrapolation of the treatment effect beyond the trial period. The company presented two scenario analyses to investigate this assumption as follows:

- Scenario in which transition probabilities informed by the ITC are calculated for the first six months for the comparator arm, and the same transition probabilities continue to be used for the rest of the first two years from baseline;
- Scenario in which transition probabilities informed by the ITC are used in the comparator arm for the first six months, with the cohort remaining stable thereafter.

The EAG considers that the second of these scenarios is likely to be more representative of clinical practice. Both scenarios led to a substantial decrease in incremental NHB compared to the company's base case.

The EAG also notes that the company’s approach to deriving transition probabilities for comparator treatments relies on the implicit assumption that the difference in CfB is the same, regardless of a patient’s aINCAT score at baseline. This appears clinically implausible, since it may be expected that efgartigimod would have a greater incremental effect for patients with a greater disease severity at baseline than for a patient with relatively mild disease. In the company’s response to clarification question B14, they stated that patients in the ADHERE trial receiving efgartigimod generally showed similar mean changes in aINCAT over the course of Stage B for different aINCAT scores at baseline; however, based on the data provided in the company’s clarification response (reproduced in Table 51), the EAG considers that there were considerable differences between aINCAT CfB for different aINCAT scores at baseline, for both patients receiving efgartigimod and placebo.

Table 51. Mean CfB in aINCAT over Stage B of the ADHERE trial (reproduced from Table 5 in the company’s clarification response)

aINCAT score at Stage B baseline	Mean aINCAT CfB over Stage B: efgartigimod arm	Mean aINCAT CfB over Stage B: placebo arm
0-1	■	■
2-3	■	■
4-6	■	■
7-8	■	■
Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment score; CfB, change from baseline.		

Finally, the EAG considers that the company’s approach is fundamentally incompatible with the company’s assumption that in the long term, on stable treatment, the distribution of patients between aINCAT categories would not change over time. In particular, based on the company’s definition of the patient population, the majority of patients entering the model in the Ig maintenance cohort would by definition already be receiving stable Ig treatment, and it is therefore illogical to model changes in the patient’s disease severity for a relatively short period of time at the start of the time horizon before assuming patients do not move between aINCAT categories in the long term due to the assumed stability of treatment thereafter.

Similarly, patients in the Ig-refractory and Ig-intolerant cohorts would be receiving a treatment in the alternative basket, and would not necessarily be stable on an individual treatment, but the company’s assumption of the distribution of patients between treatments being in steady state also extends to the distribution of patients between aINCAT categories.

Overall, the EAG's preferred approach is to assume that patients receiving comparator treatments from baseline would remain in the same aINCAT categories for the entire duration of the model time horizon. Patients discontinuing efgartigimod would be redistributed between health states in line with the baseline distribution for the comparator treatments, and continue in these health states indefinitely. This is a considerably simplified approach which assumes that all patients in the Ig maintenance cohort are fully stable on a treatment regimen at baseline, when in actuality some patients in this cohort may have been receiving Ig for a short enough time period that they are not on a fully stable treatment regimen; however, since the EAG has been unable to identify any data related to how many patients would be expected to be on a fully stable treatment regimen when switching to efgartigimod, the EAG considers that it is an appropriate simplification to assume that all patients in the Ig maintenance cohort are stable at baseline. The EAG acknowledges that this approach does not account for the fact that patients on a stable treatment regimen may not have stable severity of disease, and notes that the company's response to clarification question B9 states that, according to clinical experts, patients may in fact be expected to accumulate irreversible axonal damage over time, leading to ongoing deterioration. However, the EAG has been unable to identify any data to parametrise the degree of this deterioration over time; therefore, the EAG considers that it is more appropriate to model all patients assumed to be on a stable treatment to experience no change in aINCAT score. The EAG also notes that the company's approach to modelling long-term treatment effects does not take into account the potential impact of irreversible axonal damage. While this scenario may not be truly reflective of clinical practice, the EAG considers that this approach is fundamentally more logically coherent than the company's approach, and removes the dependence on the uncertain input values and flawed assumptions described above. In fact, given that based on the clinical evidence, it may be appropriate to assume a similar effectiveness for efgartigimod and the comparator treatments, the EAG's approach may even be considered somewhat optimistic for efgartigimod.

The approach described above is included in the EAG base case (see Section 5.2.3). The company provided a scenario analysis implementing the EAG's preferred approach as described above; this scenario resulted in a very large decrease in incremental NHB.

The approach to modelling treatment effectiveness in the comparator arm forms part of **Key Issue 10**, discussed in Section 1.3.

4.2.8 Other events

4.2.8.1 Withdrawal of active treatment and relapse

For patients in the very limited impairment, mild impairment and moderate impairment active disease health states, patients were modelled to have a per-cycle probability of withdrawing from active treatment (i.e., entering the remission health state associated with the same aINCAT score). From the remission health states, patients also had a per-cycle probability of relapse (i.e., returning to the corresponding active disease health state and recommencing active treatment). The company also presented a scenario analysis in which half of patients who relapsed were assumed to move to the next most severe aINCAT category when restarting treatment; for example, in this scenario, patients in the mild impairment, remission health state were modelled to move to the moderate impairment, active disease health state upon relapse, rather than the moderate impairment, active disease health state.

Patients receiving efgartigimod were only modelled to enter remission health states after being on maintenance treatment for at least one year, as it was assumed that patients would not undergo a dependency test unless they had been stable on maintenance treatment for at least a year; however, patients receiving Ig were assumed to be able to enter remission health states from baseline. The company explored the impact of these assumptions in the following scenario analyses:

- Patients on efgartigimod can enter remission health states from baseline;
- Patients on both efgartigimod and Ig can enter remission health states three months from baseline;
- Remission health states are removed (i.e., patients do not undergo withdrawal of treatment due to disease stability).

Patients receiving treatments in the comparator basket were assumed not to enter remission health states, as patients receiving these treatments would not be expected to have stable disease without ongoing active treatment; this assumption was confirmed by the EAG's clinical experts.

When modelling Ig-dependent subgroups (i.e., the Ig-dependent subgroup and the ultra-high dose subgroup), patients were assumed not to undergo remission at any time, regardless of the treatment received.

The per-cycle probabilities for remission and relapse were assumed to be the same, regardless of disease severity and the treatment being received. The six-month probability of relapse was assumed to be equal to the product of the following:

- Proportion of patients on a stable dose of Ig at any given time;
- Proportion of patients who are on a stable dose, who are willing and eligible to undergo a dependency test;
- Proportion of patients who successfully discontinue Ig after a dependency test and remain clinically stable for the following six months.

The first of these input values was informed by Koay *et al.* 2025, a real-world cohort study of cessation trials for patients on stable IVIg treatment for CIDP, at one centre in the UK.²⁵ The other inputs were elicited from UK clinical experts during the company’s SEE.²¹ The input values are given in Table 52. In the company’s original model, this resulted in a per-cycle probability of remission of [REDACTED]. In the analysis using a three-month cycle length for the first two years, the per-cycle probability was adjusted by assuming the time to remission event was exponentially distributed, resulting in a per-cycle probability of [REDACTED].

The per-cycle probability of relapse was calculated based on the estimated proportion of patients, among those in remission at six months, who would not remain in remission for an additional 12 months. The input value was informed by UK clinical experts during the company’s SEE, and is detailed in Table 52.²¹ The resulting probability was adjusted to align with the cycle length by assuming an exponentially-distributed time to event, resulting in a per-cycle probability of [REDACTED] for a six-month model cycle, or [REDACTED] for a three-month model cycle.

Table 52. Input values for parameters included in remission and relapse probability calculations

Parameter	Input value	Source
Proportion of patients on a stable dose of Ig at any given time	60.8%	Koay <i>et al.</i> 2025 ²⁵
Proportion of patients who are on a stable dose, who are willing and eligible to undergo a dependency test	45.2%	SEE with UK clinical experts ²¹
Proportion of patients who successfully discontinue Ig after a dependency test and remain clinically stable for the following six months	31.0%	SEE with UK clinical experts ²¹
Proportion of patients, among those in remission at 6 months, who would not remain in remission for an additional 12 months	20.6%	SEE with UK clinical experts ²¹

Abbreviations: Ig, immunoglobulin; SEE, structured expert elicitation.

4.2.8.1.1 EAG critique

The EAG considers that the company's approach to modelling remission/relapse is broadly appropriate.

The EAG notes that data from Koay *et al.* 2025 appear to also be available for the proportion of patients on a stable dose of Ig willing and eligible for a dependency test, although this was informed by expert elicitation in the company's base case; in the Koay *et al.* study, 12 out of 45 patients met these criteria (26.7%). Of the 12 patients who discontinued, eight remained stable off treatment for at least 12 months (66.7%); this is likely to be slightly lower than the input required in the company's approach, the probability of a patient remaining stable for at least six months. However, taking the product of these values (along with the proportion of patients on a stable dose of Ig at any given time) gives a total probability of 10.8%, which is very similar to the company's estimate for the per-cycle probability of entering remission (10.91%). Therefore, these data are broadly supportive of the company's approach.

4.2.8.2 Treatment discontinuation

As discussed in Section 4.2.3, patients were modelled to discontinue efgartigimod at the time of response assessment if they were considered to be non-responders (i.e., patients showing no evidence of clinical improvement). In the economic model, the proportion of responders was aligned with the response rate in ADHERE Stage A for the Ig pre-treated population, 58.8% (95% CI: 50.9% to 66.4%).¹⁴

Patients were also modelled to permanently discontinue efgartigimod and Ig in the first 18 months from baseline for reasons other than non-response. Thereafter, it was assumed that patients did not permanently discontinue treatment. Both the company's and the EAG's clinical experts agreed that this assumption was appropriate.

Treatment discontinuation data for efgartigimod was sourced from ADHERE and ADHERE+; similarly to the derivation of shift data for calculating transition probabilities, time on treatment data for individual patients were pooled between ADHERE and ADHERE+.¹⁴ In the company base case presented in the CS, only discontinuations due to AEs or safety concerns were considered; however, during the clarification stage, the company updated the base case analysis to include all treatment discontinuations. A time-to-event analysis was then performed on these data.

In the company's original analysis, parametric curves (exponential, Weibull, lognormal, log-logistic, Gompertz and gamma) were fitted to the time on treatment data from ADHERE and ADHERE+, and the exponential extrapolation to parametrise discontinuation of efgartigimod on the basis of statistical fit. However, during the clarification stage, the company updated their approach to use Kaplan-Meier (KM) data directly. The per-cycle discontinuation probabilities for efgartigimod are given in Table 53.

Table 53. Per-cycle permanent discontinuation probabilities for efgartigimod treatment

Time from baseline	Per-cycle discontinuation probability (six months)	Per-cycle discontinuation probability (three months)
0-3 months	■	■
3-6 months		■
6-9 months	■	■
9-12 months		■
12-15 months	■	■
15-18 months		■

For patients receiving Ig, the company included separate model inputs for the probability of discontinuation from baseline to six months from baseline, and for six to 18 months from baseline. The input for the first six months was informed by the ICE study and PATH study; since both studies had a time horizon of six months, the probability of discontinuation was calculated by dividing the total number of patients who discontinued treatment across both studies by the total number of exposed patients across both studies.^{26, 27} The probability of discontinuation between six and 18 months from baseline was informed by the PATH open-label extension.²⁸ For the analysis using a 12-week cycle length for the first two years, the per-cycle probabilities of treatment discontinuation were adjusted, assuming an exponentially-distributed time to discontinuation.

The input values used in the model are given in Table 54.

Table 54. Per-cycle permanent discontinuation probabilities for Ig treatment

Time from baseline	Per-cycle discontinuation probability (six months)	Per-cycle discontinuation probability (three months)	Source
0-6 months	7.49%	3.82%	Pooled data from ICE and PATH studies ^{26, 27}
6-18 months	3.36%	1.69%	PATH open-label extension ²⁸

Abbreviations: Ig, immunoglobulin.

4.2.8.2.1 EAG critique

Following the updates made during the clarification stage, the EAG considers the company's approach to modelling treatment discontinuation for efgartigimod responders and non-responders to be appropriate.

However, the EAG considers that the company's approach to modelling Ig discontinuation may not be appropriate. In particular, as discussed in Section 4.2.7.2.1, in the comparator arm, the company's modelling approach implicitly assumes that patients will be on stable treatment at baseline. Given that it is also assumed that patients will not discontinue treatment after 18 months on treatment, the EAG considers that it is more appropriate to exclude treatment discontinuation for patients on Ig. The company implemented this approach in the comparator arm in a scenario analysis at the EAG's request, which resulted in a slightly increased incremental NHB for efgartigimod.

The approach to modelling discontinuation in the comparator arm forms part of **Key Issue 10**, discussed in Section 1.3.

4.2.9 Mortality

For all health states in the model, the company assumed that the probability of death was in line with age- and sex-adjusted general population norms; input data was derived from the Office for National Statistics (ONS) UK National Life Tables.²⁹ Both the company's and the EAG's clinical experts agreed that CIDP did not generally affect patient survival.

The EAG considers that the company's approach to modelling mortality is reasonable.

4.2.10 Adverse Events

4.2.10.1 Treatment-related adverse events

Table 55 presents the probability per model cycle (six months) and duration of adverse events (AEs) included in the company's base case analysis for efgartigimod and comparators in the model. To implement the alternative approach in which a three-month cycle length was used for the first two years, the per-cycle probability was adjusted by assuming that the time to each adverse event

occurring was exponentially distributed. Adverse events were applied for the full duration of treatment. For details on the underlying data informing the AEs, please see Appendix 7.5.

Table 55. Adverse events included in the company's base case.

Adverse Event	Duration (days) (NICE TA706) ³⁰	Per-cycle probability (six months)				
		Efgartigimod	Maintenance Ig ^{26, 27, 31, 32}	PLEX ³³	Cortico-steroids ³⁴	Immuno-suppressants ³⁵
Abdominal pain	21.6	■	-	-	14.3%	-
Anaemia	21.6	■	-	-	-	0.51%
Arthralgia and pain in the extremities	11.5	■	4.5%	-	4.8%	-
Asthenia	21.6	■	4.2%	-	-	-
Back pain	11.5	■	10.5%	-	-	-
Dizziness	21.6	■	1.6%	-	-	-
Endocrine disorders	21.6	■	-	-	9.5%	-
Fatigue	21.6	■	12.1%	24.2%	-	-
Gastrointestinal disturbances	21.6	■	0.2%	-	-	3.5%
Headache	11.5	■	50.8%	-	-	-
Haemolysis	21.6	■	8.3%	-	-	-
Hypertension	21.6	■	15.9%	-	14.3%	-
Infections	21.6	■	-	24.2%	4.8%	-
Influenza	1.0	■	2.6%	-	-	-
Infusion/injection site reaction	13.0	■	18.5%	24.2%	-	-
Nasopharyngitis	21.6	■	13.5%	-	-	-
Nausea	21.6	■	16.8%	-	-	-
Peripheral oedema	21.6	■	-	-	9.5%	0.51%
Psychiatric disorders	21.6	■	-	-	23.81%	-
Pyrexia	21.6	■	9.6%	-	-	-
Upper respiratory tract infection	7.5	■	-	-	-	-

Abbreviations: PLEX, plasma exchange.

Note: For AEs that have a duration of 21.6 days, this was estimated as the average of the durations for arthralgia and pain in the extremities, back pain, headache, influenza, infusion/injection site reaction; upper respiratory tract infection and depression reported in NICE TA706.³⁰

The duration of each AE was obtained from NICE TA706 (ozanimod for treating relapsing–remitting multiple sclerosis).³⁰ If the duration of an AE was not available from TA706, the company assumed an average duration of 21.6 days based on an average of the durations of AEs reported in NICE TA706 (arthralgia and pain in the extremities, back pain, headache, influenza, infusion/injection site reaction, upper respiratory tract infection and depression).

4.2.10.2 Complications related to IV access

In addition to AEs, the company included complications related to IV administration, which impacts patients receiving IVIg and PLEX treatments. The per-cycle probability of complications related to IV administration are presented in Table 56. The company obtained data on complications related to IV administration from a published USA budget impact analysis of SCIg compared to IVIg in patients with CIDP.³⁶ The proportions of patients experiencing complications related to IV administration presented in the budget impact analysis were assumed to be annual, so the company divided the data by two to estimate the per-cycle probability for the model. The company assumed that each complication had a duration of 7 days based on data from TA352 (vedolizumab for treating moderately to severely active Crohn’s disease after prior therapy).³⁷

In their clarification response, the company justified the inclusion of complications related to IV access based on reports from specialist nurses that difficulties are common, with infusions that are split or slowed resulting in more cannulations for patients. The company states that repeated IV access can lead to vein depletion, pain and procedural anxiety.

Table 56. Per-cycle probability of complications related IV administration (reproduced from Table 60 of the CS)

Type of complication	Per-cycle probability
Permanent PICC, surgically implanted CVC, infusion port	10.0%
Catheter-related infections	0.5%
Catheter-related blood infections	0.8%
Thrombophlebitis	1.1%
Infiltration and extravasation	0.3%
Thromboembolic events	0.2%
Abbreviations: CVC, central venous catheter; IV, intravenous; PICC, peripherally inserted central catheter.	

4.2.10.3 EAG critique

The EAG considers there is a substantial amount of uncertainty with data informing AEs in the model, primarily because definitions of AEs are not consistent across treatments, driven by how data are reported for the comparators, and the differing thresholds used for inclusion in the model (see Appendix 7.5). Additionally, the durations of most of the AEs are based on an average of all AEs and may not be reflective of how long the event lasts or even clinically plausible. For example, a duration of 21.6 days was assumed for dizziness compared to a duration of one day for influenza.

All AEs reported for treatments are mild or moderate, and based on advice sought from the EAG's clinical experts, would most likely be treated by a GP (see Section 4.2.12.6.1). In their clarification response, the company considered that efgartigimod was associated with a low incidence of serious AEs and that other treatments such as PLEX are associated with a high incidence of serious AEs, but the EAG highlights that this is not reflective of the data that are included in the model (i.e., common AEs that are mild/moderate in nature).

The uncertainty around AEs is **Key Issue 11**, discussed in Section 1.3.

With regards to complications related to IV access, the EAG considers that the NHS adopts robust sterile techniques to deliver IV treatment and understands from its clinical experts that healthcare professionals delivering IVIg and PLEX are well-trained and experienced and so complications related to IV treatment are rare. Therefore, the EAG considers that the source used by the company to parametrise IV complications is unlikely to be relevant to a UK setting. The EAG also notes that, as well as the disutility related to AEs associated with IV administration, the company separately included disutilities related to IV administration which included factors other than AEs (e.g., inconvenience of long or frequent infusions), but did not exclude the impact of AEs; these disutilities are discussed in Sections 4.2.11.4 and 4.2.11.4.1. The EAG considers that the inclusion of both disutilities related to IV administrations is likely to result in double-counting.

The company supplied scenarios excluding AEs and complications related to IV administration from the model in their clarification response, and these had a substantial impact on the NMB. The EAG considers that AEs should be excluded from the model, due to the high level of uncertainty, and the mild/moderate nature of the majority of AEs reported for the intervention and comparators. The EAG also considers that complications related to IV administration should be excluded from the

model, due to lack of relevance to the UK setting. These approaches have been applied in the EAG's preferred assumptions, presented in Section 5.2.3.

The approach to modelling the HRQoL impact of IV administrations is **Secondary Issue 3**, discussed in Section 1.4.

4.2.11 Health-related quality of life

4.2.11.1 Health state utility values

The health state utility values (HSUVs) included in the model were informed by EQ-5D-5L data collected in ADHERE (both Stage A and B). Patients completed the EQ-5D-5L questionnaire at baseline of Stage A and weekly thereafter up to Week 12. For Stage B, patients completed the EQ-5D-5L questionnaire at baseline and every four weeks thereafter until Week 48. From the modified Intent-to-Treat (mITT) population (both efgartigimod and placebo patients), 315 responses were collected at baseline, and 16 responses were collected at Week 12 in Stage A. In Stage B, the following number of responses were collected: 195 responses at baseline; 137 responses at Week 12; 90 responses at Week 24; 67 responses at Week 36; and 51 responses at Week 48. Please refer to Table 43 of the company's clarification response for details of utility data collected at each timepoint in ADHERE. As the NICE methods guide recommends the use of EQ-5D-3L utility data for the reference case, the company mapped the EQ-5D-5L patient level responses from ADHERE to EQ-5D-3L using the Hernandez-Alava mapping algorithm as recommended by NICE.^{38, 39}

The company pooled utility estimates across the ADHERE Stage A and B study arms to maximise the number of observations, as it was assumed that patient HRQoL was not dependent on treatment received in the trial. Table 45 in the company's clarification response presents a descriptive analysis of HSUVs for each health state in the model.

The company used a mixed-effects model to estimate HSUVs from the mapped EQ-5D-3L data from ADHERE. The only fixed effects covariate in the model was aINCAT category, to estimate utility values for each health state in the model; a random intercept for patient identifier was also included to account for within-patient correlation. The company states a complete case approach was used as missing EQ-5D measurements were infrequent and not systematically associated with aINCAT severity. However, the EAG considers there is a lack of detail from the company around missing information for the utility analysis and so cannot determine what impact this had on the analysis.

Additionally, the company did not provide the diagnostic test results for the regression and instead simply stated there were no violations of the model assumptions.

The HSUVs applied in the company base case are presented in Table 57.

Table 57. Health state utility values included in the model (reproduced from Table 53 of the CS)

Health state	Mean (SE) utility
Very limited impairment	0.851 (0.024)
Mild impairment	0.630 (0.013)
Moderate impairment	0.426 (0.012)
Severe impairment	0.084 (0.025)
Very severe impairment	-0.216 (0.046)
Abbreviations: CS, company submission; SE standard error.	

4.2.11.1.1 EAG critique

The EAG has several concerns with the HSUVs included in the model. A key issue is that the company estimated a utility value for the very severe health state as less than zero (i.e., worse than death). In their clarification response, the company supplied mean observations by aINCAT category for each domain in the EQ-5D-5L (Table 46 of the company's clarification response). The EAG notes that for aINCAT 9-10 (very severe), the mean score for mobility and self-care domains was 5, and most scored 4 or 5 for usual activities. Pain and discomfort were on average 3 (min = 1, max = 5) and anxiety was 2.4 (min = 1, max = 5). A score of 55555 represents extreme problems in all five domains and results in a utility value of -0.285 using the EQ-5D-5L value set for England.⁴⁰ Given that the average domain scores for patients in the very severe impairment category were not consistently extreme across all five dimensions, it is surprising that the assigned HSUV for this health state is almost as low as the lowest possible HSUV attainable using the EQ-5D-5L value set for England. However, the EAG notes that the number of observations at each timepoint in ADHERE informing the utility values is variable and many of the timepoints have less than 20 responses (Table 43 of the company clarification response). Additionally, for two domains, scores were reported at both the lower and upper end of the range. As such, the utility values appear to be very uncertain.

The EAG consulted with its clinical experts, who explained that while patients with very severe disease may have a poor health-related quality of life (HRQoL), they did not consider patients would consider their HRQoL was worse than death. The EAG considers that for the very severe health state,

it may not be unreasonable that the true utility value is extremely low, even near zero, but that it may not reflect the patient reality to model it as a health state worse than death. During the clarification stage, the EAG requested, and the company provided, a scenario in which the utility value for the very severe health state was set to zero. The results of the scenario had a small impact on incremental QALYs, but the EAG considers that it is a relevant approach to include in the EAG base case (presented in Section 5.2.3). which is likely to be more reflective of patients' experience, and represents a proportionate simplification considering other key issues with the analysis that have a greater impact on the incremental NHB. However, the EAG has presented results of an analysis using the company's original HSUV for the very severe health state.

Secondary concerns with the utility data in the model include:

- The approach to the mixed-effects model was overly simplistic and as a result, estimates were not dissimilar to the descriptive analysis, suggesting limited value of the mixed effects model. The company should have explored additional covariates such as age, sex, treatment, and other prognostic factors and elicited clinical expert opinion to select the final model specification, presenting diagnostic tests for the models and the approach to handling missing data.
- The attrition rate of EQ-5D-5L responses from ADHERE in Stage A and Stage B appears to be high. The EAG would have liked the company to provide more discussion of this in their clarification response to understand what was happening in the trial and how that impacts the estimation of utilities for the model.
- It is unclear why a complete case analysis approach was used rather than imputing missing values, for example, using a multiple imputation approach, which is more commonly used for HSUV analyses, and may mitigate some of the EAG's concerns around missing data.

The appropriateness of HSUVs is **Secondary Issue 2**, discussed in Section 1.4.

4.2.11.2 Age-related utility decrements

Utilities in the model were adjusted for age, as per the NICE methods guide.⁴¹ General population utility values adjusted for age and sex were obtained from the HSE 2014 dataset, as recommended by the DSU.⁴² In the original economic model, age adjustment was applied to the utility value for the very severe health state (-0.216); however, the EAG considers applying age-related decline to a negative utility value may be inappropriate. In their clarification response, the company updated

their base case to exclude age-related decline for the very severe health state. Overall, the EAG considers the company's updated approach to age-related utility decrements is appropriate.

4.2.11.3 Adverse event disutilities

Table 58 outlines the disutility associated with each AE included in the model and its source. See Section 4.2.10 for the AE inclusion criteria in the economic model, AE incidence and duration for the intervention and comparators. The disutility of each AE was obtained from a study by Sullivan *et al.* 2011 and NICE TA706 (also used to inform the duration of AEs).^{30, 43} If the disutility of an AE was reported in both sources, the company calculated an average of both values to use in the model. Where a disutility for an AE was not available from either source, the company used an average of all the available AE disutilities for the AE.

Table 58. Adverse event disutilities included in the model (reproduced from Table presented in the company's clarification response to question C5)

Adverse Event	Decrement	Source
Arthralgia and pain in the extremities	-0.165	Average of values reported in NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}
Asthenia	-0.102	Company used the average of the reported disutilities NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}
Back pain	-0.177	Average of values reported in NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}
Dizziness	-0.102	Company used the average of the reported disutilities NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}
Fatigue	-0.102	Company used the average of the reported disutilities NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}
Headache	-0.104	Average of values reported in NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}
Haemolysis	-0.061	Sullivan <i>et al.</i> 2011 ⁴³
Hypertension	-0.046	Sullivan <i>et al.</i> 2011 ⁴³
Influenza	-0.080	NICE TA706 ³⁰
Infusion/injection site reaction	-0.010	NICE TA706 ³⁰
Nasopharyngitis	-0.019	Average of values reported in NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}
Nausea	-0.073	Sullivan <i>et al.</i> 2011 ⁴³
Pyrexia	-0.102	Company used the average of the reported disutilities NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}
Upper respiratory tract infection	-0.119	Average of values reported in NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}
Infections	-0.102	Company used the average of the reported disutilities NICE TA706 and Sullivan <i>et al.</i> 2011 ^{30, 43}

Sleep disorders	-0.095	Sullivan <i>et al.</i> 2011 ⁴³
Psychiatric disorders	-0.143	Sullivan <i>et al.</i> 2011 ⁴³
Abdominal pain	-0.044	Sullivan <i>et al.</i> 2011 ⁴³
Endocrine disorders	-0.030	Sullivan <i>et al.</i> 2011 ⁴³
Anaemia	-0.022	Sullivan <i>et al.</i> 2011 ⁴³
Gastrointestinal disturbances	-0.044	Sullivan <i>et al.</i> 2011 ⁴³
Renal dysfunction	-0.101	Sullivan <i>et al.</i> 2011 ⁴³
Peripheral oedema	-0.040	Sullivan <i>et al.</i> 2011 ⁴³
Abbreviations: CS, company submission		

As mentioned in Section 4.2.10.2, the company included complications related to IV access and included related disutilities in the model (see Table 59). The disutility of each AE was obtained from a study by Sullivan *et al.* 2011 and NICE TA804 (teduglutide for treating short bowel syndrome).^{43, 44} The company assumed the duration of complications related to IV access was seven days, based on TA352, which assumed a cycle length of seven days.³⁷

Table 59. Disutilities associated with complications related to IV access (reproduced from Table presented in the company's clarification response to question C5)

Complication	Utility decrement	Source
Permanent PICC, surgically implanted CVC, infusion port	-0.250	Company calculated an average disutility value based on the available disutility values for complications related to IV access.
Catheter-related infections	-0.520	TA804 ⁴⁴
Catheter-related blood infections	-0.520	TA804 ⁴⁴
Thrombophlebitis	-0.063	Sullivan <i>et al.</i> 2011 ⁴³
Infiltration and extravasation	-0.083	Sullivan <i>et al.</i> 2011 ⁴³
Thromboembolic events	-0.065	Sullivan <i>et al.</i> 2011 ⁴³
Abbreviations: CS, company submission; CVC, central venous catheter, IV, intravenous; PICC, peripherally inserted central catheter.		

4.2.11.3.1 EAG critique

In the model, the company extracted disutility values for most AEs from a single source (Sullivan *et al.* 2011⁴³), but for the base case also used disutilities reported in TA706, as well as calculated averages from both sources. The study by Sullivan *et al.* is a well-established source of utility values used in several NICE TAs. The EAG notes that AE disutility values from TA706 are derived from multiple sources, including NICE TAs for ocrelizumab (TA533) and cladribine (TA616).³⁰ The EAG considers that it is good practice for utility values to be based on a single source where possible.

Additionally, in TA706, duration and disutility of dizziness, fatigue, influenza, nasopharyngitis and pyrexia were assumed to be zero. However, the company has included the impact of these AEs, citing TA706 as the source. In their clarification response, the company provided a scenario analysis where all disutilities were sourced from Sullivan *et al.* and the duration and disutility of dizziness, fatigue, influenza, nasopharyngitis and pyrexia were assumed to be zero; this had limited impact on incremental QALYs.

As discussed in Section 4.2.10.3, the EAG prefers to exclude the impact of AEs and complications related to IV access from the model as the underlying AE data are for mild and moderate AEs, and inclusion criteria are not consistent across treatment. Additionally, there is no consistent reporting of data, and durations mostly rely on assumptions, which introduces a high degree of uncertainty in the model. With regards to complications related to IV access, the EAG considers that the NHS adopts robust sterile techniques to deliver IV treatment and understands from its clinical experts that healthcare professionals delivering IVIg and PLEX are well-trained and experienced and so complications related to IV treatment are rare. As such, for the EAG base case (presented in Section 5.2.3), AEs and complications related to IV access are excluded from the model.

4.2.11.4 Disutilities associated with IV administration

The company has included utility decrements associated with several aspects of IV treatment administration, presented in Table 60; these are distinct from the disutilities included as a result of complications due to IV access discussed in Section 4.2.11.1. The company reported fitting a linear regression to utility values obtained from the literature to estimate the disutility associated with IV administration, in-hospital administrations and the number of administrations per cycle. The company relied on an abstract by Jørgensen *et al.* 2017, which estimated preferences using the time-trade-off method for route of administration (SC versus IV), frequency (weekly, bi-weekly, 8-weekly and 12-weekly) and setting (home or hospital) for the general population in the UK.⁴⁵ The following regression model was fitted to the data to obtain estimate the disutilities presented in Table 59:

$$Utility = ADMIN\_ROUTE + SETTING + FREQUENCY$$

The disutility for increasing length of infusion was estimated based on data from Matza *et al.* 2013 which estimated utility values associated with route of administration and infusion duration for the general population in the UK using the time-trade-off method.⁴⁶ The company fitted the following regression model to the data:

$$Utility = ADMIN\_ROUTE + DURATION$$

To estimate the total utility decrement associated with duration of IVIg infusion, the company estimated the mean infusion duration for Privigen and Gamunex were 5.89 hours and 5.01 hours, respectively, based on the manufacturers' guidelines on infusion rate per minute and dose. For PLEX, the company assumed that the duration of infusion was the average of the durations for Privigen and Gamunex.

In the model, the total disutility per cycle associated with IVIg administration was -0.114 and -0.218 for PLEX.

