Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over

For public – confidential information redacted [redacted]

Technology appraisal committee C [8 April 2026]

Chair: Richard Nicholas

Lead team: Elizabeth Thurgar, Richard Boldero, Stella O'Brien

External assessment group: Birmingham Centre for Evidence and Implementation Science (BCEIS)

Technical team: Owen Swales, Emily Leckenby, Lorna Dunning

Company: Otsuka

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

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Background on hereditary angioedema

HAE is a rare genetic disorder causing unpredictable and severe swelling

Causes and epidemiology

- HAE is rare, estimated 1,000 to 1,500 have HAE in UK. Usually present in childhood with mean age of onset between 8 and 12 years.
- Chronic genetic disorder of uncontrolled inflammation characterised by deficiency or dysfunction of C1-INH and excess bradykinin, which increases vascular permeability and causes recurrent swelling

Diagnosis and classification

- Clinically indistinguishable subtypes. Type I (80-85%), Type II (20-15%). HAE with normal C1-INH uncommon subtype (<1%)

Symptoms and prognosis

- Episodic swelling of the skin, gastrointestinal tract, and upper airway – attacks are unpredictable. Often, the trigger is not identified.
- High rates of anxiety and depression, high impact on daily functioning
- Prognosis improves with effective long-term prophylaxis, untreated HAE can be fatal

Abbreviations: C1-INH: C1-esterase inhibitor; HAE: hereditary angioedema

Patient perspectives

People face unpredictable care and value donidalorsen

Submissions from Hereditary Angioedema (HAE) UK and patient expert

- HAE is severe, unpredictable, painful and potentially life-threatening, heavily impacting quality of life for both patients and carers
- Unmet need for psychological intervention to manage HAE-associated anxiety which is an attack trigger
- Donidalorsen offers advantages as it's a monthly SC self-administered injection that reduces hospital visits and invasive IV treatment
- Patients value having more treatment options, as HAE is highly individual
- Donidalorsen's targeted mechanism and potential to reduce attack rates offers high benefit for appropriate patients

"Attacks are highly unpredictable and last from anything between 24 and 72 hours, with a post-recovery time of 48 to 72 hours"

"Carers also live with the anxiety of the unpredictability of attacks…are trained to administer medications"

"Every single patient is different so the choice of medications is needed in order to effectively treat HAE"

"for patients who have very frequent attacks or poor outcomes…the quality of life will be hugely improved…[with] donidalorsen"

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Abbreviations: HAE: hereditary angioedema; SC: subcutaneous

Clinical perspectives

Donidalorsen may address unmet need

Submissions from BSI-CIPN, Royal College of Pathologists, and experts

- Donidalorsen efficacy expected to be comparable across populations with HAE Type 1 and Type 2
  - Current treatment algorithms favour Type 1 and Type 2 HAE
  - Rarer forms of genetically evidenced HAE (e.g FXII gain of function) also have angioedema due to excess bradykinin and would benefit
- OLE data show that 99% and 100% of donidalorsen Q4W and Q8W patients respectively experience a clinical response of ≥50% reduction from baseline in HAE attack rates during weeks 4 to 52
- Donidalorsen provides a long-acting subcutaneous option, potentially reducing treatment burden and offering an alternative approach (LICA mechanism) for patients who do not respond to existing LTP agents
- Over a lifetime (from age 2-years up, as needed) the probability of treatment failing an individual is high and alternatives are needed to ensure lifelong therapeutic options

"The long-term commitment to these treatments…carries a significant treatment burden for patients. Whilst this landscape is changing, there remains a need for multiple effective LTP options with a low treatment burden."

"There is no consensus…[on] the minimum amount of frequency and/or severity reduction [that] would be considered clinically significant. The previous NICE assessment on berotralstat used a 50% reduction in attack frequency…to allow continuation of treatment."