Table 60. IV administration disutility per cycle (reproduced from Table 64 of the CS)

Area of impact	Utility decrement	Source
Disutility associated with IV administration route	-0.022	Derived from the values reported by Jørgensen <i>et al.</i> 2017 ⁴⁵
Disutility associated with in-hospital setting	-0.011	
Disutility associated with the number of administrations per cycle (the decrement represents the marginal disutility associated with each additional administration)	-0.006	
Disutility associated with IV administration route per hour	-0.009	Matza <i>et al.</i> 2013 ⁴⁶
Abbreviations: CS, company submission; IV, Intravenous.		

As part of their clarification response, the company supplied three scenarios exploring alternative estimates of disutility associated with IV access:

1. Administration disutilities were based only on the regression results from Jørgensen *et al.* 2017 (i.e. disutility due to infusion length was excluded);
2. Only the route of administration disutility for IV access based on Jørgensen *et al.* 2017 was included in the model;
3. Route of administration and disutility associated with infusion time were included in the model, but disutilities associated with setting and administrations per cycle were excluded.

Table 35 of the company's clarification response presents the results of the scenarios.

4.2.11.4.1 EAG critique

The EAG considers the company's base case disutility value for IV administration potentially overestimates the impacts of IV administrations. The EAG's clinical experts advised that patients feel

reassured having treatment in a hospital setting and that once a patient becomes used to their treatment, it has a limited impact on their HRQoL. As such, disutility associated with setting, frequency and duration may not reflect the patient experience.

The company highlighted that vein depletion for patients is an issue associated with frequent IV administration and so the EAG considers that it is reasonable to include a disutility associated with route of administration. As such, the company's scenario 2 may be a more robust estimate of disutility for IV administration as it is based solely on IV versus SC. The EAG also notes that disutility for administration route was also the only statistically significant coefficient in the company's linear model fitted to data from Jørgensen *et al.* 2017. The disutility associated with IV administration for scenario 2 was -0.021 and -0.022 for IVIg and PLEX, respectively. The impact of the scenario on incremental QALYs was substantial, [REDACTED]. The EAG has included the company's scenario 2 in its preferred base case, presented in Section 5.2.3.

The approach to modelling the HRQoL impact of IV administrations is **Secondary Issue 3**, discussed in Section 1.4.

4.2.12 Resource use and costs

In the economic model, the company included costs relevant to drug acquisition and administration, health state resource use including disease monitoring, mobility aids, hospitalisations, and AEs. Drug costs were sourced from the British National Formulary (BNF).⁴⁷ Drug administration, health state resource use and AE costs were sourced from the NHS pay award prices workbook 2025/26, NHS 2023/24 National Cost Collection data dashboard and the Unit Costs of Health and Social Care 2024.⁴⁸⁻⁵⁰ Costs associated with professional care were included in model and these are described in Section 4.2.13.2. Where required, costs have been inflated to 2025 prices using inflation indices obtained from PSSRU.⁵⁰

Confidential medicines procurement supply chain (MPSC) prices are available for some Ig products (Gamunex and Hizentra) and so the EAG has produced a confidential appendix to this report. Please refer to Section 5.4 for further details on analyses included in the confidential appendix.

4.2.12.1 Drug acquisition costs

The proposed list price of efgartigimod per pre-filled syringe (1,000 mg in 5 ml) is [REDACTED]. The company has proposed a confidential patient access scheme (PAS) discount of [REDACTED]% on the

proposed list price of efgartigimod resulting in a discounted price of ██████ per pre-filled syringe. The treatment regimen for efgartigimod is 1,000 mg administered via a pre-filled syringe subcutaneously once weekly. The first four injections must be delivered by a health professional but thereafter can be self-administered by the patient.⁵¹

The draft SmPC outlines that based on clinical evaluation, treatment frequency can be reduced to every two weeks (Q2W), and the company has assumed that after six months patients would be eligible for the Q2W regimen. In ADHERE+, patients were eligible for Q2W dosing if they remained on treatment for a minimum of 24 weeks. Of those eligible who received the Q2W dosing in ADHERE+, ██████% remained on treatment for at least 24 weeks. Table 68 of the CS presents the detailed breakdown of Q2W data from ADHERE+.

The company calculated a one-off cost of efgartigimod induction, which was assumed to be the once weekly regimen for three months (12 administrations). The cost of efgartigimod induction including the PAS discount is ██████. This cost was applied at baseline, although the induction period for efgartigimod was not explicitly modelled. However, as discussed in Section 4.2.7.1.1, the EAG considers that the inclusion of the one-off induction cost leads to double-counting, and has adjusted the costing approach so that costs for efgartigimod treatment are applied for all patients in the efgartigimod arm for the first cycle. Additionally, the company assumed that for the first six months from baseline, patients would continue the once weekly dose.

From six months from baseline onwards, the company assumed that ██████% of patients would receive the Q2W dose and the remainder (██████%) would continue to receive the once weekly dose, in line with ADHERE+. Table 61 presents the cost per cycle of efgartigimod, inclusive of the PAS discount.

Table 61. Cost per six-month cycle of efgartigimod (with PAS)

Cycle	Efgartigimod drug acquisition cost per six-month cycle
Cycle 1	██████
Cycle 2+	██████
Abbreviations: PAS, patient access scheme.	

In clinical practice, Ig treatment can be given via IV or subcutaneously. In the model, the company assumed that 95% of patients would receive IVIg and 5% would receive SCIg, based on data from the company’s chart review study.¹⁹ Please refer to Section 4.2.2 for the EAG’s discussion on the

company's chart review study. For Ig, treatment dose is dependent on the patient and ranges from 0.50 g/kg to 2.00 g/kg per administration for IVIg, and 0.50 g/kg to 1.99 g/kg per administration for SCIg. In the model, four categories of IVIg dose and two categories of SCIg dose were used to estimate costs of treatment per model cycle; these are presented in Table 62.

The proportion of patients assumed to be on each dose category (Table 62) was obtained from the SEE conducted by the company. Please refer to Section 4.2.2 for the EAG's discussion on the company SEE. For SCIg, the company assumed that the proportion on 1.00 – 1.99 g/kg was the same as the proportion of patients on >1.00 g/kg for IVIg (84.33%), with the remainder on the lower dose of 0.50 g/kg – 0.99 g/kg (15.67%). It should be noted that SCIg treatment is weekly, while the time between treatment administrations is approximately 4 weeks for IVIg, and so the treatment dose was divided by four to estimate the weekly dose, as recommended by the Hizentra SmPC.⁵²

The company estimated a weighted average dose of IVIg and SCIg per treatment cycle by using the midpoint of the dose range (e.g. 1.50 g/kg for a dose range of 1.00 – 1.99 g/kg) and the proportion of patients on each dose (Table 62). The weighted dose was [REDACTED] mg for IVIg and [REDACTED] mg for SCIg. Based on the mean baseline patient weight of 80.6 kg from ADHERE, the total dose per treatment cycle for IVIg was estimated to be [REDACTED] mg and for SCIg was [REDACTED] mg (weekly dose).

To estimate the number of IVIg treatments per model cycle, the company obtained estimates from clinical experts as part of the company SEE on the average time between treatment cycles in weeks, presented in Table 62. The company then estimated the weighted number of IVIg doses per model cycle using the average number of Ig treatments per 6 months for each dose category and the proportion of patients in each dose category (Table 62). The average number of IVIg treatments per 6-month model cycle was estimated to [REDACTED].

Table 62. Ig dose data included in the company's base case

Dose	Proportion on dose	Average time between treatment cycles (weeks)	Average no. of Ig cycles per 6-month period
IVIg			
<0.50 g/kg	0.17%	3.63	7.19
0.50 – 0.99 g/kg	15.51%	3.79	6.88
1.00 – 1.99 g/kg	60.30%	4.08	6.39
2.00 g/kg	24.03%	4.11	6.35
SCIg			
0.50 – 0.99 g/kg	15.67%	1.00	26.09

1.00 – 1.99 g/kg	84.33%	1.00	26.09
Abbreviations: Ig, immunoglobulin; IV, intravenous; SC, subcutaneous.			

Table 72 of the company submission presents the list price of each brand of Ig treatment. The cost of treatment for each brand of Ig was estimated by multiplying the list price by the average dose per treatment and the number of treatments in a model cycle. The overall cost of Ig treatment was then estimated by weighting each Ig brand by the distribution of patients across the products (presented in Table 44). The cost of Ig per cycle in the model was estimated to be [REDACTED].

The cost of PLEX in the model was based on the NHS reference costs HRG code SA44A - Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over (502.51).⁴⁸ The company assumed 24 PLEX administrations per model cycle, resulting in a cost of £12,060.24.

For corticosteroids, the company assumed that this would be IV methylprednisolone in clinical practice; the EAG's clinical experts agreed with this assumption, although noted oral treatment may also be given in clinical practice. The company assumed that corticosteroids would be applied as a one-off cost in every model cycle, under the steady state assumption described in Section 4.2.4. The cost of IV methylprednisolone (40 mg) was £1.58, based on the BNF.⁴⁷ The company assumed the dose would be 0.5 g per day for four consecutive days every month, based on the dosing regimen presented in Nobile-Orazio *et al.* 2012.³⁴ Based on the company SEE, the mean duration of corticosteroid treatment was estimated to be 3.5 months; therefore, only a cost for 3.5 months of treatment was applied each cycle.²¹ The one-off cost of corticosteroids was estimated to be £274.94.

The company assumed mycophenolate mofetil was representative of immunosuppressants in the model. The EAG's clinical experts confirmed that this assumption was appropriate. The BNF price of fifty 500 mg mycophenolate mofetil tablets was £5.99.⁴⁷ The company assumed the dose of immunosuppressants to be 2.0 g per day, based on the dose presented in Bedi *et al.* 2010.⁵³ The cost per cycle of immunosuppressants was estimated to be £87.51.

4.2.12.1.1 EAG critique

One of the EAG's main concerns is that the split between IVIg and SCIg may not be reflective of UK clinical practice. Based on data from the Immunoglobulin Database Annual Report 2023/24, the split between IVIg and SCIg use is 76.7% for IVIg and 23.3% for SCIg.⁵⁴ In the model, it is assumed that 94.9% is IVIg and 5.13% is SCIg, with the data obtained from the interim data cut of company's UK chart review study. The EAG acknowledges that data from the Immunoglobulin Database Annual

Report 2023/24 is for treatment of all conditions, not just CIDP. However, the company's chart review data on distribution across Ig brands as a proxy for IV and SC usage is based on a [REDACTED] [REDACTED] with only [REDACTED] recorded to be on Hizentra, which is an SCIg treatment. The EAG notes that in the company's chart review study, it was recorded that [REDACTED] of patients received IVIg and [REDACTED] received SCIg, but there was no discussion on the overlap of treatments and so interpretation of these findings is problematic. As such, each source of data is associated with uncertainty.

Nonetheless, the company provided a scenario implementing the split of IVIg and SCIg from the Immunoglobulin Database Annual report and this had a substantial impact on the NMB. Based on the company's chart review study, the EAG considers that while [REDACTED] received IVIg, a single patient could be recorded to have both IVIg and SCIg as part of their treatment records. As such, the estimate that [REDACTED] of patients received SCIg as part of their treatment is supportive of the data derived from the Immunoglobulin Database Annual Report 2023/24 and has therefore included this approach as part of the EAG base case, presented in Section 5.2.3.

The proportion of patients receiving IVIg and SCIg forms part of **Key Issue 6**, discussed in Section 1.3.

The company's base case Ig dose data was informed by the company SEE, but in one of their later clarification responses (dated 16 December 2025), the company provided the final data cut from their chart review study which included RWE on Ig dose data.¹⁹ Notably, the company's chart review data found that a proportion of patients on SCIg received a dose of <0.5 g/kg, which was not included in the company base case. Table 64 presents the Ig dose data from the final data cut of the company's chart review study. It should be noted that the data are based on [REDACTED] patients for IVIg and [REDACTED] patients for SCIg. Notably, the RWE estimates a lower frequency, and thus lower number of administrations, of both IVIg and SCIg compared to the data elicited from the company's clinical experts as part of the SEE. The EAG considers that, although the sample sizes informing the dose data in the company's chart review study can be deemed small, especially for SCIg, it is based on actual NHS data rather than theoretical data obtained in the SEE and informing the company's base case. As such, the EAG prefers to use Ig dose data based on the final data cut of the company's chart review study (Table 63) in its base case, presented in Section 5.2.3.

The EAG notes that in the probabilistic analysis, the company assumed that the average time between treatment followed a gamma distribution. The company also derived the upper and lower

bounds for the deterministic sensitivity analysis (DSA) from a normal distribution. The EAG considers that this is inappropriate, and resulted in clinically implausible time input values in the probabilistic analysis and for the lower bound of the DSA. The EAG updated the model to use a shifted gamma distribution to model these parameters, with a minimum value of 1, as it is implausible that patients may receive treatment multiple times in a single week.

Table 63. Ig dose data – company chart review study¹⁹

Dose	Number of patients	Proportion on dose %	Average time between treatment cycles (weeks)	Average no. of Ig cycles per 6-month period
IVIg (N=66)				
<0.50 g/kg	■	■	■	■
0.50 – 0.99 g/kg	■	■	■	■
1.00 – 1.99 g/kg	■	■	■	■
2.00 g/kg	■	■	■	■
SCIg (N=16)				
<0.50 g/kg	■	■	■	■
0.50 – 0.99 g/kg	■	■	■	■
1.00 – 1.99 g/kg	■	■	■	■
Abbreviations: Ig, immunoglobulin; IV, intravenous; SC, subcutaneous.				

As noted above, efgartigimod can be given Q2W based on clinical evaluation and the company has assumed patients are eligible to reduce their frequency of treatment after 6-months (one model cycle), reflective of ADHERE+. The EAG considers there is uncertainty around the treatment effectiveness of moving patients from the weekly treatment regimen to Q2W, discussed in Section 3.3.3.2. As such, the EAG considers it is useful for committee to consider the cost-effectiveness results assuming the treatment regimen for efgartigimod is once weekly and has provided this as a scenario around the EAG base case in Section 5.2.3. The inclusion of biweekly dosing of efgartigimod is **Secondary Issue 1**, discussed in Section 1.4.

As discussed in Section 4.2.3.1, the EAG considers the six-monthly cycle length is not appropriate as it causes a misalignment with the model and the time of observation of clinical data informing model inputs (in particular, transition probabilities and the approach to modelling Q2W dosing). A six-month cycle length is 26.09 weeks. In ADHERE+, patients were eligible for Q2W dosing if they remained on treatment for a minimum of 24 weeks. The company considers the misalignment is minor, but the EAG considers that a model cycle of 12 weeks would be most appropriate; however, as a pragmatic alternative, the company's implementation of a three-month model cycle is

considered sufficiently granular to capture rapid changes in disease severity after starting a new treatment and have better alignment with the efgartigimod treatment regimen. This is discussed further in Section 4.2.3.

With regards to the number of PLEX treatments in a cycle, the EAG acknowledges that the treatment burden may be high, as outlined in the EFNS/PNS guideline, the recommendation for plasma exchange (PICO 10) states that, “the initial treatment may start with 5 exchanges over 2 weeks; thereafter, the plasma exchange interval should be individually adapted”.⁵ However, the EAG’s clinical experts considered that it is not a long-term treatment option. Although, as discussed in Section 4.2.4, under the company’s steady state assumption, the company’s approach may not be unreasonable and a necessary, if uncertain, simplification. The EAG’s key concern is with the assumptions used for the composition of the basket of comparator treatments, as discussed in Section 4.2.2.

4.2.12.2 Drug administration costs

For the first three months of treatment (induction), efgartigimod was assumed to be administered once weekly in a hospital setting, after which, it is assumed that 8% of patients will continue with hospital administration and the remainder transition to treatment self-administered at home. The company’s approach is in line with the draft SmPC for efgartigimod which states that, “
[REDACTED]
[REDACTED]
[REDACTED]”. In their clarification response, the company explained that the assumption that 8% of patients would receive efgartigimod in hospital was based on data from ADHERE+, in which 1 out of every 12 administrations took place in hospital. The cost of hospital administration for efgartigimod was assumed to be £171 based on NHS reference costs HRG code WF02A (Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up).⁴⁸ Home administration of treatment was assumed to incur no costs. As mentioned in Section 4.2.12.1, from cycle 2 onwards, [REDACTED]% of patients would receive the Q2W dose and [REDACTED]% would continue to receive the once-weekly dose. The total administration cost per cycle for efgartigimod was [REDACTED] for the induction period, [REDACTED] for the once-weekly dose and [REDACTED] for the Q2W dose.

All IVIg treatments and 8% of SCIg administrations were assumed to take place in a hospital setting. The proportion of SCIg hospital administrations was obtained from the company SEE.²¹ The company

assumed that each Ig treatment was administered over [REDACTED] days based on data from the company's chart review study.¹⁹ For hospital administration of Ig, the company assumed that [REDACTED] of patients are admitted overnight for both IVIg and SCIg, with the remainder treated in an outpatient setting. The unit cost of outpatient treatment administration in the model was £265 (inflated to £284.40) based on NHS reference costs HRG code SA45A (outpatient procedure, injection of Rh Immune Globulin or Other Blood Transfusion, 19 years and over).⁴⁸ The unit cost of an inpatient stay was £850 sourced from PSSRU (non-elective inpatient stays [short stay], £792) and inflated to 2025 prices.⁵⁰ The total administration cost per cycle for Ig was [REDACTED].

For patients receiving SCIg at home, no administration costs are assumed. However, once weekly treatment administration was assumed for patients receiving SCIg in hospital, including the assumption that treatment is administered over [REDACTED] days each week.

In the model, the company included the cost of NHS-funded travel for 16% of patients receiving Ig treatment in hospital. In their clarification response, the company explained that the proportion assumed to require NHS-funded transport was derived from their SEE. A unit cost of £38 per journey (inflated to £42.88) was obtained from an NHS England report on non-emergency patient transport services.⁵⁵ A return journey was therefore estimated to be £85.75. For patients receiving outpatient treatment in hospital, the transport cost was applied as a return journey per visit for the total number of days of treatment in a cycle. For patients receiving treatment in hospital with an overnight stay (3.1% of patients), the cost of a single return journey was applied.

The company did not include NHS-funded travel for patients receiving efgartigimod in hospital and explained that this was because treatment is only given on a single day and for a short duration of time, and so patients would require less support to attend hospital.

The company assumed no drug administration costs for PLEX, as this was included in the cost of treatment. No administration costs were assumed for immunosuppressants and corticosteroids, which the EAG considers appropriate.

Table 64 presents a summary of the treatment administration costs per cycle estimated in the model.

Table 64. Treatment administration costs per cycle

Treatment	Administration costs per cycle
Efgartigimod – cycle 1	[REDACTED]

Efgartigimod – cycle 2+	■
Ig (IVIg and SCIg)	■
PLEX	£0
Corticosteroid	£0
Immunosuppressants	£0
Abbreviations:	

4.2.12.2.1 EAG critique

The EAG has several concerns with the estimation of drug administration costs included in the model, which are summarised as follows:

- The EAG's clinical experts did not agree with the company's assumption that ■ of patients would be admitted to hospital overnight for Ig treatment. Instead, those receiving Ig would be given treatment in an outpatient setting. In their clarification response, the company stated that they had provided a scenario in which IVIg is only provided in an outpatient setting, although the EAG notes that in the company's implementation, administration costs for IVIg are set to zero, rather than aligning with the costs for an outpatient admission. The EAG prefers to exclude the assumption that patients are admitted overnight for Ig treatment and has included this approach in its preferred base case assumptions.
- For the 8% of SCIg administered in hospital, weekly treatment administrations were assumed to be given over an average of ■ days each week. However, the EAG considers that SC treatment is meant to be more convenient for patients. The manufacturer's guidance for administration (Hizentra) states that treatment can be delivered in 1 or 2 sessions over 1 or 2 consecutive days.⁵⁶ As such, the EAG considers that the number of administrations for SCIg is potentially overestimated and instead prefers to assume treatment is administered once per week in hospital and ran a scenario around the company's base case exploring this and has included it in its preferred base case. Additionally, a scenario exploring no hospital administration of SCIg was also conducted (Section 5.2.2).
- The EAG notes that the outpatient unit costs used in the economic model were greater for SCIg than for efgartigimod (£284.40 versus £171). In their clarification response, the company stated that both Ig and efgartigimod used the same outpatient cost of £171, but this is not reflected in the model. However, they did provide a scenario where the outpatient

administration cost of SClg was equal to that of efgartigimod and this had minimal impact on incremental costs. Nonetheless, the EAG considers this assumption is more appropriate as it assumes once weekly SClg administration, and has included this in its preferred assumptions.

- The inclusion of NHS funded transport costs for CIDP patients receiving treatment in hospital may be reasonable, but the EAG considers that this cost should be applied equally to both efgartigimod and the comparator. The EAG considers the company's justification for the exclusion of NHS funded transport costs for efgartigimod based on their view that treatment duration is shorter is irrelevant as the duration of treatment is not linked to patients' ability to get to hospital. In their clarification response, the company provided a scenario applying NHS funded transport costs to efgartigimod patients and this had minimal impact on the ICER. Nonetheless, the EAG considers that if NHS transport costs are to be included in the model, it is more appropriate to apply costs equally across both arms of the model and as such has included it in its preferred assumptions in Section 5.2.3.

Overall, the EAG considers that its alternative assumptions outlined above and included in its preferred base case represents a more unbiased approach to drug administration costs in the model.

The EAG's concerns around the approach to modelling drug administration costs are included in **Secondary Issue 4**, discussed in Section 1.4.

4.2.12.3 Disease monitoring costs

Disease monitoring costs were assumed to be the same for all health states (no distinction for severity) and for all treatments in the model. The company obtained healthcare resource use estimates from a study by Mahdi-Rogers *et al.* 2014, which estimated the economic costs of chronic inflammatory neuropathies, including CIDP, in southeast England.⁵⁷ Table 65 presents the healthcare resource use and unit costs included in the model, which covers visits with a GP, Neurologist, Physiotherapist and Occupational therapist. The total cost per cycle of disease monitoring was £1,466.80.

Table 65. Health state resource use included in the model.

Resource use	No. of visits per model cycle*	Unit cost	Source/ assumptions
General practitioner visit	2.16	£268.00	Assumed to be 1 hour in duration. Unit cost based on unit cost of a GP per hour of patient contact from PSSRU. ⁵⁰

Specialist visit, neurology out-patient	2.40	£236.00	NHS reference costs, HRG code WF01A - Non-Admitted Face-to-Face Attendance, Follow-up. ⁴⁸
Physiotherapist	1.62	£41.00	PSSRU, Unit Costs of Health and Social Care 2023 Document. Section 6.1 (Table 6.1.1.) Cost per hour community services (one to one). Physiotherapy. ⁵⁰
Occupational therapist	2.28	£68.00	PSSRU, Unit Costs of Health and Social Care 2023 Document. Section 6.1 (Table 6.1.1.) Cost per hour community services (one to one). Occupational therapy. ⁵⁰
Abbreviations: GP, general practitioner; HRG, healthcare resource group; PSSRU, Personal Social Services Research Unit. * Estimated from the monthly visits data presented in Table 75 of the CS and sourced from Mahdi-Rogers <i>et al.</i> 2014. ⁵⁷			

4.2.12.3.1 EAG critique

The EAG finds the company's assumption of a one-hour GP appointment, at a cost of £268, to be insufficiently justified. While the company cited the British Medical Association's (BMA's) opinion that the standard 10-minute appointment (used in PSSRU costings) is too short for complex patients, they failed to note the BMA recommended a 15-minute consultation, not an hour.⁵⁸ Ultimately, the EAG considers the company's assumption weakly relies on a recommendation, not actual evidence of current practice. As such, the EAG prefers to assume the cost of a GP appointment to be based on the cost of surgery consultation lasting 10 minutes (£45) from PSSRU.⁵⁰ The company provided a scenario using the cost for a 10-minute GP appointment from PSSRU and this had minimal impact on incremental costs, but the EAG considers it is more appropriate to use this cost and has included it in its preferred assumptions (Section 5.2.3).

A secondary concern, which is not resolvable, is that no distinction for health state resource use by disease severity has been made. However, the EAG acknowledges there is a lack of data for resource use by CIDP severity. As healthcare resource use is not treatment-specific, this limitation affects both arms equally, resulting in costs being potentially underestimated for patients with more severe disease and overestimated for patients with less severe disease. The magnitude and direction of the impact of this assumption on overall results is therefore unknown.

The EAG's concerns around the approach to modelling disease monitoring costs are included in **Secondary Issue 4**, discussed in Section 1.4.

4.2.12.4 Mobility aids costs

The company assumed that for patients with moderate, severe and very severe impairments, manual or motorised wheelchairs would be required. Data on the proportions of patients in each health state requiring manual or motorised wheelchairs was informed by the company's analysis of data from the Adelphi study, a linked physician and patient cross-sectional survey conducted in France, Germany, Italy, Spain, the UK, Japan, and the USA between September 2022 and April 2023, in which data related to treatment and experiences of patients with CIDP were collected. The company's analysis restricted the patients included to patients from Germany, France, Italy, Spain and the UK. An analysis was also performed in which only patients from the UK were included. Further details are given in a report included in the references for the CS.⁵⁹

The model inputs related to the proportion of patients requiring mobility aids are presented in Table 66.⁵⁹

The costs of mobility aids were sourced from NHS 2023/24 National Cost Collection data dashboard and presented in Table 67.⁴⁸

Table 66. Proportion of patients requiring mobility aids by severity (reproduced from Table 77 of the CS)

Health state	Proportion requiring manual wheelchair	Proportion requiring motorised wheelchair
Moderate impairment	■	■
Severe impairment	■	■
Very severe impairment	■	■

Table 67. Unit costs of mobility aids included in the model

Type of mobility aid	Unit cost	Source & description ⁴⁸
Manual wheelchair	£689	HRG code WCE03 (Wheelchair equipment cost, High need, Manual). ⁴⁹
Motorised wheelchair	£1,548	HRG code WCE04 (Wheelchair equipment cost, High need, Powered). ⁴⁹

Abbreviations: HRG, healthcare resource group

4.2.12.4.1 EAG critique

The EAG's clinical experts advised that the proportion of patients with very severe impairment requiring a motorised wheelchair would be higher than the proportion included in the model. The

EAG investigated the company's analysis of the Adelphi dataset, and found that the company used data corresponding to INCAT scores of 7-10 for the severe and very severe health states. However, data were available for INCAT 7-8 (severe) and INCAT 9-10 (very severe) (Table 68), which show proportions requiring mobility aid are higher for the very severe health state; this aligns with the EAG's clinical expert view. During the clarification stage the EAG requested the data in Table 68 to be explored in a scenario analysis, which the company supplied. The scenario had minimal impact on the cost-effectiveness results, but the EAG considers that the data from the company's analysis of the Adelphi dataset by INCAT score is more aligned with the definitions of the health states used in the model and has included it in its preferred assumptions (Section 5.2.3).

Table 68. Mobility aid data by severity from Table 6 of the company Adelphi study⁵⁹

Health state	Proportion requiring a manual wheelchair	Proportion requiring a motorised wheelchair
Moderate impairment (INCAT 4-6)	■	■
Severe impairment (INCAT 7-8)	■	■
Very severe impairment (INCAT 9-10)	■	■
Abbreviations: INCAT, Inflammatory Neuropathy Cause and Treatment		

The EAG's concerns around the approach to modelling disease mobility aid costs are included in **Secondary Issue 4**, discussed in Section 1.4.

4.2.12.5 Hospitalisation costs

The company has assumed that patients in the active disease health states are at risk of hospitalisation events, including intensive care unit (ICU) admissions. The risk of hospitalisation events was informed by data derived in the company analysis of the Adelphi dataset, which estimated the number and duration of hospitalisations, stratified by disease severity, in the 12 months prior to the survey, conducted between September 2022 and April 2023.⁵⁹ The annual probabilities derived from the Adelphi study were then scaled using the exponential distribution formula to six-month probabilities, presented in Table 51 (non-ICU admissions) and Table 52 (ICU admissions) of the CS. The duration of each hospitalisation event is presented in Table 79 of the CS and the unit cost associated with ICU and non-ICU hospitalisations is presented in Table 80 of the CS.

4.2.12.5.1 EAG critique

The EAG found that the unit cost of a standard bed day (£792) used in the model, based on NHS reference costs, was aligned with the costs presented in PSSRU for non-elective inpatient stays

(short stays). However, the cost per day for an ICU bed that the company estimated from NHS reference costs (£2,276), based on multiple HRG codes, did not reflect the PSSRU cost for critical care (£1,907).^{48, 50} The EAG considers that PSSRU might be a more consistent source for hospitalisation costs as it is based on the NHS reference costs and would result in the costs in the model being aligned. During the clarification stage the EAG requested, and the company supplied, a scenario in which the cost per day of ICU was based on the unit cost of critical care from PSSRU.⁵⁰ The scenario has minimal impact on the cost-effectiveness results, but the EAG considers that the PSSRU ICU cost is more appropriate to include in the model as it would be consistent with the cost per day of a standard bed used in the model; therefore, this approach is included in the EAG preferred assumptions (Section 5.2.3).

The EAG's concerns around the approach to modelling hospitalisation costs are included in **Secondary Issue 4**, discussed in Section 1.4.

4.2.12.6 Adverse event costs

Adverse event costs and costs associated with complications related to IV access were calculated by multiplying the per-cycle probability (see Section 4.2.10) by the corresponding unit cost (Table 69 and Table 70 below). The company sourced costs from the NHS Payment Scheme 2025/26 using either general HRG codes or codes associated with combined day case/ordinary elective spell costs.⁴⁹ For AEs and IV complications that were associated with multiple HRG codes, the company used an average of the cost codes for the model. In their clarification response, the company explained that AE costs for the model were extracted before June 2025, after which the NHS payment scheme prices were updated.

Table 69. Adverse event unit costs included in the model

Adverse event	Cost	HRG Code ⁴⁹	Description
Arthralgia and pain in the extremities	£1,292	Average of WH08A and WH08B	Unspecified pain
Asthenia	£2,223	WH12A	Signs or Symptoms, Involving Appearance or Behaviour, with CC Score 2+. Combined day case/ordinary elective spell
Back Pain	£1,213	Average of HC32G, HC32H, HC32J and HC32K	Low Back Pain, Combined day case

Adverse event	Cost	HRG Code ⁴⁹	Description
Dizziness	£2,223	WH12A	Signs or Symptoms, Involving Appearance or Behaviour, with CC Score 2+. Combined day case/ordinary elective spell
Fatigue	£2,223	WH12A	Signs or Symptoms, Involving Appearance or Behaviour, with CC Score 2+. Combined day case/ordinary elective spell
Headache	£940	AA31D	Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 7-10; Combined day case/ordinary elective spell
Haemolysis	£553	Average of SA03G and SA03H	Haemolytic Anaemia
Hypertension	£486	EB04Z	Hypertension
Influenza	£1,820	Average of DZ19H, DZ19J, DZ19K, DZ19L, DZ19M and DZ19N	Other respiratory disorders
Infusion/injection site reaction	£4,339	Average of WH07A, WH07B, WH07C, WH07D, WH07E, WH07F and WH07G	Infection or other complication of procedures
Nasopharyngitis	£1,820	Average of DZ19H, DZ19J, DZ19K, DZ19L, DZ19M and DZ19N	Other respiratory disorders
Nausea	£4,212	Average of FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10G, FD10H, FD10J, FD10K, FD10L and FD10M	Non-Malignant Gastrointestinal Tract Disorders
Pyrexia	£3,555	Average of WJ07A, WJ07B, WJ07C and WJ07D	Fever of unknown origin
Upper respiratory tract infection	£1,820	Average of DZ19H, DZ19J, DZ19K, DZ19L, DZ19M and DZ19N	Other respiratory disorders
Infections	£4,339	Average of WH07A-G	Infections or other complications of procedures
Sleep disorders	£579	Average of AA43A-B	Sleep disorders, excluding sleep apnoea
Psychiatric disorders	£665	Average of 10MHPS, 11MHPS, 12MHPS, 35MHPS, 36MHPS, 37MHPS, 38MHPS and 40MHPS	Average of multiple services

Adverse event	Cost	HRG Code ⁴⁹	Description
Abdominal pain	£1,677	Average of FD05A and FD05B	Abdominal pain
Endocrine disorders	£547	Average of KA80A-C	Other endocrine disorders
Anaemia	£1,367	SA01 SA03	Haemolytic anaemia - elective
Gastrointestinal disturbances	£1,677	Average of FD05A and FD05B	Abdominal pain
Renal dysfunction	£1,626	Average of LA09M, LA09N, LA09P and LA09Q	General renal disorder without intervention - elective
Peripheral oedema	£721	Average of WH10A and WH10B	Other unspecified oedema

Abbreviations: CC, complication/comorbidity; CS, company submission HRG, healthcare resource group.

Table 70. Unit costs of complications related to IV access included in the model (reproduced from Table 82 of the CS)

Complication	Cost	HRG Code	Description
Permanent PICC, surgically implanted CVC, infusion port	£1,673	Average of YR40, YR41 and YR42	Insertion of central venous catheter
Catheter-related infections	£5,731	Average of WH07A-G	Infections or other complications of procedures
Catheter-related blood infections	£7,682	Average of WJ06A-J	Sepsis
Thrombophlebitis	£4,389	Average of YQ50A-F	Peripheral vascular disorder
Infiltration and extravasation	£4,389	Average of YQ50A-F	Peripheral vascular disorder
Thromboembolic events	£3,202	Average of YQ51A-E	Deep Vein Thrombosis

Abbreviations: CS, company submission; CVC, central venous catheter; HRG, Healthcare resource group; IV, intravenous; PICC, peripherally inserted central catheter.

4.2.12.6.1 EAG critique

The EAG's clinical experts considered that most of the AEs captured in the model would be mild. They advised that back pain and peripheral oedema would be treated in an outpatient setting and all other AEs would be managed in primary care (with one GP visit). The company supplied a scenario which used a cost of £853 for an outpatient appointment for back pain based on an average of HRG codes HC32G-K, a cost of £415 for peripheral oedema based on an average of HRG codes WH10A-B from NHS reference costs and £45 for a GP appointment based on PSSRU.^{49, 50} The scenario had a substantial impact on incremental costs, [REDACTED]

[REDACTED]. The EAG considers that the scenario based on the EAG's clinical expert view on costs to treat mild AEs is more appropriate than the company's base case assumptions. However, as discussed in Section 4.2.10.3, to reduce the uncertainty in the model, the EAG prefers to exclude the impact of AEs and complications related to IV administration for its preferred assumptions, presented in Section 5.2.3.

4.2.13 Caregiver burden

4.2.13.1 Impact on informal caregivers' HRQoL

The company included disutilities in the economic model to represent the impact on caregivers' HRQoL. Since no appropriate disutilities were identified for use in the economic analysis in the company's HRQoL SLR (see Section 4.1), the company parametrised caregiver disutility using disutilities measured for caregivers of people with multiple sclerosis (MS). The disutilities were sourced from NICE Highly Specialised Technology (HST) 9 (inotersen for treating hereditary transthyretin amyloidosis).⁶⁰ The approach used was ultimately informed by Gani *et al.* 2008, a cost-effectiveness analysis of natalizumab as a treatment for people with highly active relapsing-remitting MS in the UK, and was also used in TA533 (ocrelizumab for treating relapsing-remitting multiple sclerosis).^{61, 62} The disutilities reported in Gani *et al.* 2008 were reported based on Expanded Disability Status Scale (EDSS) categories. The aINCAT categories used in the economic model were mapped to these EDSS categories based on comparable levels of impairment, as follows:

- aINCAT 0-1 (very limited impairment) was mapped to EDSS 0-3.0;
- aINCAT 2-6 (mild impairment or moderate impairment) was mapped to EDSS 3.5-7.0;
- aINCAT 7-10 (severe impairment or very severe impairment) was mapped to EDSS 7.5-9.5.

This approach was discussed with five clinical experts during a qualitative workshop, and subsequently with one additional clinical expert.²¹ The company's clinical experts stated that motor disability resulting from CIDP is comparable to the symptoms of MS, and that requirements of caregiver involvement were likely to be similar, although two clinicians noted that MS patients may experience symptoms such as bladder and bowel dysfunction, which are not observed in CIDP, and which may require differing caregiver involvement. The EAG's clinical experts broadly agreed with this characterisation.

The company also stated that the mapping from aINCAT scores to EDSS was validated with clinical experts, but the EAG can only find evidence that clinicians agreed that an EDSS of 7 or higher was

functionally comparable to an aINCAT score of 9-10, based on the company's response to clarification question B62.

The disutility applied was multiplied by the expected number of caregivers. Patients with very limited, mild or moderate impairment were assumed to have one caregiver, while patients with severe and very severe impairment were assumed to have two caregivers. This approach was also aligned with the committee's preferred approach in HST9.⁶⁰

The disutilities were applied in the model by adding directly to the patient's expected utility value, for the entire time horizon. The input values used are given in Table 71.

Table 71. Caregiver disutilities by health state

Health state	Disutility (adjusted for expected number of caregivers)
Very limited impairment	0.000
Mild impairment	-0.0025
Moderate impairment	-0.0275
Severe impairment	-0.2500
Very severe impairment	-0.2500

4.2.13.1.1 EAG critique

The EAG has several concerns around the approach to modelling informal caregiver burden.

Firstly, the EAG considers that the caregiver disutilities may be inappropriate. The EAG is concerned that the mapping from aINCAT to EDSS scores may not be appropriate, as there was limited validation of the approach with clinicians, and no validation with caregivers. The EAG also considers that the mapping of an aINCAT score of 7-8 to the EDSS category of 7.5-9.5 potentially overrepresents the functional impairment of patients, as an EDSS of 7.5-9.5 corresponds to patients who are restricted to a wheelchair or bed, whereas this is not definitively the case for an aINCAT score of 7-8 (in the ADHERE trial, patients with an aINCAT score of 7-8 had scores of 3-5 in the leg domain, whereas only a score of 5 in the leg domain corresponds to being fully restricted to a wheelchair).²³

Furthermore, the caregiver disutilities used in Gani *et al.* 2008 were not elicited from caregivers, but were instead largely based on assumption.⁶¹ In particular, disutilities were assigned by assuming that

the maximum caregiver disutility, which would be associated with the maximum disease severity health state included in the economic model, would be equal to -0.14, a value accepted by NICE as a caregiver disutility in a NICE appraisal of treatments for Alzheimer's disease.⁴⁷ Caregiver disutilities for other health states were calculated by scaling the maximum caregiver disutility by the expected time spent on caregiving for each health state, based on a survey of caregivers. In the context of the original study, this appears to have been a pragmatic approach, which was used in the absence of appropriate model inputs from existing literature.

Overall, the EAG considers that these disutilities are not appropriate for use in this economic analysis. As an alternative, the EAG notes that the company collected EQ-5D-5L data for 21 UK-based caregivers of people with CIDP in a cross-sectional observational survey of burden on informal caregivers.⁶³ While the sample size is small, and data are not available disaggregated by patients' disease severity, the EAG considers that this is still more robust than the company's original approach. The overall reported EQ-5D-5L value for carers was 0.798.

The majority of caregivers were in the 46-55 years age bracket. Therefore, the reported EQ-5D-5L value was compared against general population norms reported in the Health Survey for England 2017-2018, taking the average of the 45-49- and 50-54-year age brackets, and weighting by sex (of survey respondents who disclosed their sex, 14 identified as women and 6 identified as men). This gave a general population utility of 0.8101.⁶⁴ An overall caregiver utility decrement was derived by subtracting the caregiver utility from the general population utility, giving a decrement of -0.0121. In the EAG's preferred approach, this decrement is applied to all caregivers; while this utility decrement is likely to be greater in magnitude than the true decrement for caregivers of patients with milder disease, and smaller in magnitude than the true decrement for caregivers of patients with more severe disease, but the EAG considers that overall this simplification is reasonable, given the lack of available data. Given that this assumption has a considerable impact on the ICER, and the general uncertainty around caregiver disutilities, the EAG also presents a scenario in which the company's utility decrements are used (see Table 71).

The EAG also has concerns about the number of caregivers applied for each health state. In particular, the EAG considers that insufficient evidence was presented for the number of caregivers included in the caregiver disutility calculations. During the clarification stage, the company provided a scenario analysis in which it was assumed that patients would require at most one informal caregiver, adjusted for the proportion of patients requiring a caregiver for each health state based

on the UK Adelphi dataset; these proportions are presented in Table 72.⁵⁹ This scenario analysis slightly reduced the incremental NMB for efgartigimod. Overall, the EAG considers that this approach is more likely to be reflective of caregivers' experience in the UK.

The EAG's preferred utility decrements for caregivers, weighted by the proportion of patients requiring a caregiver, are given in Table 72.

Table 72. Proportion of patients requiring caregivers by aINCAT score, from the UK Adelphi dataset

aINCAT category	Proportion of patients requiring a caregiver	EAG-preferred disutilities
0-1 (very limited impairment)	2.8%	-0.000339
2-3 (mild impairment)	14.8%	-0.001791
4-6 (moderate impairment)	51.8%	-0.006268
7-8 (severe impairment)	70.0%	-0.00847
9-10 (very severe impairment)	100%	-0.0121

Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; EAG, External Assessment Group.

The approach to modelling informal caregiver burden forms part of **Key Issue 12**, discussed in Section 1.3.

4.2.13.2 Costs for professional care

In addition to disutilities for informal carers, the company also included the cost of professional care in the model. The company assumed professional care costs would be incurred for patients with moderate, severe and very severe impairment, based on information from their analysis of the Adelphi dataset. In their clarification response, the company explained that the Adelphi data are based on patients from UK, France, Germany, Italy, Spain, USA and Japan who previously received Ig (n=804). The company did not explain where the assumption of 21.3 hours and 45 hours of professional care per week was derived from, but stated that this falls within the range of support that may be expected for a patient with significant motor disability and dependence due to CIDP.

Table 73 presents the cost of professional care included in the model by health state. The unit cost of professional care in the model is £27 per hour, sourced from PSSRU.⁵⁰

Table 73. Professional care costs included in the model (reproduced from Table 77 of the CS)

Health state	Proportion requiring professional care	Number of hours of professional care	Total cost per model cycle
Moderate impairment	9.0%	21.3	£1,449.20

Severe impairment	80.0%	45.0	£27,215.00
Very severe impairment	80.0%	45.0	£27,215.00
Abbreviations: CS, company submission.			

4.2.13.2.1 EAG critique

The EAG consulted with its clinical experts, who advised that very few CIDP patients require professional care, and this is reflected in the data presented by the company. In the model, it is assumed that all patients receive informal care and patients in the moderate to very severe health states are assumed to receive both formal and informal care. The EAG also notes that the company performed a UK-based patient survey, which provides more detail on the level of care patients receive in the UK; this was a cross-sectional observational study of patients with CIDP conducted between April and May 2025, in which patients were recruited via Inflammatory Neuropathies UK, and asked to report on factors including treatments, quality of life, and burden of illness. Further details are given in a report included in the references for the CS.²

In the company's patient survey, only 6.3% (n=4/63) of patients required both types of care.² The EAG also notes that in the company's patient survey, 12.7% (n=8/63) received only formal care.² Additionally, the EAG found that in the UK Adelphi study [REDACTED] had a professional caregiver and the company's survey of caregivers supporting patients living with CIDP suggests that 0% of patients would receive formal care from a professional healthcare provider.^{59, 63} As such, the EAG considers that the data from the company's surveys suggests low usage of formal care.

The EAG's clinical experts explained that the aim of treatment for CIDP is to reduce disease severity and as such reduce the need for mobility aids and maintain the patient independence. The EAG's clinical experts considered that if professional care was required, it would likely only be for patients with very severe disease who are confined to a wheelchair, and that approximately five hours of care per day (35 hours per week) would be required. However, the EAG's clinical experts advised that state-funded care is usually means-tested, as it would be provided by social services, and so not all CIDP patients are eligible.

The company highlighted the NHS Continuing Healthcare initiative which provides fully funded care for patients with long-term complex health needs.⁶⁵ Eligibility for a "continuing care package" is assessed by a multidisciplinary team that considers 12 care domains and the extent of need in each

domain.⁶⁵ Needs are given a weighting based on a five level scale ranging from “no needs” to “priority”. It is reported that if a patient has at least 1 priority need or severe needs in 2 domains, they would be eligible for NHS continuing healthcare.

The EAG notes that eligibility for NHS Continuing Healthcare is not based on a particular diagnosis or condition and that if a person is not eligible, they can be referred to their local council for support, which would likely be means-tested. The company did not provide any data on the number of patients with CIDP who have NHS-funded care and the EAG was unable to identify any published literature with the relevant data.

Based on the clinical expert feedback and the NHS eligibility criteria for a “continuing care package”, the EAG considers the following:

- Applying professional care costs to all patients in the moderate and severe health states is not appropriate.
- Even though wheelchair usage is assumed for patients in the moderate, severe and very severe health states, there are no available data on what percentage of these patients are confined to a wheelchair, which could be used as an indication for requiring professional care.
- The number of hours of professional care assumed for each health state is likely overestimated.
- No data are available on the number of CIDP patients who are eligible for or receiving an NHS continuing healthcare package.

The EAG recognises that that some severe and very severe CIDP patients may fulfil the criteria of at least one priority need or severe needs in two domains to be eligible for an NHS Continuing Healthcare package and that these are likely to be patients in the very severe health state. However, even if a patient is eligible for NHS-funded care, the care and support package offered would differ between patients and may not always result in carer costs, but could be home adaptations or moving to a residential care home. The EAG highlights, that while NHS Continuing Healthcare is positive for patients with complex needs, the NHS-funded independent advice service, Beacon, states that, “*the Continuing Healthcare system is complex, dogged by lack of a clarity and understanding, and wildly inconsistent across regions. Patients and professionals alike find it extremely difficult to navigate*”.⁶⁶ Additionally, the EAG’s clinical experts considered that accessing

NHS-funded care is difficult. Therefore, NHS funded care is unlikely to be universal, as assumed in the model, for patients with moderate to very severe CIDP.

Finally, the EAG notes that the company has not considered the balance between informal care and professional care that patients are likely to receive in practice. Given that the HRQoL impacts of informal care are included for all patients, the EAG considers that additionally including full-time professional care costs for some patients leads to a double-counting of the caregiver burden.

The EAG concludes that inclusion of professional caregiver costs in the model likely overestimates the real-world costs incurred by the NHS for patients with moderate to very severe CIDP. Therefore, for the EAG base case, professional caregiver costs are excluded from the model. The company provided a scenario excluding professional caregiver costs in the model, but the EAG found the scenario was flawed as it also excluded healthcare resource use, outlined in Section 4.2.12.3. Instead, the EAG corrected the scenario included the approach in the EAG base case, presented in Section 5.2.3.

The EAG also provides a scenario around its base case where professional care costs are only applied to patients in the very severe health state, assuming 35 hours of care based on the clinical expert view. The EAG considers the scenario is useful for committee to consider the impact of this parameter on the ICER.

The approach to modelling professional care costs forms part of **Key Issue 12**, discussed in Section 1.3.

5 Cost effectiveness results

Section 5.1 summarises the company's cost-effectiveness results, section 5.2 presents the EAG's additional work and preferred assumptions, and section 5.3 explores decision modifiers, including the company's and EAG's preferred QALY weighting for severity.

5.1 Company's cost effectiveness results

Table 74 presents the pairwise cost-effectiveness results of the company's updated (i.e., post-clarification) base case deterministic and probabilistic analyses for efgartigimod versus established clinical management, which includes treatment with immunoglobulins (IV or SC), PLEX, corticosteroids and immunosuppressants. The probabilistic analysis was performed with 1,000 simulations, which showed good convergence.

In the base-case probabilistic analysis, efgartigimod was considered [REDACTED] compared to established clinical management based on [REDACTED] and an incremental quality-adjusted life-year (QALY) gain of 3.96. The net health benefit (NHB) based on the probabilistic results was [REDACTED] and [REDACTED] at the £20,000 and £30,000 threshold, respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

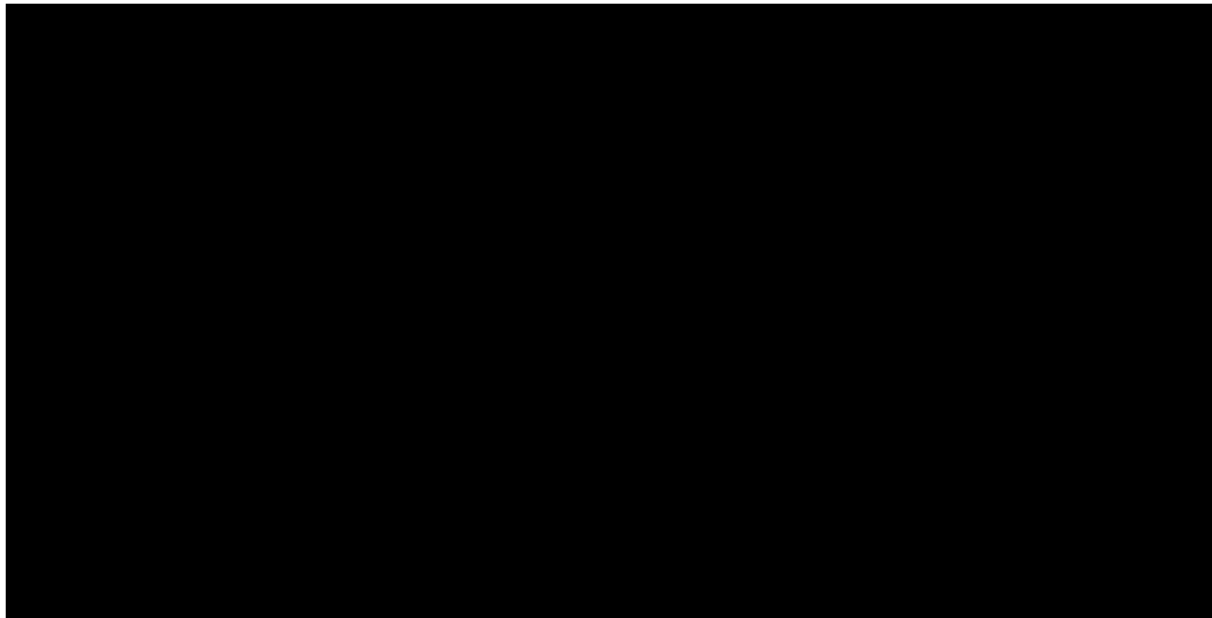
Table 74. Company's base case results

Interventions	Total Costs	Total LY	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Established clinical management*	[REDACTED]	17.17	1.65	-	-	-	-
Efgartigimod	[REDACTED]	17.17	5.91	[REDACTED]	-	4.26	[REDACTED]
Probabilistic results							
Established clinical management*	[REDACTED]	17.17	0.35	-	-	-	-
Efgartigimod	[REDACTED]	17.17	4.31	[REDACTED]	-	3.96	[REDACTED]
Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intravenous; LY, life year; PLEX, plasma exchange; QALY, quality-adjusted life-year; SC, subcutaneous.							
* Established clinical management includes treatment with immunoglobulins (IV or SC), PLEX, corticosteroids and immunosuppressants.							

The company considers a disease severity modifier of 1.0 appropriate.

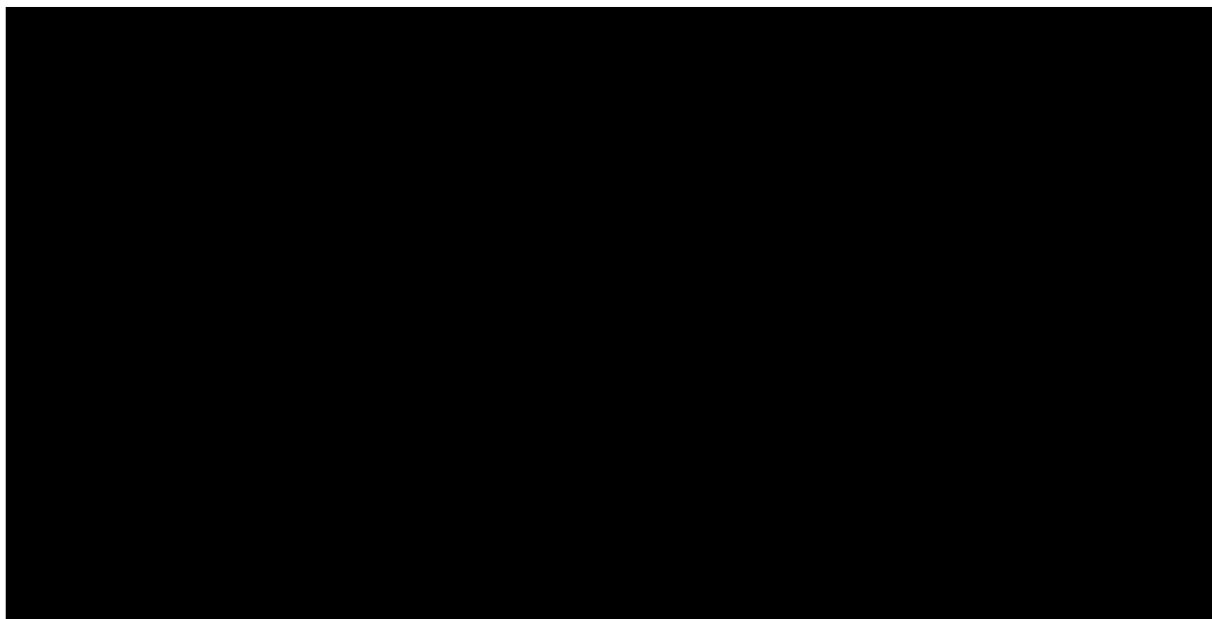
Figure 15 shows PSA scatterplot of efgartigimod versus established clinical management, with the corresponding cost-effectiveness acceptability curve (CEAC) shown in Figure 16.

Figure 15. Scatterplot of probabilistic analysis runs on a cost-effectiveness plane of efgartigimod versus established clinical management (reproduced from Figure 1 of Appendix 2 from the company's clarification response)



Abbreviations: CE, cost-effectiveness; QALY, quality-adjusted life year.

Figure 16. Cost-effectiveness acceptability curve (reproduced from Figure 2 of Appendix 2 from the company's clarification response)



Abbreviations: QALY, quality-adjusted life year.

The EAG notes that there is a large discrepancy between the company's deterministic and probabilistic results. In the original clarification response, the company stated that this was due to the asymmetry of the distribution of the proportion of the cohort receiving each Ig dose, the time between Ig treatment cycles, and the aINCAT change from baseline for efgartigimod vs Ig. However, the EAG identified several issues in the company's implementation of the probabilistic analysis which, once corrected, gave probabilistic and deterministic results which are much more closely aligned. Therefore, the EAG considers that the discrepancy between deterministic and probabilistic results in the company's analysis were likely caused by errors in the implementation of the probabilistic analysis, and that the company's probabilistic results should be disregarded. As such, the EAG reports only deterministic results for the company's analysis in the subsequent sections of this report.

The company also provided subgroup analyses for the following populations in an additional clarification response, dated 4 December 2025:

- Patients on Ig maintenance;
- Ig-dependent patients;
- Patients dependent on an ultra-high dose of Ig;
- Ig-intolerant/refractory patients (provided in the first clarification response).

Deterministic results are presented in Table 75. For patients on Ig maintenance, Ig-dependent patients, and patients dependent on an ultra-high dose of Ig, [REDACTED]. The greatest cost savings and QALY gains were realised for patients dependent on an ultra-high dose of Ig. On the other hand, in the Ig-intolerant/refractory population, incremental costs were very high, leading to a very high ICER.

Table 75. Company's deterministic subgroup analysis results vs established clinical management

Subgroup	Incremental costs	Incremental QALYs	ICER (£/QALY)
Patients on Ig maintenance	[REDACTED]	4.26	[REDACTED]
Ig-dependent patients	[REDACTED]	5.21	[REDACTED]
Patients dependent on an ultra-high dose of Ig	[REDACTED]	5.47	[REDACTED]
Ig-intolerant/refractory patients	[REDACTED]	4.03	[REDACTED]
Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; QALY, quality-adjusted life-year.			

As noted in Section 4.2.2, the EAG's preferred approach is to present results for the Ig maintenance and Ig-intolerant/refractory populations separately, since the comparators are different. Therefore, the EAG considers that the subgroup analyses for these populations should in fact be considered as key results.

5.1.1 Company's sensitivity analyses

5.1.1.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagram presented

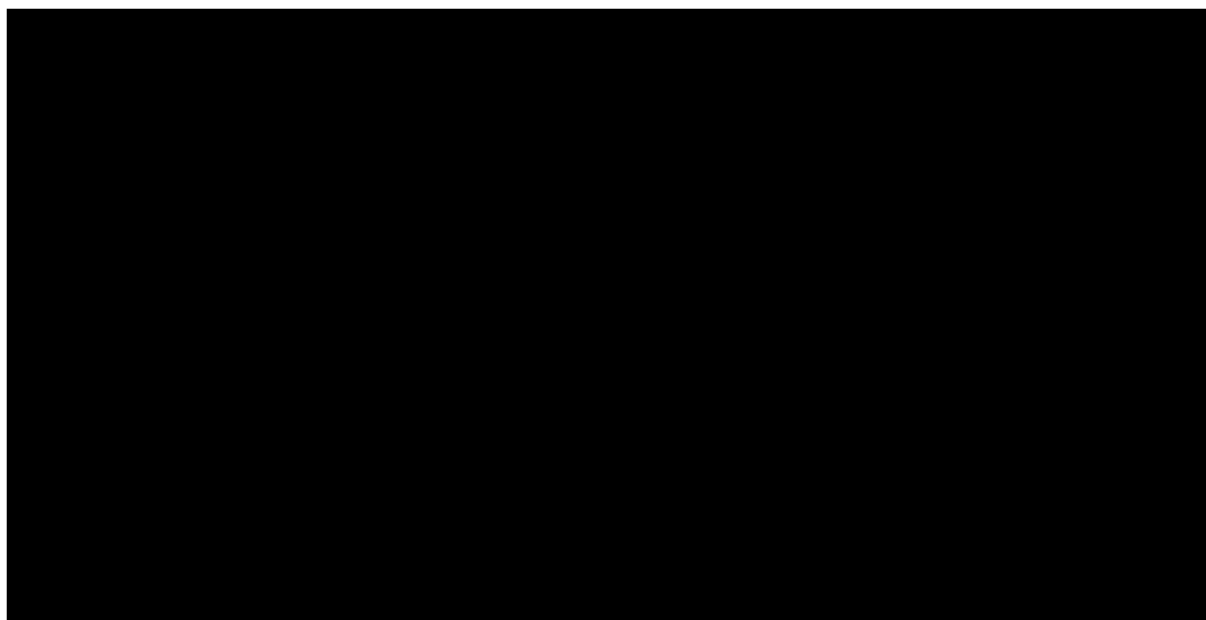
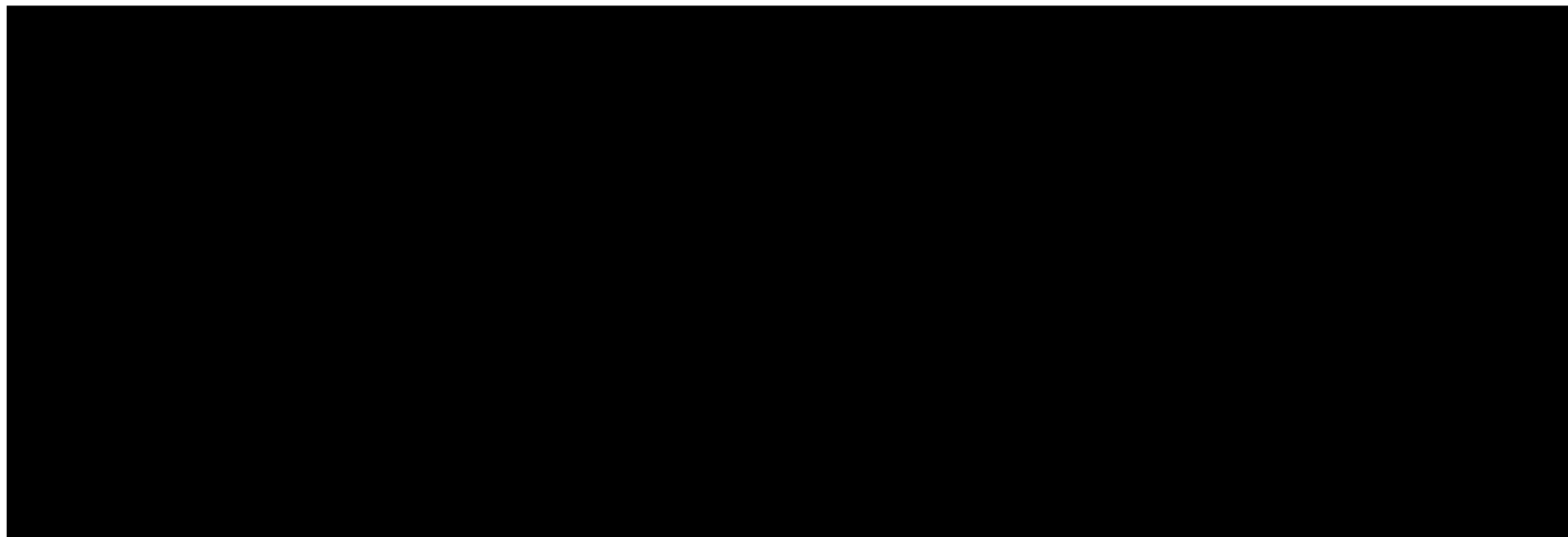


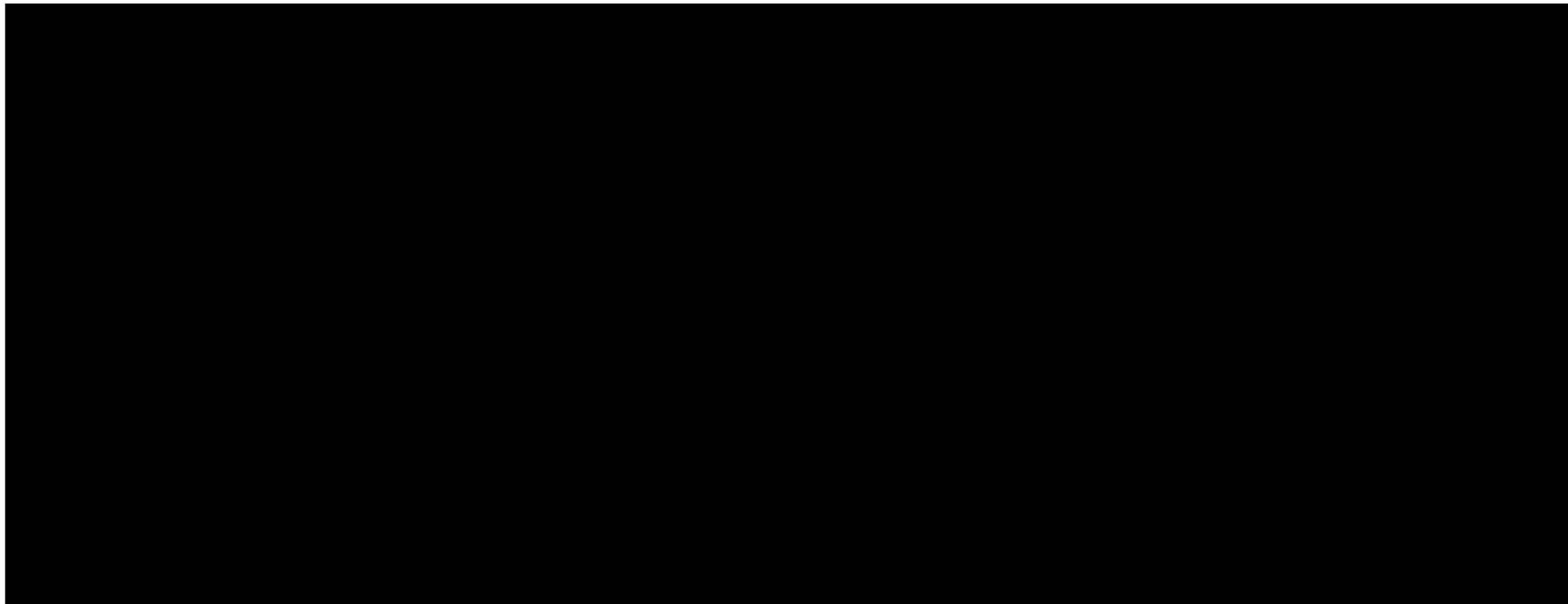
Figure 17. Due to the dominant ICER in the company's base-case analysis, it can be more difficult to intuitively interpret changes to the ICER. Therefore, the company has presented the tornado diagram showing the impact on the NMB (using a £30,000 threshold).

As shown in the figures below, varying the time between IVIg cycles for the different doses had the largest impact on the NMB.

Figure 17. Tornado plot (reproduced from Figure 3 of Appendix 2 from the company's clarification response)



Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; NMB, net monetary benefit; WTP, willingness-to-pay.



5.1.1.2 *Scenario analysis*

The company undertook an extensive series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters that are presented in their clarification response. In addition, the company conducted several additional scenario analyses requested by the EAG. Most of scenarios resulted in [REDACTED]. However, most scenarios had a substantial impact on the NMB. Several scenarios resulted in a change of direction in the ICER. The EAG considers that the company's scenario analysis highlights the inherent uncertainty in the model. A full list of all scenarios run by the company is given in Appendix 7.7. A summary of the scenarios which the EAG considers to be most pertinent are presented in Table 76.

Table 76. Key company scenario analyses: deterministic results

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30,000/QALY)
0	Company updated base case	■	4.26	■	■
General scenarios					
1	Time horizon = 2 years	■	0.36	■	■
2	A three-month model cycle is applied for the first two years, followed by a six-month cycle length thereafter	■	4.35	■	■
Comparators and treatment pathway					
3a	Distribution of treatments in the alternative treatment basket is obtained from the company's chart review study	■	4.24	■	■
3b	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	■	4.41	■	■
3c	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort is redistributed equally among other treatments.	■	4.35	■	■
3d	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	■	4.49	■	■
3e	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort redistributed equally among other treatments.	■	4.42	■	■
4a	10% of Ig maintenance patients on PLEX return to Ig	■	4.25	■	■
4b	30% of Ig maintenance patients on PLEX return to Ig	■	4.23	■	■
4c	60% of Ig maintenance patients on PLEX return to Ig	■	4.20	■	■
4d	90% of Ig maintenance patients on PLEX return to Ig	■	4.16	■	■

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30,000/QALY)
5a	Post-efgartigimod discontinuation, the same distribution as post-Ig discontinuation is applied	■■■■	4.26	■■■■	■■■■
5b	Post-efgartigimod discontinuation, the cohort is distributed based on the upper bound from the SEE	■■■■	4.24	■■■■	■■■■
5c	A majority of patients are assumed to go back into the same treatment following efgartigimod treatment discontinuation as before starting efgartigimod (i.e. 60% Ig and 40% basket of treatment)	■■■■	4.23	■■■■	■■■■
5d	Patients are assumed to go back onto the same treatment following efgartigimod treatment discontinuation as before starting efgartigimod (i.e. 95% Ig and 5% basket of treatment)	■■■■	4.18	■■■■	■■■■
Patient characteristics					
6	Alternative source for Ig dosage and frequency of treatment: UK chart review data (final data cut)	■■■■	4.20	■■■■	■■■■
Treatment effectiveness, discontinuation and other events					
7	Patients in the comparator arm remain in same aINCAT category as at baseline indefinitely	■■■■	2.14	■■■■	■■■■
8	Patients have a 100% chance of remaining in the severe and very severe health states	■■■■	3.98	■■■■	■■■■
9	Half of patients deteriorate to worse disease severity upon relapse	■■■■	4.59	■■■■	■■■■
10	Patients receiving Ig or a treatment in the comparator basket do not permanently discontinue treatment at any time	■■■■	4.28	■■■■	■■■■
AEs					
11	AEs for efgartigimod, Ig, PLEX, corticosteroids and immunosuppressants are excluded from the model.	■■■■	4.16	■■■■	■■■■
12	Complications related to IV administration are excluded	■■■■	4.25	■■■■	■■■■

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30,000/QALY)
Utilities					
13	HSUV value for very severe health state = 0	■■■■	4.17	■■■■	■■■■
14	Duration of infusion is based on data in CS	■■■■	4.12	■■■■	■■■■
15	Disutility of administration is based on Jørgensen <i>et al.</i> 2017 only	■■■■	3.84	■■■■	■■■■
16	Disutility of administration is based on Jørgensen <i>et al.</i> 2017, and includes only the coefficient for route of administration	■■■■	3.53	■■■■	■■■■
17	Disutility of administration combining the coefficient for route from Jørgensen <i>et al.</i> 2017 and infusion duration from Matza <i>et al.</i> 2013	■■■■	3.95	■■■■	■■■■
18	Disutility of IV administration is excluded	■■■■	3.35	■■■■	■■■■
Drug acquisition/administration costs					
19	IVIg /SCIg split is informed by the Immunoglobulin Database Annual Report	■■■■	4.06	■■■■	■■■■
20	All patients receiving efgartigimod are assumed to be on the weekly dosing regimen	■■■■	4.26	■■■■	■■■■
21	Funded transport is included for efgartigimod	■■■■	4.26	■■■■	■■■■
22	All funded transport is excluded	■■■■	4.26	■■■■	■■■■
23	Administration cost of SCIg is the same as efgartigimod	■■■■	4.26	■■■■	■■■■
HCRU costs					
24	Standard GP costs are applied for a 10-minute appointment (£45)	■■■■	4.26	■■■■	■■■■
25	Proportion requiring a mobility aid based on disaggregated data from the Adelphi study	■■■■	4.26	■■■■	■■■■
26	ICU costs are aligned with the PSSRU cost for critical care	■■■■	4.26	■■■■	■■■■
Caregiver burden					
27	Caregiver disutilities are excluded	■■■■	3.47	■■■■	■■■■
28	Cost of professional care is excluded	■■■■	4.26	■■■■	■■■■

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30,000/QALY)
29	Patients have at most one caregiver for any health state, with the proportion requiring a caregiver informed by UK Adelphi dataset	■	3.77	■	■

Abbreviations: AE, Adverse event; aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, Chronic inflammatory demyelinating polyneuropathy; CQ, clarification question; CS, Company Submission; GP, General practitioner; HCRU, healthcare resource use; HRQoL, health-related quality of life; ICER, Incremental cost-effectiveness ratio; ICU, Intensive care unit; Ig, Immunoglobulin; IVIg, Intravenous immunoglobulin; ITC, Indirect treatment comparison; IV, Intravenous; NHS, National Health Service; NMB, Net monetary benefit; PLEX, Plasma exchange; QALY, Quality-adjusted life year; SCIg, Subcutaneous immunoglobulin; SEE, Structured Expert Elicitation; WTP: Willingness-to-pay.

5.2 EAG additional analyses

5.2.1 *Model validation and face validity check*

The company's approach to validation of the economic model is laid out in Section 3.14.1 of the CS. The EAG also undertook its own validation of the model and checked the face validity of the assumptions and inputs with clinical experts, as well as checking model formulae and VBA code. The EAG identified multiple errors in the economic model before the clarification stage, which the company amended at the EAG's request. The EAG also identified numerous errors after the clarification stage, which the EAG corrected before conducting further analyses (see Appendix 7.1 for a full list of corrections). Overall, the EAG considers that the company failed to identify key errors in the model which should have been apparent from a robust model validation. The EAG also considers that the company's results potentially lack face validity; in particular, it is surprising that, in the company's deterministic base case, patients treated with efgartigimod accrue more QALYs than patients on established treatment, given that there is no modelled survival benefit for patients receiving efgartigimod.

A summary of the EAG's corrections is given in Section 1.5 and Appendix 7.1. The EAG notes that several of these corrections result in a large change in the ICER (in particular, the correction of the approach to modelling the efgartigimod induction phase). The EAG also notes that the company made multiple errors in the implementation of the probabilistic analysis, leading to a substantial misalignment between probabilistic and deterministic results.

5.2.2 *EAG's exploratory analyses using the company's base case*

A summary of the exploratory analysis conducted by the EAG is given in Table 77.

Table 77. Summary of EAG's exploratory analyses using company's base case

Exploratory analysis number	Company's base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1a	Patient distribution between health states at baseline aligned with baseline of ADHERE Stage A for Ig-refractory patients, and with the baseline for the ADHERE run-in period for Ig-intolerant patients.	Patient distribution between health states at baseline aligned with the baseline for the ADHERE run-in period for Ig-refractory and Ig-intolerant patients.	The EAG does not consider that different baseline distributions should be used for the Ig-refractory and Ig-intolerant patient cohorts.	4.2.3
1b	Patient distribution between health states at baseline aligned with baseline of ADHERE Stage A for Ig-refractory patients, and with the baseline for the ADHERE run-in period for Ig-intolerant patients.	Patient distribution between health states at baseline aligned with the baseline for ADHERE Stage A for Ig-refractory and Ig-intolerant patients.	The EAG does not consider that different baseline distributions should be used for the Ig-refractory and Ig-intolerant patient cohorts.	4.2.3
2	Probability of entering remission is not applied for the first two years, when a three-month cycle length is used.	Probability of entering remission is applied for the first two years, when a three-month cycle length is used.	The EAG is unsure why remission was not included in the company's implementation of the three-month cycle approach.	4.2.8.1
3	Three-month cycle transition probabilities were derived from three-month 'shift' data from ADHERE and ADHERE+.	Three-month cycle transition probabilities were derived from adjusted six-month 'shift' data from ADHERE and ADHERE+.	Many more shifts between health states are captured by the six-month 'shift' data than the three-month 'shift' data, resulting in more robust transition probabilities.	4.2.7.1
4	SCIg treatment is administered over 1 day each week in hospital.	SCIg treatment is administered once per week in hospital (treatment delivered over 1 day).	Hizentra product advice states treatment ideally delivered over 1 or 2 days.	4.2.12.2.1

Exploratory analysis number	Company's base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
5	8% of SCIg treatment is delivered in hospital.	All SCIg treatment is self-administered at home.	Explores the impact of assuming that SCIg treatment can be given at home for patient convenience.	4.2.12.2.1
6	3.1% of IVIg administrations take place in an inpatient setting.	All IVIg administrations take place in an outpatient setting.	The EAG considers that this is more reflective of clinical practice.	4.2.12.2
7	Informal caregiver utility decrements are sourced from Gani <i>et al.</i> 2008.	Informal caregiver utility decrements are sourced from the company's caregiver survey.	The EAG considers that utility decrements sourced from Gani <i>et al.</i> 2008 are unlikely to be reflective of the experience of caregivers of people with CIDP.	4.2.13.1.1
8	Professional care costs are applied to patients in the moderate, severe and very severe health state, assuming 21.3 hours of care (moderate) and 45 hours of care (severe and very severe).	Professional care costs are only applied to patients in the very severe health state, assuming 35 hours of care per week.	EAG clinical expert advice.	4.2.13.2.1
Abbreviations: CIDP, chronic EAG, External Assessment Group; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.				

Deterministic results of the EAG's analysis when applied to the company's base case are given in Table 78 for the Ig maintenance population, and Table 79 for the Ig-intolerant/refractory population. As discussed in Section 4.2.2.1, the EAG considers that it is more appropriate to consider these populations separately, due to the differing treatment pathways and comparators. However, results for a 'mixed' population, as presented in the company's results, are given in Appendix 1.1. Probabilistic results are not presented due to the flaws in the company's probabilistic analysis. Both the company and the EAG considered a severity modifier of 1.0 to be appropriate.

In the Ig maintenance population, for all of the EAG's analyses except for scenario 8 (in which professional care costs were only applied to patients in the very severe health state, assuming 35

hours of care per week), the ICER [REDACTED] for both the Ig maintenance and Ig-intolerant/refractory populations. Scenario 8 led to much reduced costs in the comparator arm, since professional caregiver costs were much reduced, particularly in the more severe impairment health states, which disproportionately affected the comparator arm.

However, scenario 2, in which remission was applied with a three-month cycle length in the first two years, considerably reduced the cost savings for efgartigimod, since remission was applied from baseline for patients receiving comparator treatments, hence reducing monitoring and other costs, but not to patients receiving efgartigimod. By contrast, scenario 3, using a three-month cycle length but deriving transition probabilities from six-month 'shift' data, considerably increased cost savings for efgartigimod. This scenario also considerably increased incremental QALYs, suggesting this assumption is favourable for efgartigimod.

The impact of the scenarios on the company's base case was similar for the Ig-intolerant/refractory population, although the base case results were considerably different (in particular, the incremental costs were positive and very large in magnitude).

Table 78. Results of EAG's exploratory analyses using company's base case (Ig maintenance population)

Exploratory analysis number	Scenario applied to company's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
0	Company base case	■	4.26	■	■	■
1a	Patient distribution between health states at baseline aligned with the baseline for the ADHERE run-in period for Ig-intolerant/refractory patients	■	4.26	■	■	■
1b	Patient distribution between health states at baseline aligned with the baseline for ADHERE Stage A for Ig-intolerant/refractory patients	■	4.26	■	■	■
2	Three-month cycle length is applied, and the probability of entering remission is applied for the first two years	■	4.09	■	■	■
3	Three-month cycle length is applied, with transition probabilities derived from adjusted six-month 'shift' data from ADHERE and ADHERE+	■	5.31	■	■	■
4	SCIg treatment is administered once per week in hospital (treatment delivered over 1 day)	■	4.26	■	■	■
5	All SCIg treatment is self-administered at home	■	4.26	■	■	■
6	All IVIg administrations take place in an outpatient setting	■	4.26	■	■	■
7	Informal caregiver utility decrements are sourced from the company's caregiver survey	■	3.51	■	■	■
8	Professional care costs are only applied to patients in the very severe health state, assuming 35 hours of care per week	■	4.26	■	■	■

Exploratory analysis number	Scenario applied to company's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; NHB, net health benefit; QALY, quality-adjusted life-year; SCIg, subcutaneous immunoglobulin.

Table 79. Results of EAG's exploratory analyses using company's base case (Ig-intolerant/refractory population)

Exploratory analysis number	Scenario applied to company's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
0	Company base case	■	4.03	■	■	■
1a	Patient distribution between health states at baseline aligned with the baseline for the ADHERE run-in period for Ig-intolerant/refractory patients	■	4.02	■	■	■
1b	Patient distribution between health states at baseline aligned with the baseline for ADHERE Stage A for Ig-intolerant/refractory patients	■	4.04	■	■	■
2	Three-month cycle length is applied, and the probability of entering remission is applied for the first two years	■	3.65	■	■	■
3	Three-month cycle length is applied, with transition probabilities derived from adjusted six-month 'shift' data from ADHERE and ADHERE+	■	4.44	■	■	■
4	SCIg treatment is administered once per week in hospital (treatment delivered over 1 day)	■	4.03	■	■	■
5	All SCIg treatment is self-administered at home	■	4.03	■	■	■
6	All IVIg administrations take place in an outpatient setting	■	4.03	■	■	■

Exploratory analysis number	Scenario applied to company's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
7	Informal caregiver utility decrements are sourced from the company's caregiver survey	■	3.13	■	■	■
8	Professional care costs are only applied to patients in the very severe health state, assuming 35 hours of care per week	■	4.03	■	■	■

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; NHB, net health benefit; QALY, quality-adjusted life-year; SCIg, subcutaneous immunoglobulin.

5.2.3 EAG preferred assumptions

5.2.3.1 Base case results

The EAG's preferred model assumptions, along with probabilistic results when these assumptions are cumulatively applied, are summarised in Table 80 (Ig maintenance population) and Table 81 (Ig-intolerant/refractory population). The probabilistic and deterministic results for the EAG's base case population are presented in Table 82 (Ig maintenance population) and Table 83 (Ig-intolerant/refractory population). Scatterplots of probabilistic results in the cost-effectiveness plane are given in Figure 18 and Figure 19. The cost-effectiveness acceptability curve (CEAC) for the Ig maintenance population is given in Figure 20 (no CEAC is given for the Ig-intolerant/refractory population, as the probability of cost-effectiveness was calculated to be zero for all willingness-to-pay thresholds up to £300,000). Convergence plots for the probabilistic analysis are given in Appendix 1.1, and show good convergence within 1,000 iterations, which were used to generate the results presented below.

The same results are given for a mixed patient population in Appendix 1.1.

The EAG's results show relatively good alignment between probabilistic and deterministic results; therefore, due to time constraints and the large number of additional analyses conducted, only deterministic results are presented.

The EAG's results are very different to the company's base case; in particular, the incremental costs are much larger and positive, and the incremental QALYs are much smaller, leading to very high ICERs. The EAG considers that the results have more face validity than the company's results. The impacts of each assumption are relatively similar between the Ig maintenance and Ig-intolerant/refractory populations. The scenarios which have the greatest impact on results have been selected as key issues by the EAG.

Table 80. Results using the EAG's preferred model assumptions (deterministic analysis, Ig maintenance population)

Preferred assumption	Exploratory analysis number	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Company base case (post-clarification)	N/A	■	4.26	■	■	■
EAG corrections applied	N/A	■	4.27	■	■	■
Three-month cycle length applied for first two years	N/A	■	4.50	■	■	■
Proportion of corticosteroids in alternative treatment basket sourced from company's chart review	N/A	■	4.48	■	■	■
Proportion of patients on PLEX who return to Ig: 95%	N/A	■	4.43	■	■	■
Assume 95% of cohort restarts Ig after discontinuation of efgartigimod	N/A	■	4.18	■	■	■
Proportion of patients on each Ig dose sourced from company's chart review (final data cut)	N/A	■	4.15	■	■	■
Ig-intolerant/refractory patients distributed according to baseline distribution from ADHERE run-in at model baseline	1a	■	4.15	■	■	■
Patients do not move between aINCAT categories in the comparator arm	N/A	■	2.10	■	■	■
Patients in the severe and very severe aINCAT categories do not move to other health states	N/A	■	1.76	■	■	■
Half of patients move to a more severe health state following relapse	N/A	■	1.90	■	■	■
Remission is applied in the first two years	2	■	2.03	■	■	■
Transition probabilities are derived from adjusted six-month probabilities	3	■	2.08	■	■	■
Unplanned discontinuation of Ig is not included	N/A	■	2.31	■	■	■
AEs excluded for all treatments	N/A	■	2.23	■	■	■

Preferred assumption	Exploratory analysis number	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
AEs for IV administrations are excluded	N/A	■	2.22	■	■	■
HSUV in the very severe health state is set to 0	N/A	■	2.21	■	■	■
Duration of Ig infusions based on data in the CS	N/A	■	2.07	■	■	■
Disutility of IV administration based on Jørgensen <i>et al.</i> 2017 and considering only the coefficient for route of administration	N/A	■	1.57	■	■	■
IVIg/SCIg split informed by the Immunoglobulin Database Annual Report	N/A	■	1.54	■	■	■
Ig and efgartigimod patients require funded transportation	N/A	■	1.54	■	■	■
Administration cost for SCIg set equal to efgartigimod	N/A	■	1.54	■	■	■
SCIg treatment is administered once per week in hospital	4	■	1.54	■	■	■
IVIg is administered in an outpatient setting	6	■	1.54	■	■	■
Duration of GP surgery consultation is set to 10 minutes	N/A	■	1.54	■	■	■
Proportion of patients requiring a wheelchair is informed by the company's Adelphi study, disaggregated by aINCAT score	N/A	■	1.54	■	■	■
Cost of ICU visit sourced from PSSRU	N/A	■	1.54	■	■	■
Professional care costs excluded	N/A	■	1.54	■	■	■
Patient requirements for caregivers aligned with UK Adelphi study data, with maximum 1 caregiver	N/A	■	1.36	■	■	■
Caregiver utility decrement sourced from company caregiver survey	7	■	1.27	■	■	■
EAG's base case	-	■	1.27	■	■	■

Preferred assumption	Exploratory analysis number	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Abbreviations: AE, adverse event; aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; CS, company submission; EAG, External Assessment Group; GP, general practitioner; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; Ig, immunoglobulin; IV, intravenous; IVIg, intravenous immunoglobulin; NHB, net health benefit; PLEX, plasma exchange; PSSRU, Personal Social Services Research Unit; QALY, quality adjusted life year; SCIg, subcutaneous immunoglobulin.						

Table 81. Results using the EAG's preferred model assumptions (deterministic analysis, Ig-intolerant/refractory population)

Preferred assumption	Exploratory analysis number	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Company base case (post-clarification)	N/A	■	4.03	■	■	■
EAG corrections applied	N/A	■	4.04	■	■	■
Three-month cycle length applied for first two years	N/A	■	3.72	■	■	■
Proportion of corticosteroids in alternative treatment basket sourced from company's chart review	N/A	■	3.59	■	■	■
Proportion of patients on PLEX who return to Ig: 95%	N/A	■	3.03	■	■	■
Assume 95% of cohort restarts Ig after discontinuation of efgartigimod	N/A	■	3.03	■	■	■
Proportion of patients on each Ig dose sourced from company's chart review (final data cut)	N/A	■	3.03	■	■	■
Ig-intolerant/refractory patients distributed according to baseline distribution from ADHERE run-in at model baseline	1a	■	3.03	■	■	■
Patients do not move between aINCAT categories in the comparator arm	N/A	■	1.06	■	■	■

Preferred assumption	Exploratory analysis number	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Patients in the severe and very severe aINCAT categories do not move to other health states	N/A	■	0.71	■	■	■
Half of patients move to a more severe health state following relapse	N/A	■	-0.07	■	■	■
Remission is applied in the first two years	2	■	-0.13	■	■	■
Transition probabilities are derived from adjusted six-month probabilities	3	■	-0.08	■	■	■
Unplanned discontinuation of Ig is not included	N/A	■	-0.08	■	■	■
AEs excluded for all treatments	N/A	■	-0.08	■	■	■
AEs for IV administrations are excluded	N/A	■	-0.07	■	■	■
HSUV in the very severe health state is set to 0	N/A	■	-0.09	■	■	■
Duration of Ig infusions based on data in the CS	N/A	■	-0.14	■	■	■
Disutility of IV administration based on Jørgensen <i>et al.</i> 2017 and considering only the coefficient for route of administration	N/A	■	0.14	■	■	■
IVIg/SCIg split informed by the Immunoglobulin Database Annual Report	N/A	■	0.14	■	■	■
Ig and efgartigimod patients require funded transportation	N/A	■	0.14	■	■	■
Administration cost for SCIg set equal to efgartigimod	N/A	■	0.14	■	■	■
SCIg treatment is administered once per week in hospital	4	■	0.14	■	■	■
IVIg is administered in an outpatient setting	6	■	0.14	■	■	■

Preferred assumption	Exploratory analysis number	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Duration of GP surgery consultation is set to 10 minutes	N/A	■	0.14	■	■	■
Proportion of patients requiring a wheelchair is informed by the company's Adelphi study, disaggregated by aINCAT score	N/A	■	0.14	■	■	■
Cost of ICU visit sourced from PSSRU	N/A	■	0.14	■	■	■
Professional care costs excluded	N/A	■	0.14	■	■	■
Patient requirements for caregivers aligned with UK Adelphi study data, with maximum 1 caregiver	N/A	■	0.26	■	■	■
Caregiver utility decrement sourced from company caregiver survey	7	■	0.31	■	■	■
EAG's base case	-	■	0.31	■	■	■
Abbreviations: AE, adverse event; aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; CS, company submission; EAG, External Assessment Group; GP, general practitioner; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; Ig, immunoglobulin; IV, intravenous; IVIg, intravenous immunoglobulin; NHB, net health benefit; PLEX, plasma exchange; PSSRU, Personal Social Services Research Unit; QALY, quality adjusted life year; SCIg, subcutaneous immunoglobulin.						

Table 82. EAG base case results (Ig maintenance population)

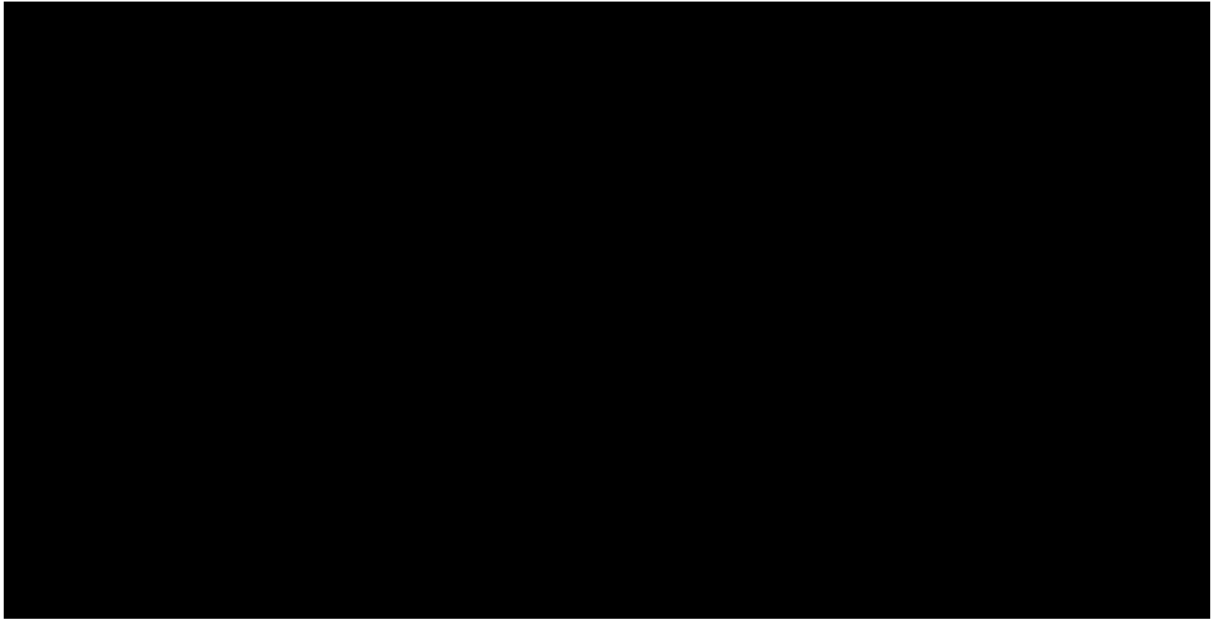
Interventions	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Deterministic results							
Ig	■	6.00	-	-	-	-	-
Efgartigimod	■	7.27	■	1.27	■	■	■
Probabilistic results							
Ig	■	6.35	-	-	-	-	-

Interventions	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Efgartigimod	■	7.56	■	1.20	■	■	■
Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; LY, life year; NHB, net health benefit; QALY, quality-adjusted life-year							

Table 83. EAG base case results (Ig-intolerant/refractory population)

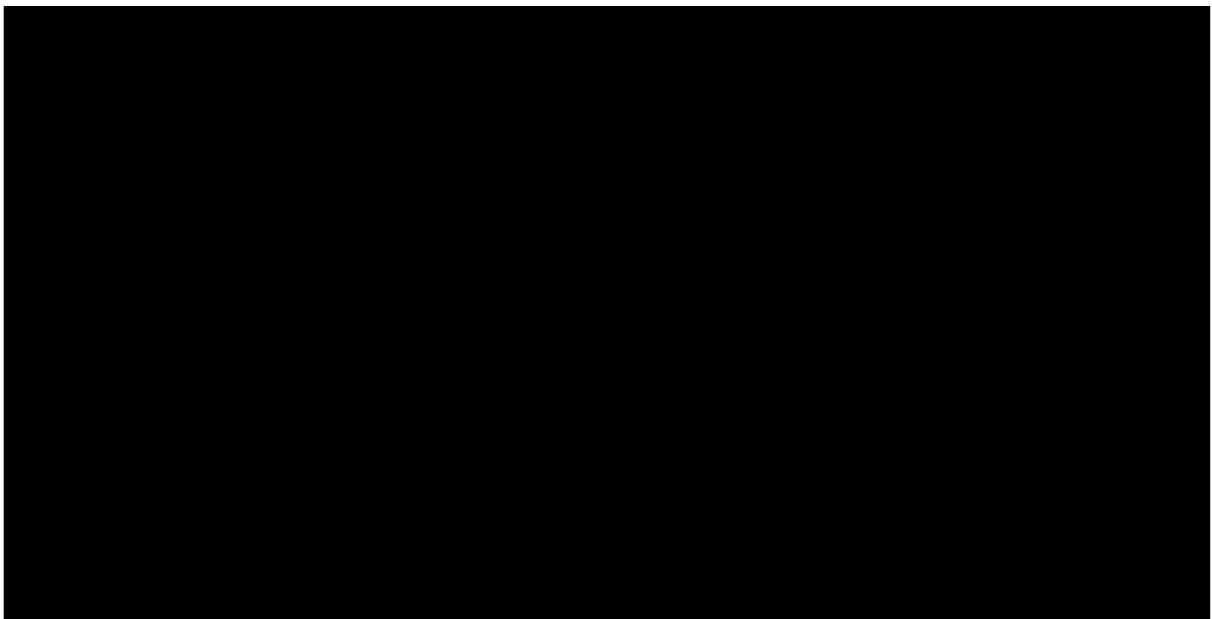
Interventions	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Deterministic results							
Alternative treatment basket	■	7.90	-	-	-	-	-
Efgartigimod	■	8.21	■	0.31	■	■	■
Probabilistic results							
Alternative treatment basket	■	7.85	-	-	-	-	-
Efgartigimod	■	8.29	■	0.44	■	■	■
Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; LY, life year; NHB, net health benefit; QALY, quality-adjusted life-year							

Figure 18. Cost-effectiveness plane, Ig maintenance population



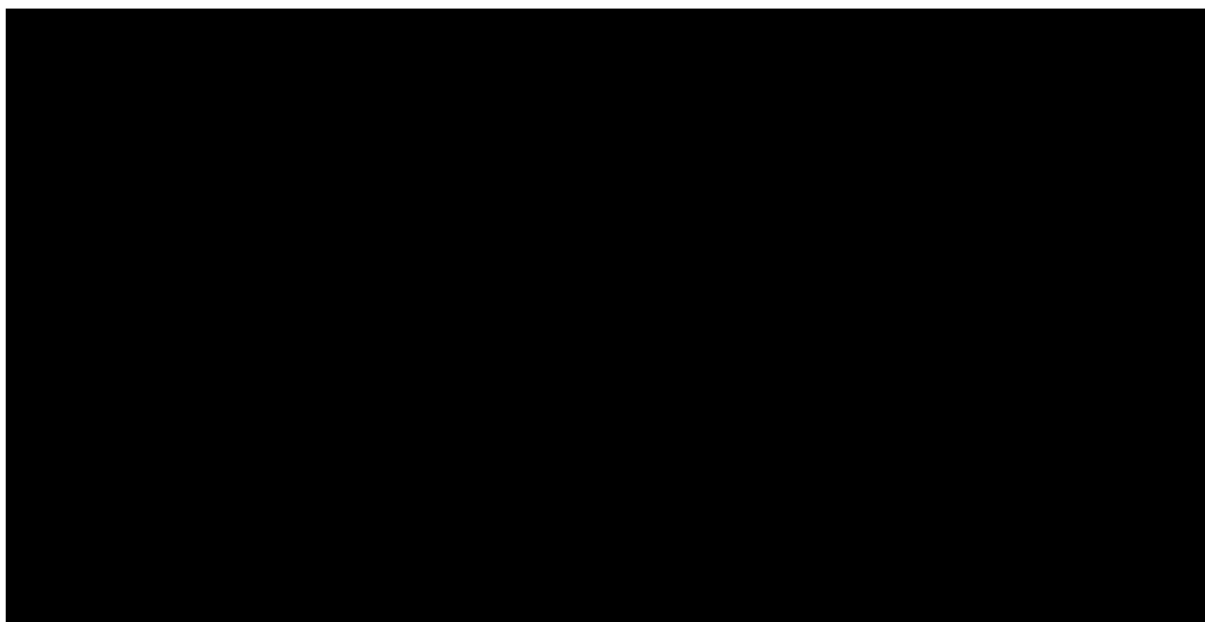
Abbreviations: CE, cost-effectiveness; Ig, immunoglobulin; QALY, quality-adjusted life year.

Figure 19. Cost-effectiveness plane, Ig-intolerant/refractory population



Abbreviations: CE, cost-effectiveness; Ig, immunoglobulin; QALY, quality-adjusted life year.

Figure 20. Cost-effectiveness acceptability curve, Ig maintenance population



Abbreviations: Ig, immunoglobulin; QALY, quality-adjusted life year; WTP, willingness-to-pay.

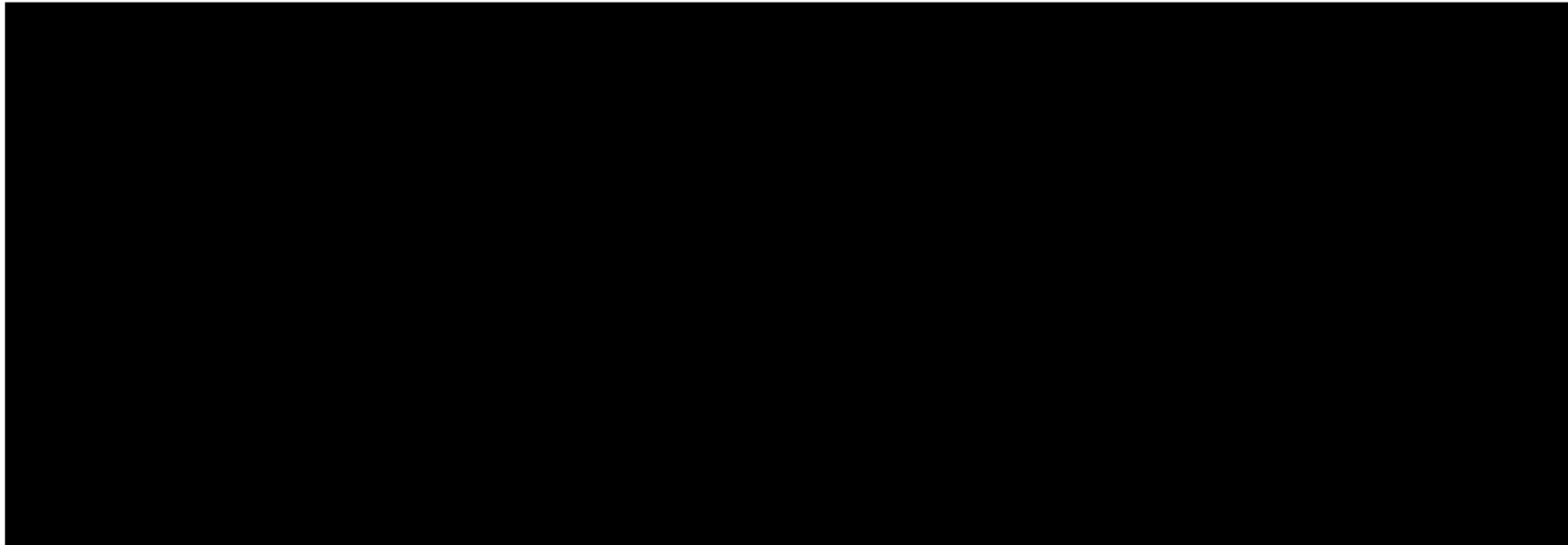
5.2.3.2 *One-way sensitivity analyses*

The EAG conducted one-way sensitivity analyses (OWSAs) to identify inputs which were key drivers of results. The EAG chose to consider the impact on incremental NHB rather than the ICER as varying some parameters gave negative ICERs, which lead to difficulties in interpretation.

The resulting tornado plots are given in Figure 21 (Ig maintenance population) and Figure 11 (Ig-intolerant/refractory population). The tornado plots for the mixed patient population are given in Appendix 1.1.

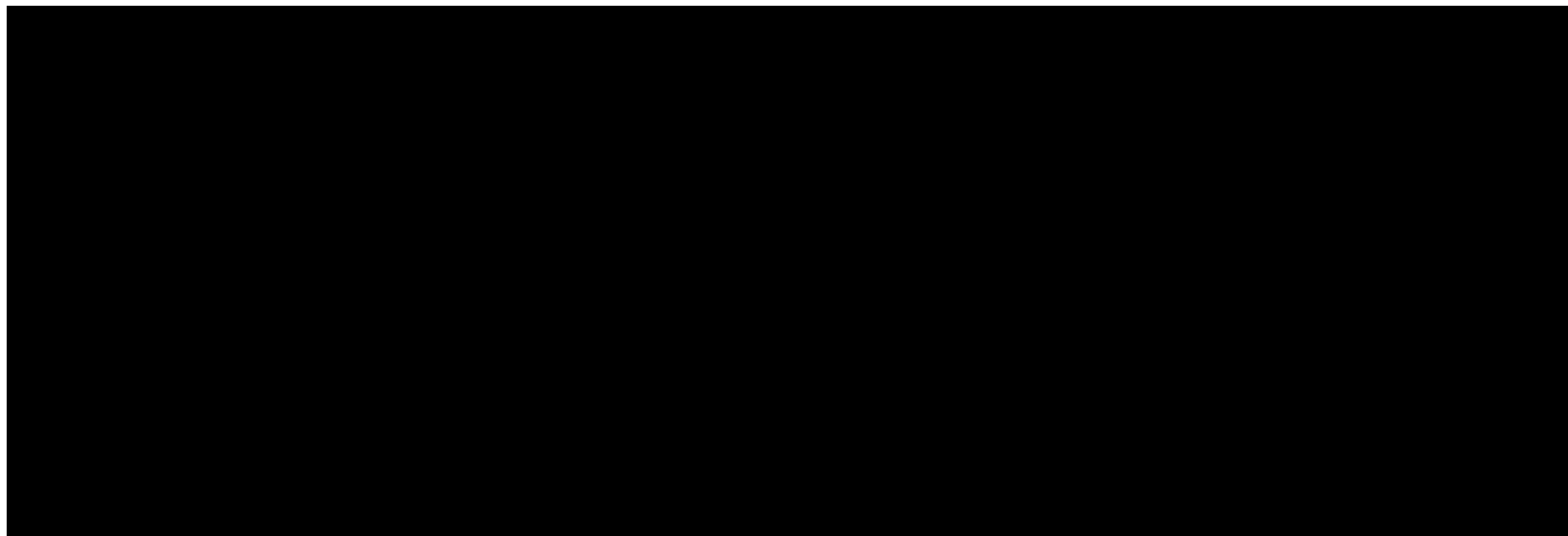
For both populations, the results are particularly sensitive to parameters associated with the probability of planned treatment withdrawal and relapse. This is unsurprising, since the rate of remission and relapse determines the proportion of patients who are on active treatment; patients who are not on active treatment accrue far fewer costs overall. The EAG also notes that in both populations, the results are also sensitive to patients' age at baseline, suggesting that the model is sensitive to the selected time horizon.

Figure 21. Tornado plot of OWSA incremental NHB (Ig maintenance population)



Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; Ig, immunoglobulin; IV, intravenous; IVIg, intravenous immunoglobulin; NHB, net health benefit; OWSA, one-way sensitivity analysis; Q2W, once every two weeks; QALY, quality-adjusted life year.

Figure 22. Tornado plot of deterministic sensitivity analysis incremental NHB (Ig-intolerant/refractory population)



Abbreviations: Ig, immunoglobulin; IV, intravenous; IVIg, intravenous immunoglobulin; NHB, net health benefit; PLEX, plasma exchange; Q2W, once every two weeks; QALY, quality-adjusted life year.

5.2.4 Scenario analyses using EAG's preferred assumptions

To investigate the impact of the EAG's modelling assumptions, the EAG ran scenarios around the EAG's base case, as described in Table 84. These include a combination of scenario analyses implemented by the company, and exploratory analyses conducted by the EAG.

Table 84. Summary of EAG's scenario analyses using the EAG preferred assumptions

	EAG's base case assumption	EAG's scenario
1	Lifetime horizon used	2-year time horizon used
2a	Post-efgartigimod discontinuation, all Ig maintenance patients return to Ig	Post-efgartigimod discontinuation, the same distribution as post-Ig discontinuation is applied
2b	Post-efgartigimod discontinuation, all Ig maintenance patients return to Ig	Post-efgartigimod discontinuation, the cohort is distributed based on the company's SEE
2c	Post-efgartigimod discontinuation, all Ig maintenance patients return to Ig	Post-efgartigimod discontinuation, the cohort is distributed based on the upper bound from the SEE
2d	Post-efgartigimod discontinuation, all Ig maintenance patients return to Ig	Post-efgartigimod discontinuation, a majority of patients are assumed to go back into the same treatment as before starting efgartigimod (i.e. 60% Ig and 40% alternative basket of treatment)
3a	Distribution of treatments in the alternative treatment basket is obtained from the company's chart review	Distribution of treatments in the alternative treatment basket is obtained from the company's SEE
3b	Distribution of treatments in the alternative treatment basket is obtained from the company's chart review	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.
3c	Distribution of treatments in the alternative treatment basket is obtained from the company's chart review	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort is redistributed equally among other treatments.
3d	Distribution of treatments in the alternative treatment basket is obtained from the company's chart review	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.
3e	Distribution of treatments in the alternative treatment basket is obtained from the company's chart review	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort redistributed equally among other treatments.
4a	90% of Ig maintenance patients on PLEX return to Ig	10% of Ig maintenance patients on PLEX return to Ig
4b	90% of Ig maintenance patients on PLEX return to Ig	30% of Ig maintenance patients on PLEX return to Ig

	EAG's base case assumption	EAG's scenario
4c	90% of Ig maintenance patients on PLEX return to Ig	60% of Ig maintenance patients on PLEX return to Ig
5	Baseline distribution from ADHERE run-in used for baseline distribution across health states for Ig-refractory and Ig-intolerant patients	Baseline distribution from ADHERE Stage A used for baseline distribution across health states for Ig-refractory and Ig-intolerant patients
6	Half of patients deteriorate to worse disease severity upon relapse	No patients deteriorate to worse disease severity upon relapse
7	HSUVs are informed by the company's regression model for all health states except for the very severe health state, for which a HSUV of 0 is used	HSUVs are informed by the company's regression model for all health states
8a	Disutility of IV administration is based on the coefficient for the route of administration from Jørgensen <i>et al.</i> 2017	Disutility of IV administration is based on all coefficients from Jørgensen <i>et al.</i> 2017 and Matza <i>et al.</i> 2013
8b	Disutility of IV administration is based on the coefficient for the route of administration from Jørgensen <i>et al.</i> 2017	Disutility of IV administration is excluded
9	Proportion of patients eligible for biweekly dosing of efgartigimod	All patients receive once-weekly dose of efgartigimod in the model
10	8% of SCIg administrations take place in a hospital setting	All SCIg treatment is self-administered at home
11	Funded transport costs are included for both efgartigimod and Ig	Funded transport costs are excluded from the model
12	HRQoL impact on informal care is included and costs for professional care are excluded	HRQoL impact on informal care is excluded and costs for professional care are included
13	Professional care costs excluded from the model	Professional care costs are only applied to patients in the very severe health state, assuming 35 hours of care
14	The caregiver utility decrement is informed by the company's caregiver survey	The caregiver utility decrement is informed by Gani <i>et al.</i> 2008
Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; HSUV, health state utility value; Ig, immunoglobulin; IV, intravenous; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin; SEE, structured expert elicitation		

The results of the EAG's scenario analyses are given in Table 85 for the Ig maintenance population, and Table 86 for the Ig-intolerant/refractory population. Results for the mixed population are presented in Appendix 1.1.

The EAG's scenario analyses suggest the following:

- The scenario analysis with a two-year time horizon (Scenario 1) shows a considerably higher ICER than the base case in the Ig maintenance population, suggesting that a considerable proportion of the modelled benefits of efgartigimod are accumulated more than two years

from baseline; this is notable, since treatment effectiveness from two years onwards is entirely informed by assumption.

- The scenarios related to the distribution of patients between treatments post-efgartigimod discontinuation (Scenarios 2a-2d) have a major impact on the Ig maintenance population, as the total costs in the intervention arm are very sensitive to the proportion of patients who restart Ig.
- The scenarios related to the distribution of patients between treatments in the alternative basket (Scenarios 3a-3e), and to the proportion of patients returning to Ig after treatment with PLEX (Scenarios 4a-4c), have a relatively small impact on the ICER, suggesting that this is not a major source of uncertainty in the model.
- The scenario in which a different baseline distribution between health states was used for the Ig-intolerant/refractory population (Scenario 5) had a small effect on the ICER, suggesting that this is not a major source of uncertainty in the model.
- The scenario in which patients do not deteriorate to a worse health state upon relapse (Scenario 6) has a considerably higher ICER than the base case in the maintenance population, and considerably lower in the Ig-intolerant/refractory population, suggesting that results are sensitive to the assumptions around deterioration upon relapse.
- The scenario in which HSUVs are informed by the company's regression model for all health states (Scenario 7) leads to a moderate reduction in ICER, demonstrating that the EAG's preferred approach is conservative.
- The scenarios in which different disutilities for IV administration are used (Scenarios 8a-8b) have a large impact on the ICER, suggesting that results are sensitive to the assumptions around IV administration.
- The scenario exploring an assumption that all patients receive a once-weekly dose of efgartigimod (Scenario 9) leads to a substantial increase in the ICER, suggesting that the plausibility of patients receiving biweekly dosing is an important assumption in the model.
- The scenarios around administration costs (Scenarios 10 and 11) have a relatively small impact on the ICER, suggesting that this is not a major source of uncertainty in the model.
- The scenarios related to caregiver burden have a substantial impact on the ICER, suggesting that results are sensitive to the approach taken to modelling caregiver burden.

Table 85. Deterministic results of EAG's exploratory analyses using EAG's preferred assumptions (Ig maintenance population)

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
0	EAG base case	████	1.27	████	████	████
1	2-year time horizon used	████	0.16	████	████	████
2a	Post-efgartigimod discontinuation, the same distribution as post-Ig discontinuation is applied	████	2.17	████	████	████
2b	Post-efgartigimod discontinuation, the cohort is distributed based on the company's SEE	████	1.88	████	████	████
2c	Post-efgartigimod discontinuation, the cohort is distributed based on the upper bound from the SEE	████	1.72	████	████	████
2d	Post-efgartigimod discontinuation, a majority of patients are assumed to go back into the same treatment as before starting efgartigimod (i.e. 60% Ig and 40% alternative basket of treatment)	████	1.60	████	████	████
3a	Distribution of treatments in the alternative treatment basket is obtained from the company's SEE	████	1.27	████	████	████
3b	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	████	1.27	████	████	████
3c	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort is redistributed equally among other treatments.	████	1.27	████	████	████
3d	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	████	1.27	████	████	████

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
3e	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort redistributed equally among other treatments.	████	1.27	████	████	████
4a	10% of Ig maintenance patients on PLEX return to Ig	████	1.27	████	████	████
4b	30% of Ig maintenance patients on PLEX return to Ig	████	1.27	████	████	████
4c	60% of Ig maintenance patients on PLEX return to Ig	████	1.27	████	████	████
5	Baseline distribution from ADHERE Stage A used for baseline distribution across health states for Ig-refractory and Ig-intolerant patients	████	1.27	████	████	████
6	No patients deteriorate to worse disease severity upon relapse	████	1.11	████	████	████
7	HSUVs are informed by the company's regression model for all health states	████	1.28	████	████	████
8a	Disutility of IV administration is based on all coefficients from Jørgensen <i>et al.</i> 2017 and Matza <i>et al.</i> 2013	████	1.68	████	████	████
8b	Disutility of IV administration is excluded	████	1.14	████	████	████
9	All patients receive once weekly dose of efgartigimod in the model	████	1.27	████	████	████
10	All SCIg treatment is self-administered at home	████	1.27	████	████	████
11	Funded transport costs are excluded from the model	████	1.27	████	████	████
12	HRQoL impact on informal care is excluded and costs for professional care are included	████	1.25	████	████	████

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
13	Professional care costs are only applied to patients in the very severe health state, assuming 35 hours of care	████	1.27	████	████	████
14	The caregiver utility decrement is informed by Gani <i>et al.</i> 2008	████	1.36	████	████	████

Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; IV, intravenous; NHB, net health benefit; PLEX, plasma exchange; QALY, quality-adjusted life year; SCIg, subcutaneous immunoglobulin; SEE, structured expert elicitation

Table 86. Results of EAG's exploratory analyses using EAG's preferred assumptions (Ig-intolerant/refractory population)

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
0	EAG base case	████	0.31	████	████	████
1	2-year time horizon used	████	0.12	████	████	████
2a	Post-efgartigimod discontinuation, the same distribution as post-Ig discontinuation is applied	████	0.30	████	████	████
2b	Post-efgartigimod discontinuation, the cohort is distributed based on the company's SEE	████	0.31	████	████	████
2c	Post-efgartigimod discontinuation, the cohort is distributed based on the upper bound from the SEE	████	0.31	████	████	████
2d	Post-efgartigimod discontinuation, a majority of patients are assumed to go back into the same treatment as before starting efgartigimod (i.e. 60% Ig and 40% alternative basket of treatment)	████	0.31	████	████	████

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
3a	Distribution of treatments in the alternative treatment basket is obtained from the company's SEE	████	0.31	████	████	████
3b	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	████	0.31	████	████	████
3c	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort is redistributed equally among other treatments.	████	0.31	████	████	████
3d	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	████	0.31	████	████	████
3e	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort redistributed equally among other treatments.	████	0.31	████	████	████
4a	10% of Ig maintenance patients on PLEX return to Ig	████	0.37	████	████	████
4b	30% of Ig maintenance patients on PLEX return to Ig	████	0.36	████	████	████
4c	60% of Ig maintenance patients on PLEX return to Ig	████	0.34	████	████	████
5	Baseline distribution from ADHERE Stage A used for baseline distribution across health states for Ig-refractory and Ig-intolerant patients	████	0.32	████	████	████
6	No patients deteriorate to worse disease severity upon relapse	████	0.97	████	████	████
7	HSUVs are informed by the company's regression model for all health states	████	0.32	████	████	████

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
8a	Disutility of IV administration is based on all coefficients from Jørgensen <i>et al.</i> 2017 and Matza <i>et al.</i> 2013	████	0.03	████	████	████
8b	Disutility of IV administration is excluded	████	0.34	████	████	████
9	All patients receive once weekly dose of efgartigimod in the model	████	0.31	████	████	████
10	All SCIg treatment is self-administered at home	████	0.31	████	████	████
11	Funded transport costs are excluded from the model	████	0.31	████	████	████
12	HRQoL impact on informal care is excluded and costs for professional care are included	████	0.30	████	████	████
13	Professional care costs are only applied to patients in the very severe health state, assuming 35 hours of care	████	0.31	████	████	████
14	The caregiver utility decrement is informed by Gani <i>et al.</i> 2008	████	0.26	████	████	████

Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; IV, intravenous; NHB, net health benefit; PLEX, plasma exchange; QALY, quality-adjusted life year; SCIg, subcutaneous immunoglobulin; SEE, structured expert elicitation

5.3 Decision Modifiers

5.3.1 *QALY weighting for severity*

The company has not made a case for a severity modifier to be applied to the base case QALY estimate. The EAG considers this to be appropriate.

5.3.2 *Uncaptured benefits*

Outlined in section 6.2.36 of the NICE health technology evaluations manual, committees can consider uncaptured benefits when making recommendations about a technology if:

- its decisions have a bearing on broader social considerations and the extent that these are covered by principles on social value judgements on the NICE website.
- there are strong reasons to suggest that the health benefits of the technology have been inadequately captured and may therefore misrepresent the health utility gained.
- a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services, or are associated with significant benefits other than health, only when requested specifically by the Department of Health and Social Care as part of the remit.

The company has considered there are several uncaptured benefits of efgartigimod that are not captured in the QALY calculation including:

- Improved disease control and reduced treatment burden for patients.
- Greater workforce and community participation.
- Reduced work absence due to sickness.
- Fewer hours of informal care required.
- Lower absenteeism and improved well-being for informal carers.
- Reduced service burden to the NHS by assumed reduced use of intravenous (IV) treatments.
- NHS system resilience and supply security by reducing the need for plasma-derived treatments.

The EAG considers that none of the company's claims around uncaptured benefits meet the guidance committees are required to consider when making a recommendation about a technology.

Furthermore, several of the uncaptured benefits the company has discussed in their submission are already captured within the economic model.

For example, disease control and treatment burden are captured in the company base case through the modelling of treatment effectiveness and treatment administration, as well as disutilities associated with IV treatment. Additionally, informal carer well-being is captured in the company's base case analysis via caregiver disutilities.

Many of the other uncaptured benefits are related to the company's own assumption that use of IV treatments will reduce with the introduction of efgartigimod. In the company's base case, 95% of the modelled population are stable IVIg patients. However, the EAG's clinical experts consider that patients are unlikely to switch to efgartigimod if they are stable on IV immunoglobulin (IVIg). Therefore, it is unclear to what extent the introduction of efgartigimod would mitigate IVIg usage.

Overall, the EAG considers that there is no strong argument for the consideration of uncaptured benefits.

5.3.3 *Health inequalities*

No information on health inequalities has been presented by the company. The EAG considers this to be appropriate.

5.4 Confidential comparator and subsequent treatment prices

The EAG has produced a confidential appendix to the EAG report, which takes into account the confidential arrangements for Gamunex and Hizentra Ig products. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

5.5 Conclusions of the cost effectiveness sections

Overall, the EAG considers that the cost effectiveness results for efgartigimod are extremely uncertain. This is partly due to the many uncertainties in the evidence from the ADHERE and ADHERE+ trials, which informs key model inputs (i.e. the proportion of patients who respond to efgartigimod, and the transition probabilities for patients receiving efgartigimod); the EAG also considers that there is a lack of evidence in the existing literature related to the effectiveness of comparator treatments. The EAG considers that this is an unresolvable area of uncertainty.

However, the EAG also notes that there are many uncertainties in other model parameters, as well as in the assumptions informing the treatment pathway and model structure. The EAG considers that in their base case, the company has made multiple assumptions around the effectiveness of efgartigimod compared to other treatments which are biased in favour of efgartigimod, which have an extremely large impact on the ICER. As far as possible, the EAG has attempted to provide more realistic alternatives; although some of the EAG's preferred assumptions are potentially somewhat simplistic), the EAG considers that these assumptions are still more robust than the company's approach, and may be the most appropriate route forward given the unresolvable uncertainty in some of the clinical evidence informing the economic analysis. In the case of some of the EAG's preferred assumptions, particularly the EAG's preferred approach to modelling comparator effectiveness, the EAG acknowledges that these approaches may in fact still present an optimistic view of the benefits of efgartigimod (for example, an approach which assumed no gain in treatment effectiveness would be less optimistic, but also not unreasonable).

The EAG notes that the EAG's approach leads to very different results compared to the company's approach. Overall, the results from the EAG's approach appear to be more plausible than the company's approach, showing increased rather than decreased costs when efgartigimod is used compared to established management, which is as expected, given the high cost of efgartigimod. The EAG's approach also results in much reduced incremental QALYs compared to the company's approach, which is more plausible, given that efgartigimod is not expected to have a survival benefit. The EAG notes that the estimated QALY gains are potentially still surprisingly large in the EAG's base case (1.17 QALYs in the Ig maintenance population, and 0.42 for the Ig-intolerant/refractory population). This is likely due to differences in treatment effectiveness between efgartigimod and comparator treatments being amplified over the time horizon of the model; patients enter the model aged 55, and survival is expected to be in line with general population norms, but patients are not modelled to move between aINCAT categories from two years from baseline up to death, which on average occurs several decades later. This also shows that the EAG's preferred assumptions are not uniformly pessimistic with regard to the benefits of efgartigimod.

The EAG also notes that results for the Ig-intolerant and Ig-refractory populations are consistently less favourable than results for the Ig maintenance population. This is due to the fact that many treatment options in the alternative treatment basket are cheaper than Ig. However, the EAG notes that there is a greater deal of unresolvable uncertainty related to treatment effectiveness in these

populations than in the Ig maintenance population, as Ig-intolerant and Ig-refractory patients were not included in the ADHERE trial. Therefore, results in this population are highly uncertain.

6 References

1. CIDP & the associated chronic variant. Gain Charity.
2. argenx. Patient survey research report - Patient experiences living with chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. 2025.
3. Bunschoten C, Jacobs BC, Van Den Bergh PYK, Cornblath DR, Van Doorn PA. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. *The Lancet Neurology* 2019; **18**: 784-94.
4. Hughes RaC, Bouche P, Cornblath DR, Evers E, Hadden RDM, Hahn A, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *European journal of neurology* 2006; **13**: 326-32.
5. Van Den Bergh PYK, Van Doorn PA, Hadden RDM, Avau B, Vankrunkelsven P, Allen JA, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision. *European journal of neurology* 2021; **28**: 3556-83.
6. argenx. Market research survey report - Treatment patterns for chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. Data on file. 2025.
7. Saiju J, Farrugia ME, Hewamadduma C, Norwood F, Hill M, Leite MI, et al. Association of British Neurologists (ABN) autoimmune myasthenia gravis management guidelines (2025 update). *Pract Neurol* 2025; **25**: 422-37.
8. Markvardsen LH, Sindrup SH, Christiansen I, Olsen NK, Jakobsen J, Andersen H. Subcutaneous immunoglobulin as first-line therapy in treatment-naïve patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study. *European journal of neurology* 2017; **24**: 412-8.
9. Miah S, Japzon N, Elsaddig A, Koay S, Compton L, Lunn MP, et al. Mycophenolate Facilitates Improvement in Outcome Measures in Treatment Resistant Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *Muscle Nerve* 2025; **72**: 250-7.
10. Allen JA, Lin J, Basta I, Dysgaard T, Eggers C, Guptill JT, et al. Safety, tolerability, and efficacy of subcutaneous efgartigimod in patients with chronic inflammatory demyelinating polyradiculoneuropathy (ADHERE): a multicentre, randomised-withdrawal, double-blind, placebo-controlled, phase 2 trial. *The Lancet Neurology* 2024; **23**: 1013-24.
11. Open-label Extension of the ARGX-113-1802 Trial to Investigate the Long-term Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Patients With Chronic Inflammatory Demyelinating Polyneuropathy (ADHERE+). *ClinicalTrials.gov*.
12. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019: l4898.
13. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. Available from: <http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about>. Date accessed: Nov 2025.
14. argenx. Clinical study report ARGX-113-1802, Efgartigimod PH20 SC—CIDP. Data on file. 2023.
15. Allen JA, Lin J, Stettner M, Guptill J, Istas G, editors. ADHERE+ Trial Interim Analysis: Long-Term Safety and Efficacy of Efgartigimod in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. Presented at the 2025 Peripheral Nerve Society (PNS) Annual Meeting; May 17–20, 2025; Edinburgh, UK 2025 2025/05/17/20.
16. Van den Bergh PYK, Hadden RDM, Bouche P, Cornblath DR, Hahn A, Illa I, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European

Federation of Neurological Societies and the Peripheral Nerve Society - first revision. *European journal of neurology* 2010; **17**: 356-63.

17. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC medical research methodology* 2014; **14**: 135.
18. Population-adjusted indirect comparisons (MAIC and STC). 2025.
19. argenx. UK Chart review study. Data on file. argenx; 2025.
20. argenx. UK Chart review interim report. Data on file. argenx; 2025.
21. argenx. Qualitative clinical validation and structured expert elicitation. Data on file. 2025.
22. Oakley J, T OH. The Sheffield Elicitation Framework (SHELF). 2025. Available from: <https://shelf.sites.sheffield.ac.uk/home>. Date accessed: 05/12/2025.
23. argenx. Development and validation of a cost-effectiveness model concept of chronic inflammatory demyelinating polyneuropathy (model validation report). Data on file. 2024.
24. NHS England. Health Survey for England, 2021 part 1. 2022. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2021/part-4-trends>. Date accessed: 05/12/2025.
25. Koay S, Chen Y-C, Ransley G, Compton L, Lunn MP, Carr AS. Safety and Cost Analysis of Immunoglobulin Cessation Trials in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. *Journal of the peripheral nervous system: JPNS* 2025; **30**: e70007.
26. Hughes RAC, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *The Lancet Neurology* 2008; **7**: 136-44.
27. van Schaik IN, Bril V, van Geloven N, Hartung H-P, Lewis RA, Sobue G, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Neurology* 2018; **17**: 35-46.
28. van Schaik IN, Mielke O, Bril V, van Geloven N, Hartung H-P, Lewis RA, et al. Long-term safety and efficacy of subcutaneous immunoglobulin IgPro20 in CIDP: PATH extension study. *Neurol Neuroimmunol Neuroinflamm* 2019; **6**: e590.
29. Office for National Statistics (ONS). United Kingdom population mid-year estimate - 2024. 2024. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/ukpop/pop>. Date accessed: 05/12/2025.
30. National Institute for Health and Care Excellence. Ozanimod for treating relapsing–remitting multiple sclerosis [TA706]. 2021. Available from: <https://www.nice.org.uk/guidance/ta706>. Date accessed: 05/12/2025.
31. Mielke O, Bril V, Cornblath DR, Lawo J-P, van Geloven N, Hartung H-P, et al. Restabilization treatment after intravenous immunoglobulin withdrawal in chronic inflammatory demyelinating polyneuropathy: Results from the pre-randomization phase of the Polyneuropathy And Treatment with Hizentra study. *Journal of the peripheral nervous system: JPNS* 2019; **24**: 72-9.
32. Waheed W, Ayer GA, Jadoo CL, Badger GJ, Aboukhatwa M, Brannagan TH, et al. Safety of intravenous immune globulin in an outpatient setting for patients with neuromuscular disease. *Muscle & Nerve* 2019; **60**: 528-37.
33. Dorst J, Fillies F, Dreyhaupt J, Senel M, Tumani H. Safety and Tolerability of Plasma Exchange and Immunoabsorption in Neuroinflammatory Diseases. *Journal of clinical medicine* 2020; **9**: 2874.
34. Nobile-Orazio E, Cocito D, Jann S, Uncini A, Beghi E, Messina P, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. *The Lancet Neurology* 2012; **11**: 493-502.

35. Narayanaswami P, Sanders DB, Thomas L, Thibault D, Blevins J, Desai R, et al. Comparative effectiveness of azathioprine and mycophenolate mofetil for myasthenia gravis (PROMISE-MG): a prospective cohort study. *The Lancet Neurology* 2024; **23**: 267-76.
36. Mallick R, Carlton R, Van Stiphout J. A Budget Impact Model of Maintenance Treatment of Chronic Inflammatory Demyelinating Polyneuropathy with IgPro20 (Hizentra) Relative to Intravenous Immunoglobulin in the United States. *Pharmacoecon Open* 2023; **7**: 243-55.
37. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. [TA352]. 2015. Available from: <https://www.nice.org.uk/guidance/ta352>. Date accessed.
38. Hernández Alava M, Wailoo A, Pudney S. Methods for mapping between the EQ-5D-5L and the 3L for technology appraisal. Report by the Decision Support Unit. 2017.
39. Hernández-Alava M, Pudney S. Mapping between EQ-5D-3L and EQ-5D-5L: A survey experiment on the validity of multi-instrument data. *Health Economics* 2022; **31**: 923-39.
40. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Econ* 2018; **27**: 7-22.
41. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual [PMG36], 2022. Available from: <https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741>. Date accessed: 18/12/2025.
42. Hernandez-Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. 2022. Report No.
43. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Medical Decision Making: An International Journal of the Society for Medical Decision Making* 2011; **31**: 800-4.
44. National Institute for Health and Care Excellence. Teduglutide for treating short bowel syndrome [TA804]. 2022. Available from: <https://www.nice.org.uk/guidance/ta804>. Date accessed: 05/12/2025.
45. Jørgensen T, Worbes-Cerezo M, Lelli F, Lee X, Bøgelund M, Alulis S. Preferences for Route of Administration, Frequency and Location – A Time-Trade-Off Study in the United Kingdom General Population. *Value in Health* 2017; **20**: A637.
46. Matza LS, Cong Z, Chung K, Stopeck A, Tonkin K, Brown J, et al. Utilities associated with subcutaneous injections and intravenous infusions for treatment of patients with bone metastases. *Patient preference and adherence* 2013; **7**: 855-65.
47. National Institute for Health and Care Excellence. British National Formulary. 2025. Available from: <https://bnf.nice.org.uk/>. Date accessed: November 2025.
48. England N. 2024/25 National Cost Collection data. Available from: <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>. Date accessed.
49. NHS England. 2025/26 NHS Payment Scheme. Available from: <https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/>. Date accessed: 05/12/2025.
50. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. *Unit Costs of Health and Social Care 2024 Manual*: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2025.
51. European Medicines Agency. Summary of product characteristics - Vyvgart. 2025. Available from: https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf. Date accessed: 05/12/2025.
52. European Medicine Agency. Hizentra 200 mg/ml solution for subcutaneous injection - Summary of Product Characteristics.

53. Bedi G, Brown A, Tong T, Sharma KR. Chronic inflammatory demyelinating polyneuropathy responsive to mycophenolate mofetil therapy. *Journal of Neurology, Neurosurgery, and Psychiatry* 2010; **81**: 634-6.
54. NHS. National Immunoglobulin Database Annual Report 2023/24, 2025. Available from: https://igd.mdsas.com/wp-content/uploads/Igd_AnnualReport_202324.pdf. Date accessed: 16/12/2025.
55. NHS England. Improving non-emergency patient transport services, 2021. Available from: <https://www.england.nhs.uk/wp-content/uploads/2021/08/B0682-fnal-report-of-the-non-emergency-patient-transport-review.pdf>. Date accessed: 02/12/2025.
56. CSL Behring. Hizentra for CIDP: administration. 2025. Available from: <https://www.hizentrahcp.com/administration/cidp>. Date accessed: 02/12/2025.
57. Mahdi-Rogers M, McCrone P, Hughes RAC. Economic costs and quality of life in chronic inflammatory neuropathies in southeast England. *European journal of neurology* 2014; **21**: 34-9.
58. British Medical Association. 2025. [08/12/2025]. Available from: <https://www.bma.org.uk/advice-and-support/gp-practices/managing-workload/safe-working-in-general-practice/appointments>.
59. argenx. Analysis of Adelphi dataset on patients with CIDP in support of NICE submission. Data on file. 2025 2025/08/26/. Report No.
60. National Institute for Health and Care Excellence (NICE). Inotersen for treating hereditary transthyretin amyloidosis [HST9]. 2019. Available from: <https://www.nice.org.uk/guidance/hst9>. Date accessed: 05/12/2025.
61. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *PharmacoEconomics* 2008; **26**: 617-27.
62. National Institute for Health and Care Excellence (NICE). Ocrelizumab for treating relapsing-remitting multiple sclerosis [TA533]. 2018. Available from: <https://www.nice.org.uk/guidance/ta533>. Date accessed: 05/12/2025.
63. argenx. Caregiver research survey report - Experiences of individuals supporting adults living with chronic inflammatory demyelinating polyneuropathy (CIDP) in the UK. Data on file. 2025.
64. NHS England. Health Survey for England 2017 2018. Date accessed: 19/01/2026.
65. NHS England. NHS continuing healthcare. 2024. Available from: <https://www.nhs.uk/social-care-and-support/money-work-and-benefits/nhs-continuing-healthcare/>. Date accessed: 18/12/2025.
66. Beacon. What is NHS Continuing Healthcare? 2025. Available from: <https://beaconchc.co.uk/what-is-nhs-continuing-healthcare/>. Date accessed: 18/12/2025.

7 Appendices

7.1 EAG corrections in the economic model

Table 87. Full details of EAG corrections in the economic model

Sheet	Cell	Details of correction	Impact
Efgartigimod_non_responders	C129:DB129	Corrected baseline distribution for Ig-refractory population non-responders in efgartigimod arm	Affects all analyses
Efgartigimod_responders	LT14:MB14; MU14:MY14; NC14	Removed redundant efgartigimod induction phase cost (admin and acquisition) from efgartigimod responders	Affects all analyses
Efgartigimod_non_responders	JF13:JJ13; JN13; JX13:KB13; KF13	Removed redundant comparator induction phase cost (admin and acquisition) from efgartigimod non-responders.	Affects all analyses
Efgartigimod_non_responders	EV13:FR13; EV130:FR130; EV247:FR247; IG13; IG130; IG247	Adjusted AE rates in first cycle to align with efgartigimod, and removed IV complications from first cycle.	Affects all analyses
Efgartigimod_non_responders	KP13:KT13; KX13; KP130:KT130; KX130; KP247:KT247; KX247	Adjusted AE costs in first cycle to align with efgartigimod	Affects all analyses
Efgartigimod_non_responders	C129:DB129	Corrected baseline distribution for Ig-refractory population non-responders in efgartigimod arm	Affects all analyses
Clinical	L125	Corrected error in link to PSA sheet (wrong cell referenced)	Only affects probabilistic analysis
Transition_probabilities	CC199:CM200	Corrected error in link to PSA sheet (wrong cell referenced)	Only affects probabilistic analysis
Transition_probabilities	AC17:AG18	Corrected errors in formulae (wrong cells referenced)	Only affects analysis with 3-month cycle length
Efgartigimod_responders	N13:R123; N130:R240; N247:R357; N364:R474	Corrected error in calculation of mortality probability for 3-month cycle length	Only affects analysis with 3-month cycle length
Efgartigimod_non_responders	N12:R122; N129:R239; N246:R356	Corrected error in calculation of mortality probability for 3-month cycle length	Only affects analysis with 3-month cycle length
Comparator	N12:R122; N129:R239	Corrected error in calculation of mortality probability for 3-month cycle length	Only affects analysis with 3-month cycle length
Efgartigimod_non_responders	KG14:KN122; KG131:KN239; KG248:KG356	Corrected error in implementation of 3-month cycle length (formula had not been filled down columns)	Only affects analysis with 3-month cycle length

Sheet	Cell	Details of correction	Impact
Transition_probabilities	Q47:U48	Corrected incorrect row reference in transition probabilities	Only affects analysis with 3-month cycle length
Cost_HCR_U_data	G7	Updated to adjust starting point for biweekly dosing if 3-month cycle length used	Only affects analysis with 3-month cycle length
AEs	F213, F224, F228	Corrected error in implementation of scenario in which only hypertension, endocrine disorders, peripheral oedema included as AEs for corticosteroids	Only affects scenario in question
HRQoL_data	R9	Corrected error in input value	Only affects scenario using descriptive analysis of ADHERE data for HSUVs
HRQoL_data	Q57:Q58	Corrected formula incorrectly copied into cell	Only affects scenario in which disutility of IV administration is excluded
Cost_HCR_U_data	C198:G198	Corrected incorrect implementation of scenario in which caregiver costs are removed (costs for interactions with HCPs should not be removed)	Only affects scenario in question
Cost	F59:G62; J59:L62; F87:G89; J87:L89	Updated to use shifted gamma distribution for PSA and OWSA (minimum value = 1)	Only affects probabilistic analysis and OWSA
Clinical	J11:K11; J48:K48; J80:K84; J88:K92; J125:K127; J136:K136	Corrected error in calculation of beta distribution parameters	Only affects probabilistic analysis
HRQoL	J15:K19; J25:K29; J35:K38; J93:K115; J131:K136	Corrected error in calculation of beta distribution parameters	Only affects probabilistic analysis
AEs	L11:M33; L39:M61; L67:M89; L95:M117; L123:M145; L178:M200; L206:M228; L234:M256; M262:N267	Corrected error in calculation of beta distribution parameters	Only affects probabilistic analysis
Cost	J19:K20; J33:K33; J162:K165; J172:K173; J202:K205; J223:L227; J231:K235;	Corrected error in calculation of beta distribution parameters	Only affects probabilistic analysis

Sheet	Cell	Details of correction	Impact
Transition_probabilities	AD173:AN183; AD199:AN209; AD225:AN235; AD251:AN261; CO173:CY183; CO199:CY209; CO225:CY235; CO251:CY261; EX173:FH183; EX199:FH209; EX225:FH235; EX251:FH261	Multiplied gamma distribution parameters by 1000 in gamma samples to generate Dirichlet samples for transition probabilities (this stabilises the generated probabilities)	Only affects probabilistic analysis
Cost_HCRU_data	R42:R45; W35:W38; P36:P38	Imputed SE from SD and mean rather than assuming 10% of mean	Only affects probabilistic analysis
Cost	L52:L55	Adjusted formulae to deal with SE of 0	Only affects probabilistic analysis
Cost	J59:K62	Updated to use formulae to calculate alpha and beta from mean and SE, rather than pulling through incorrect alpha and beta from Cost_HCRU_data sheet	Only affects probabilistic analysis
OWSA_data	D11:E12	Updated to remove discount rate from OWSA	Only affects OWSA
Cost_HCRU_data	I144:I147; I151:I153; K144:K147; K151:K153	Updated to remove hard-coded OWSA thresholds for Ig dosage information	Only affects OWSA
OWSA_data	I135:I138; I147:I149	Updated error handling to avoid errors when running OWSA for the Ig-intolerant/refractory population	Only affects OWSA
Abbreviations: AE, adverse event; HCP, healthcare provider; HSUV, health state utility value; Ig, immunoglobulin; IV, intravenous; OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; SD, standard deviation; SE, standard error.			

7.2 Quality assessment

Table 88. EAG's summary of the design, conduct and analysis of the PATH trial

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Van Schaik <i>et al.</i> 2018	Appropriate Patients were randomised 1:1:1 to low dose SCIg, high dose SCIg or placebo using an Interactive Web Response System. Randomisation was stratified by region (Japan or non-Japan).
Concealment of treatment allocation	Van Schaik <i>et al.</i> 2018	Appropriate Participants were centrally assigned to randomised treatment using an Interactive Web Response System. Treatment allocation was only revealed to personnel not involved in the conduct or analysis of the trial.
Eligibility criteria	Van Schaik <i>et al.</i> 2018	Some concerns regarding the applicability of the trial population to the company's proposed population Patients were included if they received their last dose of IVIg within 8 weeks of trial enrolment. Inclusion criteria does not appear to be based on CIDP disease status. Patients were excluded if they were intolerant to IVIg and so do not meet this aspect of the company's proposed population. No information is available to determine whether any patients would meet the company's definition of a high treatment burden.
Blinding	Van Schaik <i>et al.</i> 2018	Appropriate The trial was double-blind. The only unblinded study personnel were those not involved in the conduct or analysis of the trial.
Baseline characteristics	Van Schaik <i>et al.</i> 2018	Concerns about differences to ADHERE in CIDP diagnosis and prior treatments Time since diagnosis was shorter for patients in the PATH trial than in ADHERE. Some patients in PATH (low dose SCIg, 11%; high dose SCIg, 9%; placebo: 7%) had probable, rather than definite CIDP. Information was not provided for the percentage of patients with typical or atypical CIDP. All patients in PATH had received prior Ig, compared to 44.1% of patients in the efgartigimod arm and 42.7% of patients in the placebo arm of ADHERE. No patients were treatment-naïve in ADVANCE-CIDP-1, compared to 32.4% for efgartigimod and 35.5% for placebo in ADHERE. Therefore, the EAG has concerns that the population may not align with that proposed by the company. It also has concerns that there are considerable differences between the prior treatment history of

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
		patients in the two trials which introduces heterogeneity into the ITCs.
Dropouts	Van Schaik <i>et al.</i> 2018	Appears reasonable The number of discontinuations were similar between high dose and low dose SCIg trial arms, and this was primarily due to relapse.
Statistical analysis		
Sample size and power	Van Schaik <i>et al.</i> 2018	Appears reasonable The target sample size was chosen to achieve a power of 90% (p=0.025) based on the assumption that the proportion of patients who reached the primary endpoint would be 35% for the high dose, 52% for the low dose, and 65% for placebo.
Handling of missing data	Van Schaik <i>et al.</i> 2018	Unclear No information is reported about missing data
Outcome assessment	Van Schaik <i>et al.</i> 2018	Appropriate for I-RODS and MGS. Some concerns for aINCAT Change in aINCAT score, I-RODS score and MGS from baseline were reported as a secondary endpoint. Mean (SE) of change in aINCAT was not reported in the trial and so the company calculated this outcome based on the sample number, the median and inter-quartile range using the approach published by Wan <i>et al.</i> 2014. ¹⁷
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; EAG, External Assessment Group; ITC, indirect treatment comparison; I-RODS, Inflammatory Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulin; MGS, mean grip strength; SCIg, subcutaneous immunoglobulin; SE, standard error		

Table 89. EAG's summary of the design, conduct and analysis of the ICE trial

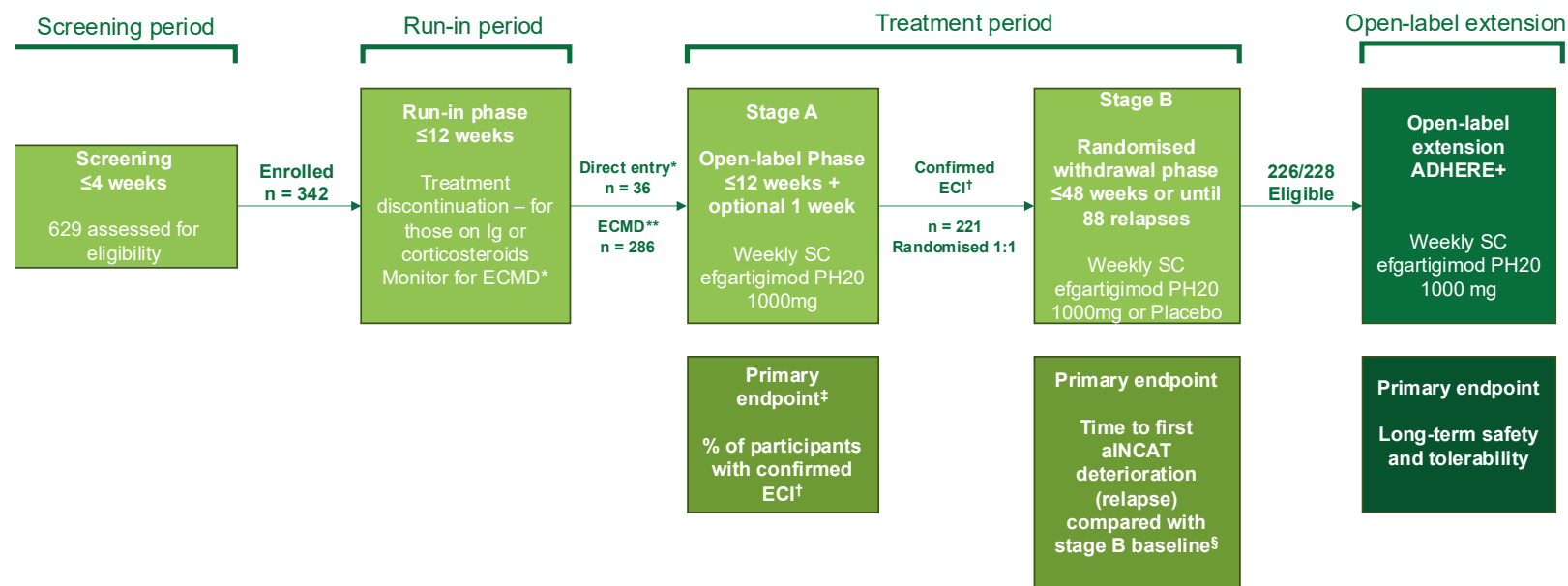
Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Hughes <i>et al.</i> 2008	Appropriate Patients were randomised to IVIg or placebo using computer-generated random codes.
Concealment of treatment allocation	Hughes <i>et al.</i> 2008	Appropriate Random codes were generated by an independent group. Only people involved in checking the drug batch logs were aware of treatment allocation.
Eligibility criteria	Hughes <i>et al.</i> 2008	Concerns about prior treatments and the applicability of the trial population to the company's proposed population Patients were included if they had a diagnosis of CIDP, progressive or relapsing motor and sensory dysfunction of at least one limb

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
		resulting from neuropathy over the two months before study entry, and significant disability defined by an overall INCAT disability score of 2–9. An INCAT disability score of 2 had to be exclusively from leg disability. Patients were excluded if they received steroids, IVIg or PLEX in the 3 months prior to study entry. No information is available to determine whether any patients would meet the company's definition of a high treatment burden.
Blinding	Hughes <i>et al.</i> 2008	Appropriate The trial was double-blind. The only unblinded study personnel were those who were responsible for checking the drug batch logs.
Baseline characteristics	Hughes <i>et al.</i> 2008	Appears reasonable Baseline characteristics for the first period appear similar to ADHERE, although time since diagnosis was shorter for patients in the ICE trial than in ADHERE. Information was not provided for the percentage of patients with typical or atypical CIDP and it is unclear if concomitant medications were allowed. Baseline characteristics were not reported for the extension phase of the trial. Less than half of patients enrolled in the first period of the trial (49%) progressed to the extension phase and so it is unclear how well the baseline characteristics from the first period represent those in the extension phase.
Dropouts	Hughes <i>et al.</i> 2008	Pre- and post-crossover stages appear reasonable. Some concerns about re-randomisation stage Pre-crossover stage: A low number of dropouts and similar between trial arms. Post-crossover stage: Dropouts were similar between trial arms. Re-randomisation stage: 11 out of 31 patients discontinued from the placebo arm. While higher dropouts due to relapse in the placebo arm are expected, only 16 placebo patients completed the re-randomisation stage.
Statistical analysis		
Sample size and power	Hughes <i>et al.</i> 2008	Appears reasonable The target sample size was chosen to detect a difference in proportions of patients who were first-period aINCAT non-responders with a power of 80% ($p < 0.05$) based on a response rate of 15% in the placebo group and 40% in the IVIg group.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Handling of missing data	Hughes <i>et al.</i> 2008	Unclear No information was reported about the handling of missing data.
Outcome assessment	Hughes <i>et al.</i> 2008	Method of outcome assessment appears reasonable. Outcomes assessed in the extension phase are most relevant to the decision problem Change in aINCAT score from baseline was reported as a primary endpoint and change in MGS was a secondary endpoint. Outcomes were assessed at three points: • Following randomisation but before cross-over. These patients had no treatment in 3 months prior to the trial and therefore differ to the company's proposed population; • Post-crossover. These results are confounded by the inclusion of some patients who received their original treatment and others who switched treatment. There is no differentiation between the two groups in the results; • Following re-randomisation (extension phase). These results appear appropriate for comparisons, including only patients who responded to IVIg in the first period or crossover period of the trial
Abbreviations: aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; EAG, External Assessment Group; ITC, indirect treatment comparison; IVIg, intravenous immunoglobulin; MGS, mean grip strength; PLEX, plasma exchange		

7.3 Study design of ADHERE and ADHERE+.

Figure 23. ADHERE and ADHERE+ study design. Reproduced from Figure 4 of the CS



*Off-treatment participants (treatment-naïve or no CIDP treatment within six months) with documented aINCAT worsening in the three months before screening versus a prior score within six months entered Stage A directly.

** ECMD was defined as an aINCAT increase of ≥1 points, an I-RODS decrease of ≥4 points, or a grip strength decrease of ≥8 kPa.

† ECI was defined as a clinical improvement on the parameters that the participant worsened in during run-in (≥4-point increase in I-RODS and/or ≥8-kPa increase in MGS) or clinical improvement (≥1-point decrease) in INCAT. ECI was confirmed after these criteria were met after 4 injections and 2 consecutive visits.

‡ The primary endpoint was assessed once 88 total relapses or events were achieved in Stage B and was based on the HR for the time to first aINCAT deterioration (i.e., relapse).

§ aINCAT deterioration was defined as an increase of ≥1 points in aINCAT score compared to Stage B baseline, which was confirmed at a consecutive visit after the first 1-point increase in aINCAT or not confirmed for participants with ≥2-point increase in aINCAT compared with Stage B baseline.

Abbreviations: aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; ECI, Evidence of Clinical Improvement; ECMD, Evidence of Clinically Meaningful Deterioration; Ig, Immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-Built Overall Disability Score; MGS, Mean grip strength; SC, Subcutaneous.

7.4 EAG-preferred three-month transition probabilities

Table 90. EAG-preferred three-month transition probabilities, 0-6 months from response assessment

	To very limited impairment	To mild impairment	To moderate impairment	To severe impairment	To very severe impairment
From very limited impairment	■	■	■	■	■
From mild impairment	■	■	■	■	■
To moderate impairment	■	■	■	■	■
To severe impairment	■	■	■	■	■
To very severe impairment	■	■	■	■	■

Table 91. EAG-preferred three-month transition probabilities, 6-12 months from response assessment

	To very limited impairment	To mild impairment	To moderate impairment	To severe impairment	To very severe impairment
From very limited impairment	■	■	■	■	■
From mild impairment	■	■	■	■	■
To moderate impairment	■	■	■	■	■
To severe impairment	■	■	■	■	■
To very severe impairment	■	■	■	■	■

Table 92. EAG-preferred three-month transition probabilities, 12-18 months from response assessment

	To very limited impairment	To mild impairment	To moderate impairment	To severe impairment	To very severe impairment
From very limited impairment					
From mild impairment					
To moderate impairment					
To severe impairment					
To very severe impairment					

Table 93. EAG-preferred three-month transition probabilities, 18-24 months from response assessment

	To very limited impairment	To mild impairment	To moderate impairment	To severe impairment	To very severe impairment
From very limited impairment					
From mild impairment					
To moderate impairment					
To severe impairment					
To very severe impairment					

7.5 Company's approach to modelling adverse events in the economic analysis

7.5.1 Adverse events for efgartigimod

In the company's base-case analysis, common AEs of any grade/severity for efgartigimod occurring in $\geq 5\%$ of patients from stage B of ADHERE were included in the model. The EAG notes that Grade ≥ 3 treatment-emergent AEs from the ADHERE CSR are available and were provided by the company in their clarification response; this approach would be more consistent with standard health economic modelling conventions. The company explained that common AEs were selected for the model to aid consistency with the AE data reported for the comparators in the model.

7.5.2 Adverse events for Ig

Frequencies of adverse events for maintenance Ig were informed by several different studies specific to different administration types (IVIg and SCIg) and brands (Privigen, Hizentra and Gamunex) and are summarised below.

- Privigen (IVIg) AEs were obtained from the PATH study (Mielke *et al.* 2019).³¹ The most common AEs from the PATH study were included in the model, but the EAG notes that severity was not defined. However, applying the threshold of occurring in $\geq 5\%$ of patients as per the inclusion criteria for efgartigimod, the only AEs that are applicable are headache (16.4%) and nasopharyngitis (5.8%). The company has assumed the AEs associated with Privigen would be the same for Flebogamma DIF. In their clarification response, the company explained that both products are IVIg with a comparable composition and administration. Therefore, in the absence of AE data for Flebogamma, the company considered it was reasonable to assume the same AE data as for Privigen.
- Hizentra (SCIg) AEs were obtained from the open label extension of the PATH study (van Schaik *et al.* 2019), which reported all AEs occurring in $\geq 2\%$ of patients (overall population).²⁷ Applying the threshold of occurring in $\geq 5\%$ of patients as per the inclusion criteria for efgartigimod, the only AEs that are applicable are local reactions (22.0%) and nasopharyngitis (13.4%).
- Gamunex (IVIg) AEs were obtained from the ICE study (Hughes *et al.* 2008), which reported all AEs occurring in $\geq 5\%$ of patients, irrespective of causality.²⁶

Different doses of IVIg are accounted for and are presented in Table 70 of the CS. The company noted that the IVIg dose used in the PATH pre-randomisation phase and the ICE studies was 1.00 g/kg. To estimate AE probabilities associated with other doses, the company used odds ratios (ORs) from a study by Waheed *et al.* 2019 which estimated the odds of experiencing an AE based on categories of IVIg dose (Table 94).³² The dose of 0.05 — 0.99 g/kg was used as the reference dose to align with the dose using in the PATH and ICE studies. The company used the ORs to estimate the probability of each AE for Privigen and Gamunex associated with each dose category. The company then estimated a weighted average probability of each AE for Privigen and Gamunex based on the proportion of patients on each dose, presented in Table 44.

Table 94. Odds ratios of experiencing an AE for different doses of IVIg (Waheed *et al.* 2019)³²

IVIg dose	Odds ratio
<0.50 g/kg	1.36
0.50 – 0.99 g/kg	1.00
1.00 – 1.75 g/kg	2.34
>1.75 g/kg	3.87

Abbreviations: AE, adverse event; IVIg, intravenous immunoglobulin.

The weighted AEs for IVIg and the AEs for SCIg were then weighted by the proportions of each brand’s usage assumed in the model (see Section 4.2.2 for details) to produce the overall probability of each AE for maintenance Ig presented in Table 55.

7.5.3 Adverse events for PLEX

Adverse events associated with PLEX were taken from a study by Dorst *et al.* 2020.³³ The EAG notes that no severe AEs were recorded in the study and the authors stated that, “*adverse events were uncomplicated and did not necessitate any specific therapy*”.

7.5.4 Adverse events for corticosteroids

A study by Nobile-Orazio *et al.* 2012 was used to inform the AEs for IV methylprednisolone, which the company has assumed to be the corticosteroid treatment in the model.³⁴ The study did not report AEs by severity and the EAG notes that most reported AEs occurred in one patient, although it is not clear from the paper if it was the same patient for each event. If the threshold of occurring in $\geq 5\%$ of patients is applied as per the inclusion criteria for efgartigimod, the only AEs that are applicable for corticosteroids are hypertension (14.29%), endocrine disorders (9.52%) and peripheral oedema (9.52%).

7.5.5 Adverse events for immunosuppressants

For immunosuppressants, the company assumed AEs associated with mycophenolate mofetil obtained from a study by Narayanaswami *et al.* 2024 were appropriate to include in the model.³⁵ The paper reported that one out of nine AEs reported for mycophenolate mofetil was Grade 3 (no detail given on which AE), with the rest reported as Grade 1 and 2. In the model, applying the threshold of occurring in $\geq 5\%$ of patients as per the inclusion criteria for efgartigimod, the only AE that is applicable for immunosuppressants is gastrointestinal disturbances (14.89%).

7.6 Price sources for treatments included in the confidential appendix

Table 95. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Gamunex (IVIg)	MPSC
Hizentra (SCIg)	MPSC
Abbreviations: IVIg, intravenous immunoglobulin; MPSC, medicines procurement supply chain; SCIg, subcutaneous immunoglobulin.	

7.7 Full list of scenario analyses performed by the company

Table 96. Deterministic results for all scenario analyses performed by the company

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30k)
0	Company updated base case	████	4.26	████	████
Original company scenarios					
1	Transition probabilities from Cycle 4 are reused for the rest of the time horizon for patients treated with efgartigimod	████	4.25	████	████
2	Transition probabilities from Cycle 4 are reused for the rest of the time horizon for patients treated with Ig	████	5.94	████	████
3	Shorter treatment effect of efgartigimod vs Ig (6 months)	████	2.08	████	████
4	Comparator treatment efficacy is informed by the company's ITC vs all comparator studies (ADVANCE-CIDP-1; PATH; ICE)	████	3.99	████	████
5	Time on treatment with efgartigimod is applied over the entire time horizon (exponential curve)	████	2.79	████	████
6	Caregiver disutilities are excluded	████	3.47	████	████
7a	Time of eligibility for treatment dependency test: efgartigimod cohort eligible from simulation start – included at bottom of response table	████	4.32	████	████
7b	Time of eligibility for treatment dependency test: Ig cohort eligible from Cycle 3 onwards	████	4.67	████	████
8	Half of patients deteriorate to worse disease severity upon relapse	████	4.59	████	████
9	Induction costs for efgartigimod are removed	████	4.26	████	████
10	Alternative source for Ig dosage and frequency of treatment: UK chart review data	████	4.26	████	████
11a	Post-efgartigimod discontinuation, the same distribution as post-Ig discontinuation is applied	████	4.26	████	████
11b	Post-efgartigimod discontinuation, the cohort is distributed based on the upper bound from the SEE	████	4.24	████	████

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30k)
11c	A majority of patients are assumed to go back into the same treatment following efgartigimod treatment discontinuation as before starting efgartigimod (i.e. 60% Ig and 40% basket of treatment)	████	4.23	████	████
11d	Patients are assumed to go back onto the same treatment following efgartigimod treatment discontinuation as before starting efgartigimod (i.e. 95% Ig and 5% basket of treatment)	████	4.18	████	████
12	HSUVs in the severe and very severe health states are linearly extrapolated from the estimates for Very limited, Mild, and Moderate health states	████	3.87	████	████
13a	5% discount on Ig list price	████	4.26	████	████
13b	10% discount on Ig list price	████	4.26	████	████
13c	20% discount on Ig list price	████	4.26	████	████
13d	25% discount on Ig list price	████	4.26	████	████
13e	17% discount on Ig list price	████	4.26	████	████
14	Alternative source for Ig dosage and frequency of treatment: UK chart review data (final data cut)	████	4.20	████	████
Scenarios requested by the EAG					
15	Time horizon = 2 years	████	0.36	████	████
16a	Distribution of treatments in the alternative treatment basket obtained from the company's chart review study	████	4.24	████	████
16b	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	████	4.41	████	████
16c	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort is redistributed equally among other treatments.	████	4.35	████	████
16d	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	████	4.49	████	████

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30k)
16e	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort redistributed equally among other treatments.	████	4.42	████	████
17a	10% of Ig maintenance patients on PLEX return to Ig	████	4.25	████	████
17b	30% of Ig maintenance patients on PLEX return to Ig	████	4.23	████	████
17c	60% of Ig maintenance patients on PLEX return to Ig	████	4.20	████	████
17d	90% of Ig maintenance patients on PLEX return to Ig	████	4.16	████	████
18	Patient weight informed by UK-real world evidence	████	4.26	████	████
19	Patients in the comparator arm remain in same aINCAT category as at baseline indefinitely	████	2.14	████	████
20	Patients have a 100% chance of remaining in the severe and very severe health states	████	3.98	████	████
21	The comparator arm is modelled by recycling the transitions in the first 6 months up to 24 months, then the identity matrix is applied indefinitely	████	3.60	████	████
22	The comparator arm is modelled by applying identity matrix from 6 months onwards	████	2.64	████	████
23	Discontinuation of efgartigimod is based on time-to-event analysis of discontinuations due to AEs, rather than all discontinuations	████	4.60	████	████
24	Permanent treatment discontinuation is applied indefinitely over the time horizon of the model for efgartigimod and Ig	████	2.59	████	████
25a	Discontinuation of Ig in the first treatment cycle is aligned with ADVANCE-CIDP-1	████	4.26	████	████
25b	Discontinuation of Ig in the first treatment cycle is based on ADVANCE-CIDP-1, PATH and ICE	████	4.26	████	████

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30k)
26	Patients receiving Ig or a treatment in the comparator basket do not permanently discontinue treatment at any time	████	4.28	████	████
27	Grade ≥3 treatment-related AEs occurring in ≥5% efgartigimod patients included	████	4.26	████	████
28	AEs based on the inclusion criteria of occurring in ≥5% of patients are included in the model for IVIg and SCIg	████	4.25	████	████
29	AEs for PLEX are excluded from the model	████	4.27	████	████
30	Corticosteroid AEs: only AEs occurring in ≥5% of patients are included	████	4.26	████	████
31	Immunosuppressant AEs: only AEs occurring in ≥5% of patients are included	████	4.26	████	████
32	AEs for efgartigimod, Ig, PLEX, corticosteroids and immunosuppressants are excluded from the model.	████	4.16	████	████
33	Complications related to IV administration are excluded	████	4.25	████	████
34	Age-adjustment for patients in the very severe health state is included	████	4.27	████	████
35	HSUV value for very severe health state = 0	████	4.17	████	████
36	HSUVs are based on a descriptive analysis of ADHERE data (stage A and B)	████	4.25	████	████
37	HSUVs are based on the Adelphi study (UK cohort)	████	3.85	████	████
38	AE disutilities are based on Sullivan <i>et al.</i> 2011, disutility and duration for dizziness, fatigue, influenza, nasopharyngitis and pyrexia are set to 0	████	4.21	████	████
39	Duration of infusion is based on data in CS	████	4.12	████	████
40a	Disutility of administration is based on Jørgensen <i>et al.</i> 2017 only	████	3.84	████	████

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30k)
40b	Disutility of administration is based on Jørgensen <i>et al.</i> 2017, and includes only the coefficient for route of administration	■	3.53	■	■
40c	Disutility of administration combining the coefficient for route from Jørgensen <i>et al.</i> 2017 and infusion duration from Matza <i>et al.</i> 2013	■	3.95	■	■
41	Disutility of IV administration is excluded	■	3.35	■	■
42	IVIg /SCIg split is informed by the Immunoglobulin Database Annual Report	■	4.06	■	■
43	All patients receiving efgartigimod are assumed to be on the weekly dosing regimen	■	4.26	■	■
44	Ig is only delivered in an outpatient setting	■	4.17	■	■
45	Funded transport is included for efgartigimod	■	4.26	■	■
46	All funded transport is excluded	■	4.26	■	■
47	Administration cost of SCIg is the same as efgartigimod	■	4.26	■	■
48	Standard GP costs are applied for a 10-minute appointment (£45)	■	4.26	■	■
49	Proportion requiring a mobility aid based on disaggregated data from the Adelphi study	■	4.26	■	■
50	ICU costs are aligned with the PSSRU cost for critical care	■	4.26	■	■
51	AE costs sourced from NHS reference costs	■	4.26	■	■
52	Implementation of EAG's clinical experts' advice on treatment setting, using NHS reference cost of GP visit as £45 for all AEs other than back pain and peripheral oedema	■	4.26	■	■
53	HRQoL impact on informal care is excluded	■	3.47	■	■
54	Cost of professional care is excluded	■	4.26	■	■
55	Patients have at most one caregiver for any health state, with the proportion requiring a caregiver informed by UK Adelphi dataset	■	3.77	■	■

	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NMB (£30k)
56	A three-month model cycle is applied for the first two years, followed by a six-month cycle length thereafter	■	4.35	■	■

Abbreviations: AE, Adverse event; aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, Chronic inflammatory demyelinating polyneuropathy; CQ, clarification question; CS, Company Submission; GP, General practitioner; HRQoL, health-related quality of life; ICER, Incremental cost-effectiveness ratio; ICU, Intensive care unit; Ig, Immunoglobulin; IVIg, Intravenous immunoglobulin; ITC, Indirect treatment comparison; IV, Intravenous; NHS, National Health Service; NMB, Net monetary benefit; PLEX, Plasma exchange; QALY, Quality-adjusted life year; SCIg, Subcutaneous immunoglobulin; SEE, Structured Expert Elicitation; WTP: Willingness-to-pay.

7.8 Results of EAG analyses with mixed population

7.8.1 EAG's exploratory analyses using the company's base case

Table 97. Results of EAG's exploratory analyses using company's base case (mixed population)

Exploratory analysis number	Scenario applied to company's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
0	Company base case	████	4.26	████	████	████
1a	Patient distribution between health states at baseline aligned with the baseline for the ADHERE run-in period for Ig-intolerant/refractory patients	████	4.26	████	████	████
1b	Patient distribution between health states at baseline aligned with the baseline for ADHERE Stage A for Ig-intolerant/refractory patients	████	4.26	████	████	████
2	Three-month cycle length is applied, and the probability of entering remission is applied for the first two years	████	4.08	████	████	████
3	Three-month cycle length is applied, with transition probabilities derived from adjusted six-month 'shift' data from ADHERE and ADHERE+	████	5.27	████	████	████
4	SCIg treatment is administered once per week in hospital (treatment delivered over 1 day)	████	4.26	████	████	████
5	All SCIg treatment is self-administered at home	████	4.26	████	████	████
6	All IVIg administrations take place in an outpatient setting	████	4.26	████	████	████
7	Informal caregiver utility decrements are sourced from the company's caregiver survey	████	3.50	████	████	████

Exploratory analysis number	Scenario applied to company's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
8	Professional care costs are only applied to patients in the very severe health state, assuming 35 hours of care per week	████	4.26	████	████	████

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; NHB, net health benefit; QALY, quality-adjusted life-year; SCIg, subcutaneous immunoglobulin.

7.8.2 EAG preferred assumptions: base case results

Table 98. Results using the EAG's preferred model assumptions (probabilistic analysis, mixed population)

Preferred assumption	Exploratory analysis number	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Company base case (post-clarification)	N/A	████	4.26	████	████	████
EAG corrections applied	N/A	████	4.27	████	████	████
Three-month cycle length applied for first two years	N/A	████	4.47	████	████	████
Proportion of corticosteroids in alternative treatment basket sourced from company's chart review	N/A	████	4.44	████	████	████
Proportion of patients on PLEX who return to Ig: 95%	N/A	████	4.36	████	████	████
Assume 95% of cohort restarts Ig after discontinuation of efgartigimod	N/A	████	4.12	████	████	████
Proportion of patients on each Ig dose sourced from company's chart review (final data cut)	N/A	████	4.09	████	████	████

Preferred assumption	Exploratory analysis number	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Ig-intolerant/refractory patients distributed according to baseline distribution from ADHERE run-in at model baseline	1a	████	4.09	████	████	████
Patients do not move between aINCAT categories in the comparator arm	N/A	████	2.05	████	████	████
Patients in the severe and very severe aINCAT categories do not move to other health states	N/A	████	1.70	████	████	████
Half of patients move to a more severe health state following relapse	N/A	████	1.80	████	████	████
Remission is applied in the first two years	2	████	1.91	████	████	████
Transition probabilities are derived from adjusted six-month probabilities	3	████	1.97	████	████	████
Unplanned discontinuation of Ig is not included	N/A	████	2.18	████	████	████
AEs excluded for all treatments	N/A	████	2.11	████	████	████
AEs for IV administrations are excluded	N/A	████	2.10	████	████	████
HSUV in the very severe health state is set to 0	N/A	████	2.09	████	████	████
Duration of Ig infusions based on data in the CS	N/A	████	1.96	████	████	████
Disutility of IV administration based on Jørgensen <i>et al.</i> 2017 and considering only the coefficient for route of administration	N/A	████	1.50	████	████	████
IVIg/SCIg split informed by the Immunoglobulin Database Annual Report	N/A	████	1.47	████	████	████
Ig and efgartigimod patients require funded transportation	N/A	████	1.47	████	████	████
Administration cost for SCIg set equal to efgartigimod	N/A	████	1.47	████	████	████
SCIg treatment is administered once per week in hospital	4	████	1.47	████	████	████
IVIg is administered in an outpatient setting	6	████	1.47	████	████	████

Preferred assumption	Exploratory analysis number	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Duration of GP surgery consultation is set to 10 minutes	N/A	████	1.47	████	████	████
Proportion of patients requiring a wheelchair is informed by the company's Adelphi study, disaggregated by aINCAT score	N/A	████	1.47	████	████	████
Cost of ICU visit sourced from PSSRU	N/A	████	1.47	████	████	████
Professional care costs excluded	N/A	████	1.47	████	████	████
Patient requirements for caregivers aligned with UK Adelphi study data, with maximum 1 caregiver	N/A	████	1.31	████	████	████
Caregiver utility decrement sourced from company caregiver survey	7	████	1.22	████	████	████
EAG's base case	-	████	1.22	████	████	████

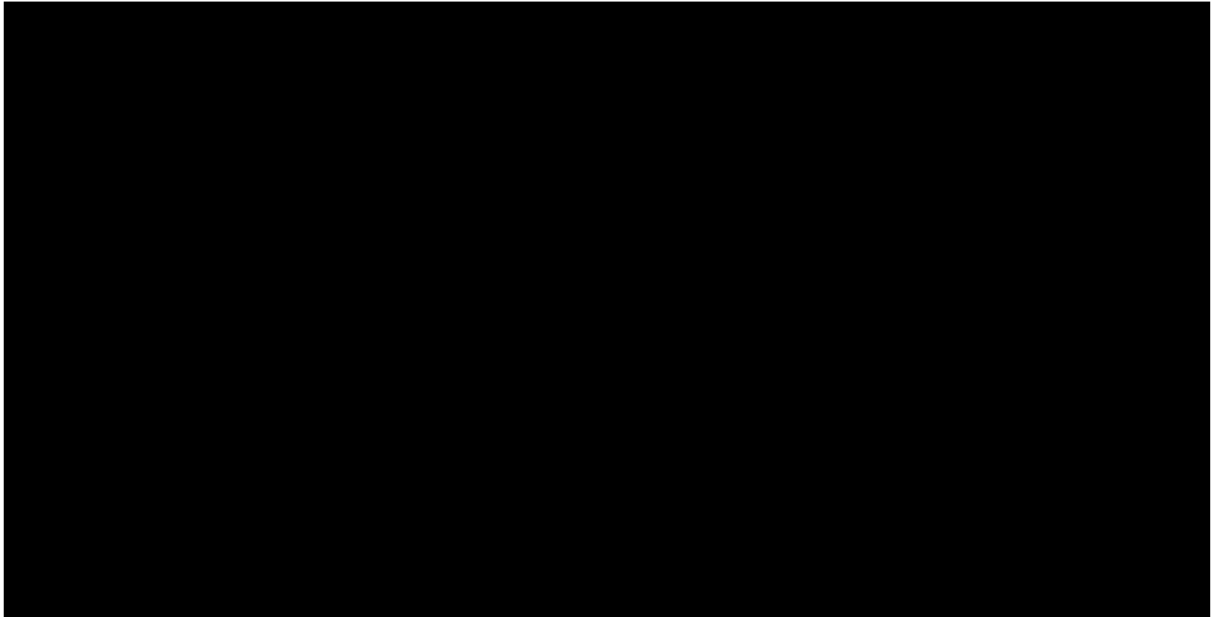
Abbreviations: AE, adverse event; aINCAT, Adjusted Inflammatory Neuropathy Cause and Treatment; CS, company submission; EAG, External Assessment Group; GP, general practitioner; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; Ig, immunoglobulin; IV, intravenous; IVIg, intravenous immunoglobulin; NHB, net health benefit; PLEX, plasma exchange; PSSRU, Personal Social Services Research Unit; QALY, quality adjusted life year; SCIg, subcutaneous immunoglobulin.

Table 99. EAG base case results (mixed population)

Interventions	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Deterministic results							
Current management	████	6.10	-	-	-	-	-
Efgartigimod	████	7.32	████	1.22	████	████	████
Probabilistic results							
Current management	£1,075,403	6.43	-	-	-	-	-

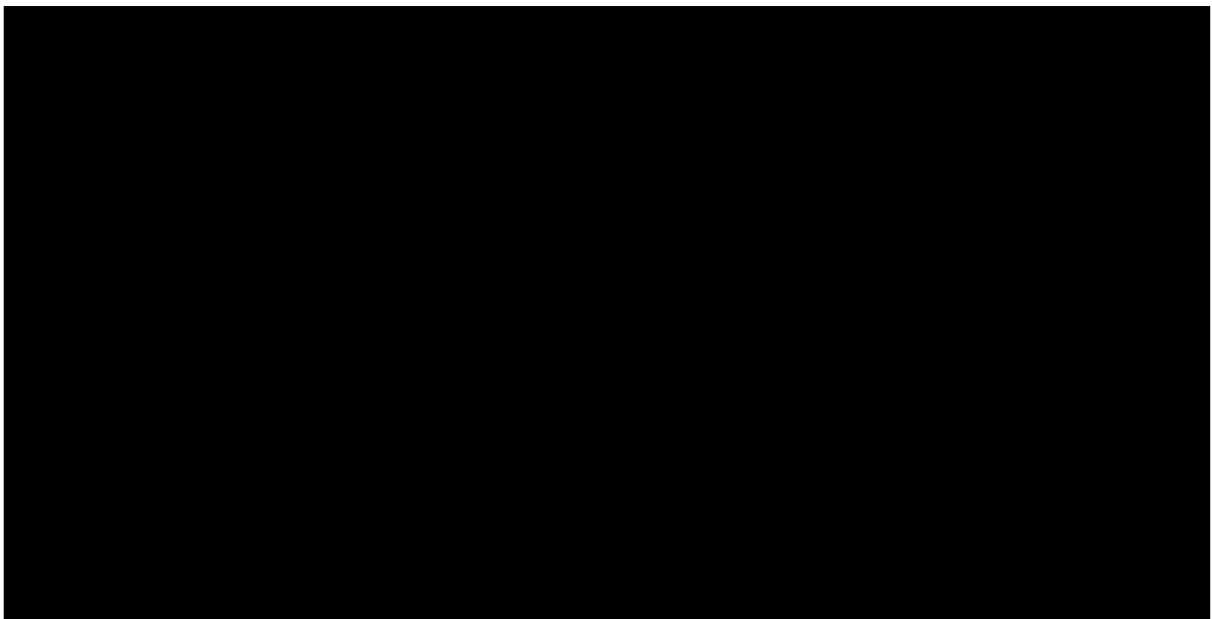
Interventions	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
Efgartigimod	■	7.59	■	1.17	■	■	■
Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; LY, life year; NHB, net health benefit; QALY, quality-adjusted life-year							

Figure 24. Cost-effectiveness plane, mixed population



Abbreviations: CE, cost-effectiveness; Ig, immunoglobulin; QALY, quality-adjusted life year.

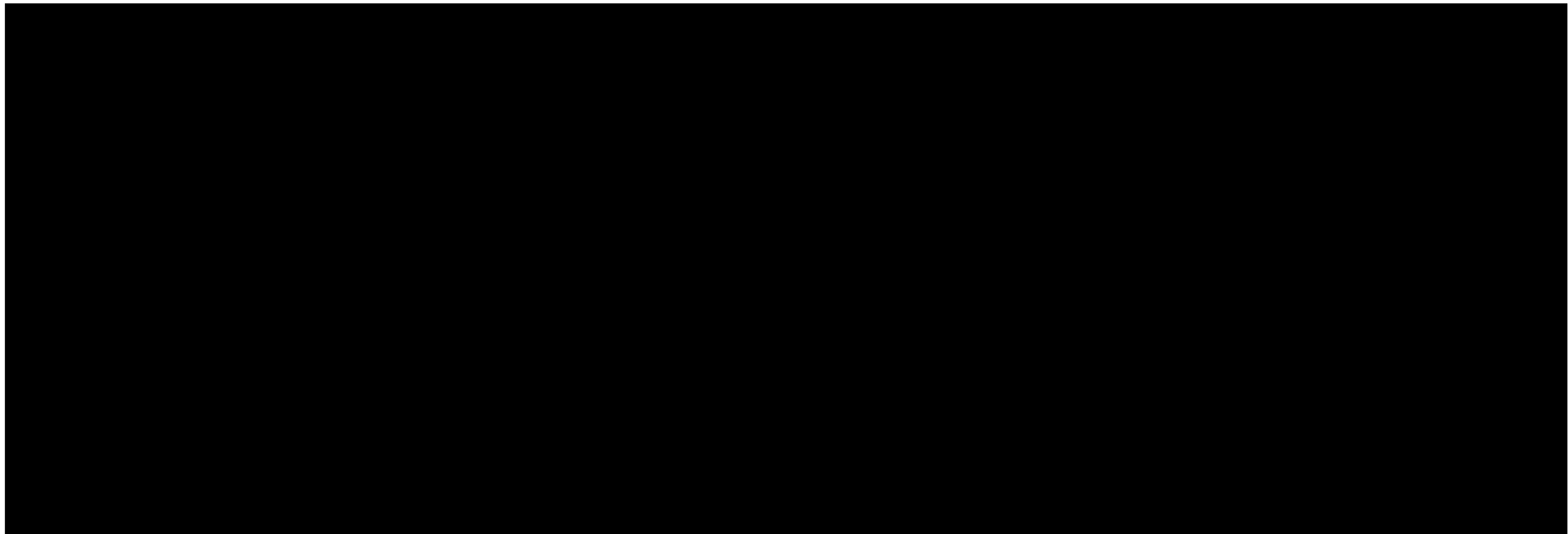
Figure 25. Cost-effectiveness acceptability curve, mixed population



Abbreviations: QALY, quality-adjusted life year; WTP, willingness-to-pay.

7.8.3 EAG preferred assumptions: deterministic sensitivity analyses

Figure 26. Tornado plot of deterministic sensitivity analysis incremental NHB (mixed population)



Abbreviations: Ig, immunoglobulin; IVIg, intravenous immunoglobulin; NHB, net health benefit; Q2W, once every two weeks; QALY, quality-adjusted life year.

7.8.4 Scenario analyses using EAG's preferred assumptions

Table 100. Results of EAG's exploratory analyses using EAG's preferred assumptions (Ig maintenance population)

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
0	EAG base case	■	1.22	■	■	■
1	2-year time horizon used	■	0.16	■	■	■
2a	Post-efgartigimod discontinuation, the same distribution as post-Ig discontinuation is applied	■	2.07	■	■	■
2b	Post-efgartigimod discontinuation, the cohort is distributed based on the company's SEE	■	1.80	■	■	■
2c	Post-efgartigimod discontinuation, the cohort is distributed based on the upper bound from the SEE	■	1.64	■	■	■
2d	Post-efgartigimod discontinuation, a majority of patients are assumed to go back into the same treatment as before starting efgartigimod (i.e. 60% Ig and 40% alternative basket of treatment)	■	1.54	■	■	■
3a	Distribution of treatments in the alternative treatment basket is obtained from the company's SEE	■	1.22	■	■	■
3b	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	■	1.22	■	■	■
3c	Assuming 25% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort is redistributed equally among other treatments.	■	1.22	■	■	■

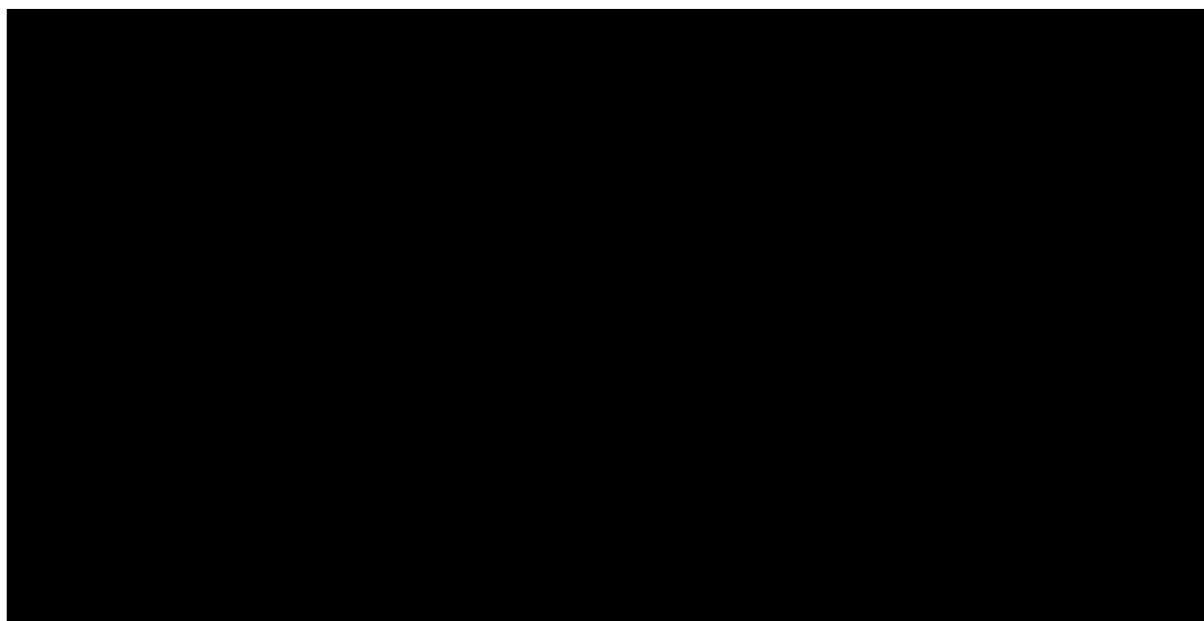
Scenario analysis number	Scenario applied to EAG's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
3d	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and the percentage of the other treatments is obtained from the SEE with the residual redistributed equally among them.	■	1.22	■	■	■
3e	Assuming 0% of cohort in the alternative treatment basket is on corticosteroids and 75% of cohort redistributed equally among other treatments.	■	1.22	■	■	■
4a	10% of Ig maintenance patients on PLEX return to Ig	■	1.22	■	■	■
4b	30% of Ig maintenance patients on PLEX return to Ig	■	1.22	■	■	■
4c	60% of Ig maintenance patients on PLEX return to Ig	■	1.22	■	■	■
5	Baseline distribution from ADHERE Stage A used for baseline distribution across health states for Ig-refractory and Ig-intolerant patients	■	1.22	■	■	■
6	No patients deteriorate to worse disease severity upon relapse	■	1.11	■	■	■
7	HSUVs are informed by the company's regression model for all health states	■	1.23	■	■	■
8a	Disutility of IV administration is based on all coefficients from Jørgensen <i>et al.</i> 2017 and Matza <i>et al.</i> 2013	■	1.60	■	■	■
8b	Disutility of IV administration is excluded	■	1.10	■	■	■
9	All patients receive once weekly dose of efgartigimod in the model	■	1.22	■	■	■
10	All SCIg treatment is self-administered at home	■	1.22	■	■	■
11	Funded transport costs are excluded from the model	■	1.22	■	■	■

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental NHB (£20,000/QALY)	Incremental NHB (£30,000/QALY)
12	HRQoL impact on informal care is excluded and costs for professional care are included	■	1.20	■	■	■
13	Professional care costs are only applied to patients in the very severe health state, assuming 35 hours of care	■	1.22	■	■	■
14	The caregiver utility decrement is informed by Gani <i>et al.</i> 2008	■	1.31	■	■	■

Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; IV, intravenous; NHB, net health benefit; PLEX, plasma exchange; QALY, quality-adjusted life year; SCIg, subcutaneous immunoglobulin; SEE, structured expert elicitation

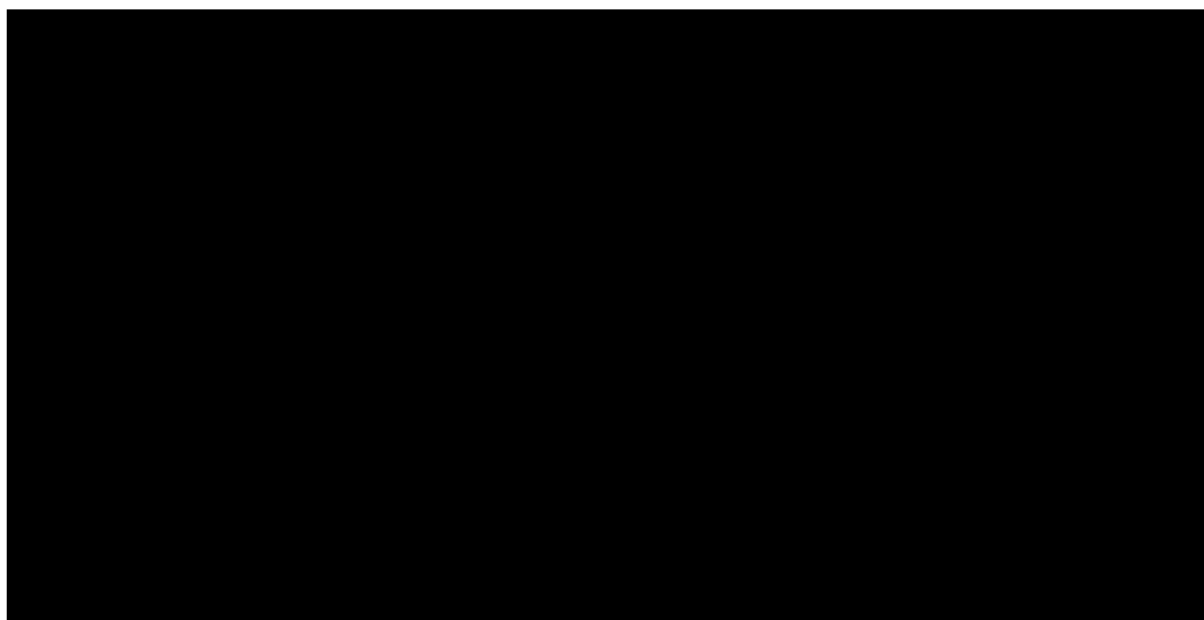
7.9 Probabilistic analysis convergence plots

Figure 27. ICER convergence plot, Ig maintenance population



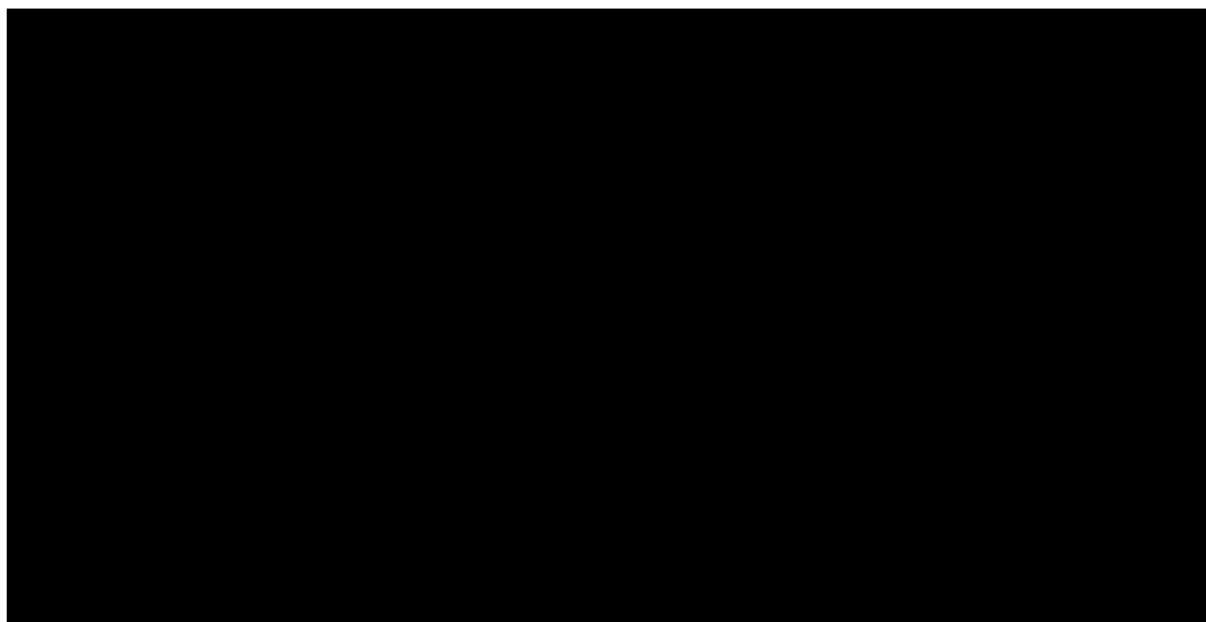
Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; PSA, probabilistic sensitivity analysis.

Figure 28. ICER convergence plot, Ig-intolerant/refractory population



Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; PSA, probabilistic sensitivity analysis.

Figure 29. ICER convergence plot, mixed population



Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; PSA, probabilistic sensitivity analysis.

Single Technology Appraisal

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy [ID6409]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 13 February 2026** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as ‘**depersonalised data**’ in pink.

Issue 1 Missing or incorrect information

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 22, page 53, EAG comment column EAG comments that “...some of the patients included in the company’s proposed population, such as those who are intolerant or refractory to Ig, were not included in the ADHERE trial.”	New text proposed: <i>“However, it notes that some of the patients included in the company’s proposed population, such as those who are intolerant or refractory to Ig, were not identified and examined as a subgroup in the ADHERE trial.”</i>	The wording suggests that these individuals were excluded from the trial, rather than not differentiated within the trial population.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Table 22, page 54, EAG comment column <i>“In addition, ADHERE did not include patients who were intolerant or refractory to Ig, preventing an assessment of the effects of efgartigimod for these patients.”</i>	Remove this sentence.	The wording suggests that these individuals were excluded from the trial, which is incorrect.	Thank you for highlighting this factual inaccuracy. The wording of this section has been updated to <i>“In addition, it was not possible to identify which patients were intolerant or refractory to Ig, preventing an assessment of the effects of efgartigimod for these patients.”</i>
Section 2.3.1, page 56, final paragraph	Amend text (delete EAG opinion) to read:	The wording suggests that these individuals were	Thank you for highlighting this factual inaccuracy. The

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>“While some of these patients could be refractory or intolerant to Ig, this information was not recorded as part of the ADHERE trial, and the EAG considers it unlikely that this group is represented in the current evidence base.”</i>	<i>“While some of these patients could be refractory or intolerant to Ig, this information was not recorded as part of the ADHERE trial.”</i>	excluded from the trial, which is incorrect.	proposed amendment has been made to the report.
Table 26, page 77, rows titled: “Ongoing in Stage A at 88th relapse event in Stage B” and “Discontinued early for other reasons” Table 26 in the EAG report does not accurately reproduce the corresponding Table 11 in the CS; the final two rows of the EAG table are incorrect. In the CS, Table 10 presents confirmed ECI responders in Stage A by prior CIDP therapy (Stage A safety analysis set), whereas Table 11 presents confirmed ECI responders in	The penultimate row of Table 26 in the EAG report should be removed. The “discontinued early for other reasons” row should be amended to align exactly with the values reported in Table 11 of the CS (Stage A safety analysis set excluding participants ongoing in Stage A at the 88th relapse event in Stage B). Replace with the corrected Table 26 of the EAG report as shown below:	The current Table 26 in the EAG report does not accurately reflect the data presented in the CS.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.

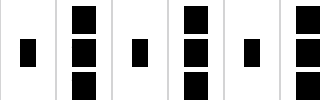
Description of problem	Description of proposed amendment					Justification for amendment	EAG response
Stage A by prior CIDP therapy in the Stage A safety analysis set excluding participants who were ongoing in Stage A at the time of the 88th relapse event in Stage B. Table 26 in the EAG report appears to conflate these two analysis sets.		An y pri or the rap y N= 30 4 n (%)	Cortico steroids n=59 n (%)	IV lg or S CI g n= 15 8 n (%))	Off treat men t n=8 7 n (%)		
	Numb er of parti pants with confir med ECI	21 4 (70)	49 (83)	97 (6 1)	68 (78)		
	95% CI	64. 9- 75. 5	71.0- 91.6	53 .3- 69 .0	68.0 - 86.3		
	Numb er of parti	90 (30)	10 (17)	61 (3 9)	19 (22)		

Description of problem	Description of proposed amendment					Justification for amendment	EAG response
	pants without confirmed ECI						
	Completed Stage A treatment without confirmed ECI	21 (7)	2 (3.4)	8 (5)	11 (13)		
	Discontinued treatment in Stage A	69 (23)	8 (14)	53 (34)	8 (9)		
	Discontinued early for other	69 (23)	8 (14)	53 (34)	8 (9)		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response														
	reasons Source: Clinical Study Report ARGX-113-1802¹³¹ Abbreviations: CI, confidence interval; ECI, evidence of clinical improvement; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.																
Table 30, page 87 under the subheading “Change in I-RODS score from ADHERE+ baseline”, row titled “Patients who experienced clinical deterioration during ADHERE” The number of patients (n) reported in the efgartigimod column and the “all participants” column are incorrect and do not align with Table 10 of the clarification questions document.	Amend the n values in this row so that the efgartigimod column reports n = 27 and the “all participants” column reports n = 83, consistent with Table 10 of the clarification questions document. The corrected EAG Table 30 section is provided below: Change in I-RODS score from ADHERE+ baseline <table><tr><td>Patients who completed Week</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td></td><td>■</td><td>■</td><td>■</td><td>■</td><td>■</td><td>■</td></tr></table>	Patients who completed Week								■	■	■	■	■	■	The reported n values do not reflect the source data in Table 10 of the clarification questions document. Correcting these values will ensure accurate and consistent reporting for this subgroup.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Patients who completed Week																	
	■	■	■	■	■	■											

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	48 of ADHERE		
	Patients who experienced clinical deterioration during ADHERE		
	Patients ongoing in ADHERE at the stopping point in the trial		

Table 30, page 87, under the subheading “Change in MGS (dominant hand, kPa) from ADHERE+ baseline”, row titled “Patients who experienced clinical deterioration during ADHERE” The values reported in this row are incorrect. It appears that, when populating the table using Table 10 of the clarification questions document, data from the non-dominant hand were inadvertently used instead of the dominant hand data.	Replace the values in this row with the correct data for “Change in mean grip strength (dominant hand, kPa) from ADHERE+ baseline – Patients who experienced clinical deterioration during ADHERE” as reported in Table 10 of the clarification questions document. The corrected table section is provided below: <table><tr><th colspan="7">Change in MGS (dominant hand, kPa) from ADHERE+ baseline</th></tr><tr><td>Patients who completed Week 48 of ADHERE</td><td>■</td><td>■</td><td>■</td><td>■</td><td>■</td><td>■</td></tr><tr><td>Patients who experienced clinical deterioration</td><td>■</td><td>■</td><td>■</td><td>■</td><td>■</td><td>■</td></tr></table>	Change in MGS (dominant hand, kPa) from ADHERE+ baseline							Patients who completed Week 48 of ADHERE	■	■	■	■	■	■	Patients who experienced clinical deterioration	■	■	■	■	■	■	The current values do not align with Table 10 of the clarification questions document and appear to reflect non-dominant hand data. Updating the row will ensure consistency with the source data and accurate reporting.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Change in MGS (dominant hand, kPa) from ADHERE+ baseline																								
Patients who completed Week 48 of ADHERE	■	■	■	■	■	■																		
Patients who experienced clinical deterioration	■	■	■	■	■	■																		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	deterioration during ADHERE Patients ongoing in ADHERE at the stopping point in the trial 		
Section 3.6.1; page 95, 2nd bullet point <i>“Patients in ADVANCE-CIDP-1 were not assessed for their response to SCIg prior to comparisons with placebo”</i>	New text proposed: <i>“Patients in ADVANCE-CIDP-1 were required to have previously responded to IgG treatment and were receiving a stable dose of IVIG treatment for ≥12 weeks before screening”</i>	The wording suggests that patients in ADVANCE-CIDP-1 were not assessed for their response status, which is incorrect.	Thank you for highlighting this factual inaccuracy. The wording of this section has been updated to <i>“Patients in ADVANCE-CIDP-1 were required to have previously responded to IgG treatment and were receiving a stable dose of IVIg treatment for ≥12 weeks before screening, but</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			<i>enrolment in the RCT was not based on how well they responded to SCIg</i> ".
Section 3.6.1; page 99, 2nd bullet point <i>"In ICE, patients were randomised to IVIg or placebo for 24 weeks. Following this period, non-responders were able to cross over to the alternative treatment for an additional 24 weeks."</i>	New text proposed: <i>"In ICE, patients were randomised to IVIg or placebo for 24 weeks. Non-responders were required to switch to the alternative treatment if they did not show any response by Week 6 or if they had deteriorated at any time point during the 24-week period."</i>	The wording excluded a criterion for requiring patients to switch treatment during the 24-week period.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Section 3.6.2.1; page 100 <i>"As discussed in Section 3.2.1, only efgartigimod responders were included in the RCT phase of ADHERE, which may have resulted in an overestimation of the treatment effect compared to the standard RCT</i>	Remove this sentence.	The EAG state that only efgartigimod responders were included in the RCT phase of ADHERE, whereas ADVANCE-CIDP-1 also included patients who were explicitly required to have responded to Ig.	This is not a factual accuracy; no change is required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>methodology used in ADVANCE-CIDP.”</i>			
Section 3.6.2.1; page 101, table 34 The EAG outlines the prognostic factors and treatment effect modifiers identified by the company’s clinical experts. The table states that ‘total INCAT’ was not adjusted for in the ITC analysis.	Remove ‘total INCAT’ from the table.	The total INCAT score at baseline was included in the ITC.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Section 3.6.2.1; page 105, <i>“Other covariates included in the regression model, but not included in the MAIC were baseline age, percentage male, I-RODS, MRC sum score and proportion on prior corticosteroids.”</i>	Replace the text with: <i>“Other covariates included in the MAIC but not included in the regression model were baseline age, percentage male, I-RODS, MRC sum score and proportion on prior corticosteroids.”</i>	Incorrect reporting of the regression model and MAIC.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
Section 3.6.2.1; page 106, Table 38	Remove this data due to it being incorrectly reported.	The SEE numbers reported in this table refer to the re-weighted efgartigimod arm,	Thank you for highlighting this factual inaccuracy. The

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Weighted ESS, n (%) column. This column reports the change from baseline in the unweighted and weighted placebo arm of ADHERE and the comparator trials.	The values described are the ESS of the full sample used in the full MAIC analyses (i.e., including Ig-pre-treated patients in both efgartigimod and placebo arm of ADHERE). They are not the ESS of the placebo arm.	not the re-weighted placebo arm. This is incorrect.	proposed amendment has been made to the report.
EAG model: Sheet: Transition_probabilities Cells: V19, W20, X21, V34, W35, X36, V49, W50, X51, V64, W65, X66, V92, W93, X94, V107, W108, X109, V122, W123, X124, V137, W138, X139, AH19, AI20, AJ21, AH34, AI35, AJ36, AH49, AI50, AJ51, AH64, AI65, AJ66, AH92, AI93, AJ94, AH107, AI108, AJ109, AH122, AI123, AJ124, AH137, AI138, AJ139	The EAG has calculated the probability of remaining stable in remission as (1-m_prob_remission), which corresponds to the probability of remaining in active disease, not of remaining in remission. The probability of remaining in remission should be calculated as (1-m_prob_relapse), i.e., the complement of the probability of relapsing.	Incorrect formula.	Thank you for highlighting this error in the model. The EAG has corrected this error, and has updated results for the economic analysis in the report and confidential appendix.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG model: Sheet: Transition_probabilities Cells: Q29:X36, Q44:X51, Q59:X66, Q87:X94, Q102:X109, Q117:X124, Q132:X139, AC29:AJ36, AC44:AJ51, AC59:AJ66, AC87:AJ94, AC102:AJ109, AC117:AJ124, AC132:AJ139	The EAG proposed formulas to include probability of remission during the first 2 years (when 3-month cycles are used) fail to account for lack of remission in scenarios investigating Ig dependent populations. The company believes that this is a key error with considerable impact on the results under these scenarios. The company suggests that the formulas in all 3-month transition probability matrices (apart from the first TPs for the intervention arm), are corrected to exclude remission when scenarios with Ig-dependent and ultra-high-Ig-dose-dependent patients are selected.	Incorrect modelling of the EAG scenarios.	The EAG has not updated the model since the EAG does not consider the subgroups affected to be key subgroups, and the scenario analyses mentioned by the company were not included in the report (beyond reproducing the company's original subgroup analysis results). Furthermore, the proposed changes would not affect results for these scenario analyses applied to either the EAG or the company base case, as the company's three-month transition probabilities are not used in either base case. Therefore, the EAG does not consider that it is necessary to make any amendments to the model or report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG model Sheet: Efgartigimod_responders Cells: N13:R123, N130:R240, N247:R357, N374:R474	When 3-month cycles are used for the first 2 years, the EAG-proposed formulas to adjust the mortality for the shorter (3 months) cycle duration lead to a 2-fold increase in mortality during each of the first 8 cycles.	Incorrect formula.	The EAG would like to clarify that the formulae for per-cycle general population mortality were adjusted to account for the change from a six-month to a three-month cycle length (i.e., the time period for which the mortality probability was calculated was adjusted). The hazard used to calculate the probability has not been changed. The EAG also considers that it is more appropriate to adjust the mortality probability in the trace sheets than in the Mortality_data sheet, as this allows flexibility to use differing cycle lengths and baseline ages.
EAG model Sheet: Efgartigimod_non_responders Cells: N12:R122, N129:R239, N246:R356	The company is unable to understand the logic behind the formula, which multiplies the hazard ratio for mortality by two. It is unclear why a different cycle duration should impact the hazard of death of CIDP patients vs the general population.		
EAG model Sheet: Comparator Cells: N12:R122, N129:R239	The company believes that, if mortality is adjusted for a shorter cycle length, then the probability of death should decrease rather than increasing. Also, the HR of CIDP patients vs general population should remain not		However, the EAG acknowledges that there was an error in the implementation of the relevant formulae; when three-month cycles are used, the mortality probability

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	change for different cycle durations The company believes that the correct approach to adjust the probability of death for different cycle duration is to adjust the general population probability in the Mortality_data sheet, without any change to the patients' HR of death.		formula should multiply the hazard (which is expressed in six-month units) by 0.5 rather than by 2. The EAG has corrected this error in the model, and updated the results in the report and confidential appendix.

Issue 2 Requests to clarify ambiguous wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.4.3; page 127 <i>“The EAG does not consider the approach to modelling the treatment pathway to be appropriate, for several reasons. Firstly, the EAG considers that for the Ig maintenance cohort, the proportion of patients returning to treatment with Ig after discontinuing efgartigimod is implausibly low.”</i>	Update the text to say: <i>“The EAG does not consider the approach to modelling the treatment pathway to be appropriate, for several reasons. Firstly, the EAG considers that for the Ig maintenance cohort for the intervention arm....”</i>	Greater clarity should be provided to show which treatment arm is being described.	The EAG does not consider the statement ambiguous; no change is required.
Section 4.2.7.2; page 134, 1 st bullet point (1) <i>“A new set of shift data was generated for patients who would experience a one point greater improvement in aINCAT CfB...”</i>	Update the text to say: <i>“A new set of shift data was generated for patients who would experience a one-point greater change....”</i>	Incorrect terminology was used.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report. The text immediately preceding the numbered list has also been updated to align with this amendment.
Section 4.2.7.2; page 134, 1 st bullet point	Update the text to say:	Incorrect description.	Thank you for highlighting this factual inaccuracy. The proposed amendment has

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>“In aINCAT CfB if they were treated with efgartigimod rather than Ig”</i>	<i>“In aINCAT CfB if they were treated with Ig rather than efgartigimod”</i>		been made to the report. The text immediately preceding the numbered list has also been updated to align with this amendment.

Issue 3 Markings that are incorrect or require updating

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 43 Marking relating to marketing authorisation indication Marking relating to marketing authorisation indication: “as monotherapy for the treatment of adult patients with progressive or relapsing active CIDP after prior treatment with corticosteroids or immunoglobulins”.	This can be unredacted as the marketing authorisation has been granted in the UK and the indication wording is in the public domain.	“as monotherapy for the treatment of adult patients with progressive or relapsing active CIDP after prior treatment with corticosteroids or immunoglobulins”.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 55 Marking related to marketing authorisation indication: “adult patients with progressive or relapsing active CIDP after prior treatment with corticosteroids or Igs”.	This can be unredacted as the marketing authorisation has been granted in the UK and the indication wording is in the public domain.	“adult patients with progressive or relapsing active CIDP after prior treatment with corticosteroids or Igs”.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 58 Marking related to marketing authorisation summary of product characteristics (SmPC): “treatment is initiated before the clinical effect of any prior therapies starts to decrease.”	This can be unredacted as the summary of product characteristics (SmPC) is now available in the public domain.	“treatment is initiated before the clinical effect of any prior therapies starts to decrease.”	Thank you for highlighting this factual inaccuracy. The proposed amendment has been made to the report.
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 76 Markings on the following text on page 76: “A pre-specified sensitivity analysis excluding the 18 participants who were ongoing in Stage A at study completion (after the 88th relapse in Stage B) resulted in a higher percentage (70% (n=214/304) [95% CI: 64.9% to 75.5%]) of all participants in Stage A with confirmed ECI (CS Table 11). A	The company has elected to unredact the data presented in this excerpt, and the EAG report can be updated accordingly to reflect these changes.	ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 76 Markings on the following text on page 76: “A pre-specified sensitivity analysis excluding the 18 participants who were ongoing in Stage A at study completion (after the 88th relapse in Stage B) resulted in a higher percentage (70% (n=214/304) [95% CI: 64.9% to 75.5%]) of all participants in Stage A with confirmed ECI (CS Table 11).	Thank you for highlighting this change. The proposed amendments have been made to the report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
smaller proportion of patients (61%) demonstrated confirmed ECI with efgartigimod when only the subgroup of patients with prior IVIg or SCIg treatment was considered.” “Based on the results in Error! Reference source not found., the EAG considers it important to note that a substantial proportion of patients in the pre-specified sensitivity analysis (██████ of all patients and ██████ those who received IVIg or SCIg prior to enrolment in ADHERE).”		A smaller proportion of patients (61%) demonstrated confirmed ECI with efgartigimod when only the subgroup of patients with prior IVIg or SCIg treatment was considered.” “Based on the results in Table 26, the EAG considers it important to note that a substantial proportion of patients in the pre-specified sensitivity analysis (30% of all patients and 39% those who received IVIg or SCIg prior to enrolment in ADHERE).”	

ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 77, Table 26	The company has elected to unredact the data presented in Table 26, and the EAG report can be updated accordingly to reflect these changes.		An y pri or the rap y N= 30 4 n (%)	Cortico steroids n=59 n (%)	IV lg or S CI g n= 15 8 n (%)	Off treat men t n=8 7 n (%)
		Numb er of parti cips with confir med ECI	21 4 (70)	49 (83)	97 (6 1)	68 (78)
		95% CI	64. 9- 75. 5	71.0- 91.6	53 .3- 69 .0	68.0 - 86.3
		Numb er of parti cips withou t	90 (30)	10 (17)	61 (3 9)	19 (22)

		con- fir- med ECI					
		Com- pl- eted Stage A treat- ment with- out con- fir- med ECI	21 (7)	2 (3.4)	8 (5)	11 (13)	
		Dis- con- tinued treat- ment in Stage A	69 (23)	8 (14)	53 (3 4)	8 (9)	
		Dis- con- tinued early for other reason s	69 (23)	8 (14)	53 (3 4)	8 (9)	
		Source: Clinical Study Report ARGX-113-1802 ¹³¹ Abbreviations: CI, confidence interval; ECI, evidence of clinical improvement; IVIg,					

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.	
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 77 Markings on the following text on page 77: “The median time to initial confirmed ECI with efgartigimod in Stage A was 43.0 (95% CI: 31.0 to 51.0) days and 40% of patients had ECI by week 4 (n=128).”	The company has elected to unredact the data presented in this excerpt, and the EAG report can be updated accordingly to reflect these changes.	“The median time to initial confirmed ECI with efgartigimod in Stage A was 43.0 (95% CI: 31.0 to 51.0) days and 40% of patients had ECI by week 4 (n=128).”	Thank you for highlighting this change. The proposed amendment has been made to the report.
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 78, Table 27	The company has elected to unredact some of the data presented in Table 27, and the EAG report can be updated accordingly to reflect these changes.	Secondary endpoint	Thank you for highlighting this change. The proposed amendments have been made to the report.
		aINCAT	
		N	
		Mean change from baseline (SD)	-0.9 (1.71)
		Median change from baseline (min, max)	
		I-RODS score	
		N	
		Mean change from baseline (SD)	7.7 (15.48)
		Median change from baseline (min, max)	
		MGS (dominant hand), kPa	

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		N	
		Mean change from baseline (SD)	
		Median change from baseline (m	
		MGS (non-dominant hand), kPa	
		N	
		Mean change from baseline (SD)	
		Median change from baseline (m	
		MRC sum score mean change from baseli	
		TUG test score mean change from baselin	
		EQ-5D-5L VAS	
		n	
		Change from baseline (SE)	
		Source: Clinical Study Report ARGX-113-1802 ¹	
		Abbreviations: aINCAT, Adjusted Inflammatory of Life 5 Dimensions Visual Analogue Scale; I-R mean grip strength; MRC, Medical Research Co	

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 80 Markings on the following text on page 80: “was seen in the prior treatment with IVIg or SCIg (HR 0.30 [95% CI: 0.15 to 0.57] and corticosteroid subgroups (HR 0.29 [95% CI: 0.11 to 0.81])). The difference in the baseline off-treatment subgroup was substantially smaller, with a non-statistically significant difference between efgartigimod and placebo (HR 0.72 [95% CI: 0.34 to 1.53]).”	The company has elected to unredact the data presented in this excerpt, and the EAG report can be updated accordingly to reflect these changes.	“was seen in the prior treatment with IVIg or SCIg (HR 0.30 [95% CI: 0.15 to 0.57] and corticosteroid subgroups (HR 0.29 [95% CI: 0.11 to 0.81])). The difference in the baseline off-treatment subgroup was substantially smaller, with a non-statistically significant difference between efgartigimod and placebo (HR 0.72 [95% CI: 0.34 to 1.53]).”	Thank you for highlighting this change. The proposed amendments have been made to the report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 84 Markings on the following text on page 84: “the company reported that [REDACTED]	The company has elected to unredact the data presented in this excerpt, and the EAG report can be updated accordingly to reflect these changes.	“the company reported that 200 patients enrolled in ADHERE+ from Stage B (although 1 of these did not receive treatment in ADHERE+), and the remaining patients came directly from the run-in phase (n=7) or Stage A (n=22) as they were still ongoing in these earlier phases when the 88th relapse event occurred in Stage B leading to termination of ADHERE.”	Thank you for highlighting this change. The proposed amendments have been made to the report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 89 Markings on the following text on page 89: “The EAG notes that there was a [REDACTED] of ECI responders with efgartigimod in the subgroup of patients with unstable disease activity (CDAS score of 5) than those with stable disease activity (CDAS score of 2 to 4) ([REDACTED] [REDACTED] respectively).”	The company has elected to unredact the data presented in this excerpt, and the EAG report can be updated accordingly to reflect these changes.	“The EAG notes that there was a higher percentage of ECI responders with efgartigimod in the subgroup of patients with unstable disease activity (CDAS score of 5) than those with stable disease activity (CDAS score of 2 to 4) (73.6% vs 55.2%, respectively).”	Thank you for highlighting this change. The proposed amendments have been made to the report.
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 90 Markings on the following text on page 90: “[REDACTED] compared to those with >6 years since first	The company has elected to unredact the data presented in this excerpt, and the EAG report can be updated accordingly to reflect these changes.	“[72.2% responded] compared to those with >6 years since first diagnosis [55.2% responded]).”	Thank you for highlighting this change. The proposed amendments have been made to the report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response																																																				
diagnosis [REDACTED] responded]).”																																																							
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 90, Figure 9	The company has elected to unredact Figure 9, and the EAG report can be updated accordingly to reflect these changes.	<table><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td>Region</td><td>NORTH-AMERICA (N=4)</td></tr><tr><td></td><td>ASIA (N=87)</td></tr><tr><td></td><td>EUROPE (N=130)</td></tr><tr><td></td><td>REST OF WORLD (N=57)</td></tr><tr><td>CDAS</td><td>2 - 4 (N=125)</td></tr><tr><td></td><td>5 (N=197)</td></tr><tr><td>CIDP Disease Evolution</td><td>PROGRESSIVE (N=174)</td></tr><tr><td></td><td>RELAPSING (N=147)</td></tr><tr><td>Adjusted INCAT at Stage A baseline</td><td>0-<=3 (N=90)</td></tr><tr><td></td><td>>3-<=6 (N=179)</td></tr><tr><td></td><td>>6 (N=48)</td></tr><tr><td>I-RODS at Stage A baseline</td><td>0-<=33 (N=94)</td></tr><tr><td></td><td>>33-<=66 (N=215)</td></tr><tr><td></td><td>>66 (N=12)</td></tr><tr><td>MGS Dominant Hand at Stage A baseline</td><td>0-<=40 kPa (N=173)</td></tr><tr><td></td><td>>40-<=80 kPa (N=129)</td></tr><tr><td></td><td>>80 kPa (N=16)</td></tr><tr><td>MGS Non-dominant at Stage A baseline</td><td>0-<=40 kPa (N=170)</td></tr><tr><td></td><td>>40-<=80 kPa (N=129)</td></tr><tr><td></td><td>>80 kPa (N=19)</td></tr><tr><td>Time since Diagnosis</td><td>0-<=3 years (N=169)</td></tr><tr><td></td><td>>3-<=6 years (N=66)</td></tr><tr><td></td><td>>6 years (N=87)</td></tr></table>							Region	NORTH-AMERICA (N=4)		ASIA (N=87)		EUROPE (N=130)		REST OF WORLD (N=57)	CDAS	2 - 4 (N=125)		5 (N=197)	CIDP Disease Evolution	PROGRESSIVE (N=174)		RELAPSING (N=147)	Adjusted INCAT at Stage A baseline	0-<=3 (N=90)		>3-<=6 (N=179)		>6 (N=48)	I-RODS at Stage A baseline	0-<=33 (N=94)		>33-<=66 (N=215)		>66 (N=12)	MGS Dominant Hand at Stage A baseline	0-<=40 kPa (N=173)		>40-<=80 kPa (N=129)		>80 kPa (N=16)	MGS Non-dominant at Stage A baseline	0-<=40 kPa (N=170)		>40-<=80 kPa (N=129)		>80 kPa (N=19)	Time since Diagnosis	0-<=3 years (N=169)		>3-<=6 years (N=66)		>6 years (N=87)	Thank you for highlighting this change. The proposed amendment has been made to the report.
Region	NORTH-AMERICA (N=4)																																																						
	ASIA (N=87)																																																						
	EUROPE (N=130)																																																						
	REST OF WORLD (N=57)																																																						
CDAS	2 - 4 (N=125)																																																						
	5 (N=197)																																																						
CIDP Disease Evolution	PROGRESSIVE (N=174)																																																						
	RELAPSING (N=147)																																																						
Adjusted INCAT at Stage A baseline	0-<=3 (N=90)																																																						
	>3-<=6 (N=179)																																																						
	>6 (N=48)																																																						
I-RODS at Stage A baseline	0-<=33 (N=94)																																																						
	>33-<=66 (N=215)																																																						
	>66 (N=12)																																																						
MGS Dominant Hand at Stage A baseline	0-<=40 kPa (N=173)																																																						
	>40-<=80 kPa (N=129)																																																						
	>80 kPa (N=16)																																																						
MGS Non-dominant at Stage A baseline	0-<=40 kPa (N=170)																																																						
	>40-<=80 kPa (N=129)																																																						
	>80 kPa (N=19)																																																						
Time since Diagnosis	0-<=3 years (N=169)																																																						
	>3-<=6 years (N=66)																																																						
	>6 years (N=87)																																																						

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 91, Figure 10	The company has elected to unredact Figure 10, and the EAG report can be updated accordingly to reflect these changes.		Thank you for highlighting this change. The proposed amendment has been made to the report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 133 Markings on the following text on page 133: “The ITC suggested that the mean change in aINCAT from baseline to the end of study visit was 0.88 points greater for patients receiving efgartigimod than patients receiving Ig; since aINCAT is a discrete scale, the company assumed that this would be equivalent to 88% of patients achieving a one point greater improvement in aINCAT change from baseline (CfB) if they were hypothetically treated with efgartigimod rather than Ig, with the remainder of patients assumed to have the same response to efgartigimod and Ig.”	The statistics and outcomes describing the mean change in aINCAT score should be redacted as per NICE confidential marking guidelines, with the data having not being published.	The ITC suggested that the mean change in aINCAT from baseline to the end of study visit was 0.88 points greater for patients receiving efgartigimod than patients receiving Ig; since aINCAT is a discrete scale, the company assumed that this would be equivalent to 88% of patients achieving a one point greater improvement in aINCAT change from baseline (CfB) if they were hypothetically treated with efgartigimod rather than Ig, with the remainder of patients assumed to have the same response to efgartigimod and Ig.	Thank you for highlighting this change. The proposed amendments have been made to the report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; page 133 Markings on the following text on page 133: “The transition probabilities used for patients receiving comparator treatments in the model were calculated by taking a weighted average of the transition probabilities derived in Step 2, and the original transition probabilities for efgartigimod, with a weight of 88% given to the transition probabilities derived in Step 2.”	The statistics and outcomes describing the mean change in aINCAT score should be redacted as per NICE confidential marking guidelines, with the data having not being published.	The transition probabilities used for patients receiving comparator treatments in the model were calculated by taking a weighted average of the transition probabilities derived in Step 2, and the original transition probabilities for efgartigimod, with a weight of 88% given to the transition probabilities derived in Step 2.	Thank you for highlighting this change. The proposed amendment has been made to the report.

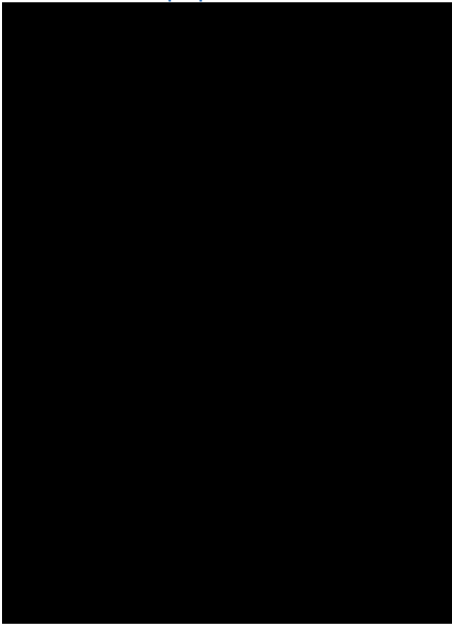
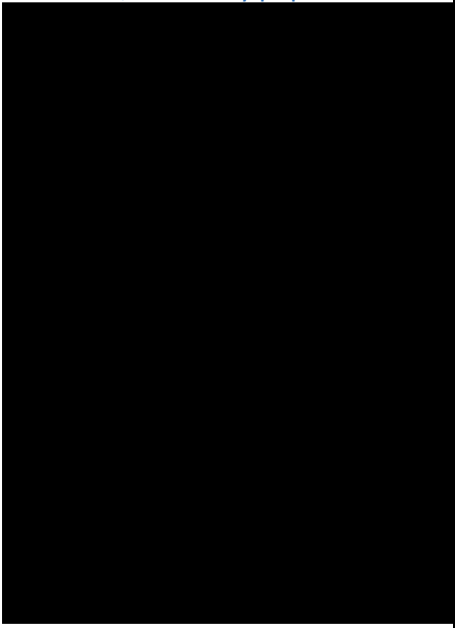
Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6409 Efgartigimod CIDP EAG report v0.1 040226ds [CON]; pages 252-253 ICER convergence plots (Figures 27-29)	Figures 27-29 of the ICER convergence plots should be redacted due to the ICERs being redacted	Figure 1. ICER convergence plot, Ig maintenance population  Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; PSA, probabilistic sensitivity analysis.	Thank you for highlighting this change. The proposed amendment has been made to the report.

		Figure 2. ICER convergence plot, Ig-intolerant/refractory population  Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; PSA, probabilistic sensitivity analysis. Figure 3. ICER convergence plot, mixed population	

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		Abbreviations: ICER, incremental cost-effectiveness ratio; Ig, immunoglobulin; PSA, probabilistic sensitivity analysis.	

Issue 4 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Tables 1 and 8; pages 21, 29 <i>“Choice of cycle length for first-two years”</i>	<i>“Choice of cycle length for first two years”</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Table 2; page 22 <i>“... experience AEs that impact on treatment tolerability or quality of life or have a schedule of Ig infusions that significantly impacts their daily life”</i>	<i>“... experience AEs that impact treatment tolerability or quality of life or have a schedule of Ig infusions that significantly impacts their daily life”</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Table 3; page 24 <i>“...both trials are associated with other methodological concerns which limits their use in decision making”</i>	<i>“...both trials are associated with other methodological concerns, which limit their use in decision making”</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Table 9; page 29 <i>“...ICER is [REDACTED], incremental NHB is [REDACTED] (£30,000/QALY)”</i>	<i>“...ICER is [REDACTED], incremental NHB is [REDACTED] (£30,000/QALY)”</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 19 heading; page 37 <i>“ICER (change from company base case)”</i>	<i>“ICER (change from company base case)”</i>	To correct a typographical error	The EAG has removed ‘change from company base case’ from the table headings in Table 19 and Table 20, as this wording was included in error.
Tables 19 and 20; pages 37, 39 <i>“Assume 95% of cohort restarts Ig after discontinuation of efgartigimod (Key issue 10)”</i>	<i>“Assume 95% of cohort restarts Ig after discontinuation of efgartigimod (Key Issue 10)”</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 2.3.1; page 55 <i>“... experience AEs that impact the tolerability of treatment or quality of life;”</i>	<i>“... experience AEs that impact the tolerability of treatment or quality of life;”</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 2.3.1; page 56 <i>“... and 43.4% in Stage B received priori IVIg or SCIg).”</i>	<i>“... and 43.4% in Stage B received prior IVIg or SCIg).”</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3.2; page 58 “... before starting an anti-FcRn following IVIg treatment”..”	“... before starting an anti-FcRn following IVIg treatment”..”	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 2.3.4: page 62 “...considered these to be appropriate, validated, measures of disease severity and response to treatment”	“...considered these to be appropriate and validated measures of disease severity and response to treatment”	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 3; page 64 “...provide a critique of the included studies and clinical-effectiveness analyses.”	“...provide a critique of the included studies and clinical effectiveness analyses.”	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 3.2; page 66 “Two studies of efgartigimod were included in the CS; ADHERE and the ongoing long term extension study, ADHERE+.”	“Two studies of efgartigimod were included in the CS: ADHERE and the ongoing long-term extension study, ADHERE+.”	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1; page 67 “...randomised 1:1 to receive double blind weekly subcutaneous efgartigimod”	“...randomised 1:1 to receive double-blind weekly subcutaneous efgartigimod”	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 3.3.2; page 79 “ADHERE Stage B efficacy results (double blinded , randomised)”	“ADHERE Stage B efficacy results (double-blinded , randomised)”	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 3.3.2.3; page 83 “Stage B post hoc endpoint efficacy results for longitudinal mean aINCAT scores of Stage A responders”	“Stage B post-hoc endpoint efficacy results for longitudinal mean aINCAT scores of Stage A responders”	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 3.3.2.3; page 83 “It also comprises a post hoc analysis, ...)	“It also comprises a post-hoc analysis, ...)	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 3.4.1; page 89	“The company conducted post-hoc subgroup analyses ...”	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>"The company conducted post hoc subgroup analyses ..."</i>			
Section 3.5.1; page 91 <i>"The CS presented information on treatment emergent adverse events ..."</i>	<i>"The CS presented information on treatment-emergent adverse events ..."</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 3.6.2; page 101 <i>".. and the percentage of treatment naïve patients were addressed by the company's population restrictions"</i>	<i>".. and the percentage of treatment-naïve patients were addressed by the company's population restrictions"</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 3.6.3.2; page 109 <i>"... [REDACTED]"</i>	<i>"... [REDACTED]"</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 4.1; page 112 <i>"Two reviewers were double blinded during screening..."</i>	<i>"Two reviewers were double-blinded during screening..."</i>	To correct a typographical error	Thank you for highlighting this typographical error. This has been corrected.
Section 4.2.7.1.1; page 132	<i>"The EAG also notes that, as discussed in Section Error!"</i>	To correct a typographical error	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>"The EAG also notes that, as discussed in SectionError! Reference source not found., ..."</i>	<i>Reference source not found., ..."</i>		

Committee Briefing

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name:

Efgartigimod with recombinant human hyaluronidase PH20 for treating chronic inflammatory demyelinating polyneuropathy

Topic ID:

6409

Managed Access Lead:

Milena Wobbe

Date of assessment(s):

16/02/2026

Feasibility of successful managed access	Comments / Rationale	
No managed access proposal	Rationale for rating	To consider managed access, a committee will need a managed access proposal, along with a feasibility assessment from the NICE managed access team. Currently no managed access proposal has been submitted. The managed access team should be contacted if a managed access proposal is expected to be requested or submitted at a later point in the NICE evaluation process.
	Previous ratings and rationale for change	

Managed Access Proposal	No	
Managed Access Team input at Committee meeting	Low	As there is no proposal, this can only enter CDF if a proposal is received after the first committee meeting

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	No	It is unlikely that data collection would resolve the key uncertainties.
Are there outstanding uncertainties that could be resolved with further data collection?	Low	Whilst there are key uncertainties with significant impact on the ICER, these uncertainties cannot be resolved through further data collection either because there is no identified data source or because the methodology of the trial is the source of the uncertainty.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Unclear	There is an ongoing open label trial. However, this would not help resolve the key uncertainties as identified by the EAG, which are more concerned with the set up of the trial.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	Low	This has not been assessed in detail, as there is no managed access proposal and no sources have been identified.
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	Unclear	As there is no proposal, this has not been investigated in detail

Key questions for committee if Managed Access is considered

1	N/A

Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	N/A