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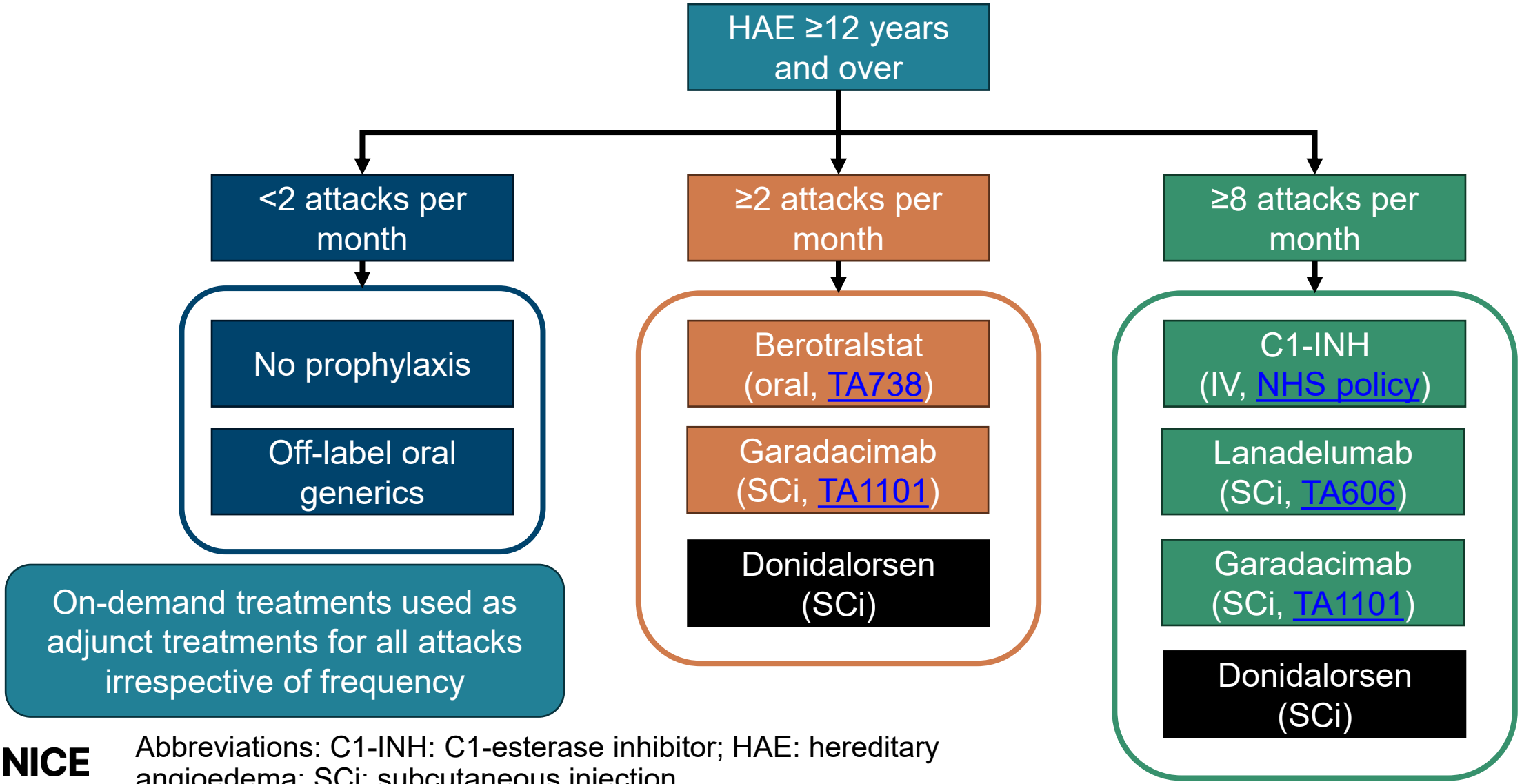
Abbreviations: HAE: hereditary angioedema; LICA: ligand-conjugated antisense; LTP: long term prophylaxis; OLE: open-label extension

Treatment pathway – long-term prophylaxis

NHSE treatment algorithm defines eligibility for long-term preventive treatment by attack frequency, splitting this into 3 categories for which treatment options vary:



Abbreviations: C1-INH: C1-esterase inhibitor; HAE: hereditary angioedema; SCi: subcutaneous injection

Donidalorsen (Dawnzera, Otsuka)

Marketing authorisation	• EMA marketing authorisation: "for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older" • The anticipated marketing authorisation for donidalorsen is: • [redacted] • Marketing authorisation expected to be granted via [redacted] in [redacted]
Mechanism of action	• RNA-targeted antisense oligonucleotide that binds to PKK mRNA in the liver thereby promoting the degradation of PKK-encoding mRNA • By preventing PKK protein synthesis and reducing circulating PKK levels, donidalorsen inhibits the plasma kallikrein-kinin system • This prevents the production of bradykinin which causes vasodilation and increased vascular permeability, leading to angioedema
Administration	• Administered subcutaneously (SC) via an auto-injector pen • Starting dose of [redacted] • [redacted]
Price	• List price of [redacted] per 80 mg pre-filled pen, a patient access scheme is applicable • List price for 12 months of treatment of [redacted]

Abbreviations: IRP: International Recognition Procedure; mRNA: messenger ribonucleic acid; PKK: prekallikrein; RNA: ribonucleic acid

Equality considerations

Access to current treatments may be limited by patient age and religious beliefs

Potential equality issue raised		Related considerations
Age	1. Access to treatment is based on age 2. Access criteria based on attack frequency can disadvantage children and young people because they may have attack frequencies below current access criteria • Children and young people are significantly affected by HAE despite fewer attacks than adults • Impact on children can include missed school days → impacts education attainment effects (uncaptured)	• NICE committee makes recommendations within a technology's marketing authorisation • Donidalorsen EMA marketing authorisation is for use in people aged 12 years and older • Attack frequency criteria
Religion and beliefs	1. Religious groups may be unwilling to have blood product-derived treatments • C1-INH comparators (Cinryze and Berinert) are derived from human plasma 2. Ethical concerns as above	• Lanadelumab and garadicamab are not derived from human plasma • Donidalorsen is not derived from human plasma

Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema

Key issues

Key issues for discussion	ICER impact
Exclusion of garadacimab as comparator	Large
Use of other treatments in trial	Unknown
Equal efficacy across treatments	Large
Berotralstat stopping rule	Large

Additional issues identified	ICER impact
Baseline characteristics in OASIS-HAE	Unknown
Extrapolation of long-term attack rates	Unknown
Trial generalisability to NHS practice	Unknown

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Key clinical trials

Clinical trial designs and outcomes

	OASIS-HAE	OASISplus
Design	Phase III, double-blind, randomised, placebo-controlled study	Open-label extension (OLE) of OASIS-HAE
Population	≥ 12 years with confirmed Type I or II HAE with ≥ 2 attacks in previous 56 days	OASISplus OLE: cohort from OASIS-HAE OASISplus switch: de novo cohort who had prior LTP that was not donidalorsen
Intervention	Donidalorsen 80 mg Q4W (n=45) Donidalorsen 80 mg Q8W (n=23)	Donidalorsen OLE 80 mg Q4W (n=69) Donidalorsen OLE 80 mg Q8W (n=14) Donidalorsen switch 80 mg Q4W (n=64)
Comparator	Placebo (n=22)	N/A
Duration	24-week treatment period	52-week treatment period
Primary outcome	HAE attacks (per 4 weeks) from Week 1 to Week 25 compared to placebo	Safety of long-term dosing with donidalorsen
Locations	21 sites in Europe, 11 in North America, 5 in Middle East and 3 in UK	
Used in model?	Yes	No

Abbreviations: HAE: hereditary angioedema; Q4W: once every 4 weeks, Q8W: once every 8 weeks

Key clinical trial results – OASIS-HAE

Donidalorsen significantly reduces attack rates compared with placebo

Table: Investigator-confirmed HAE attack rate (per 4 weeks) from Week 5 to Week 25 (FAS)

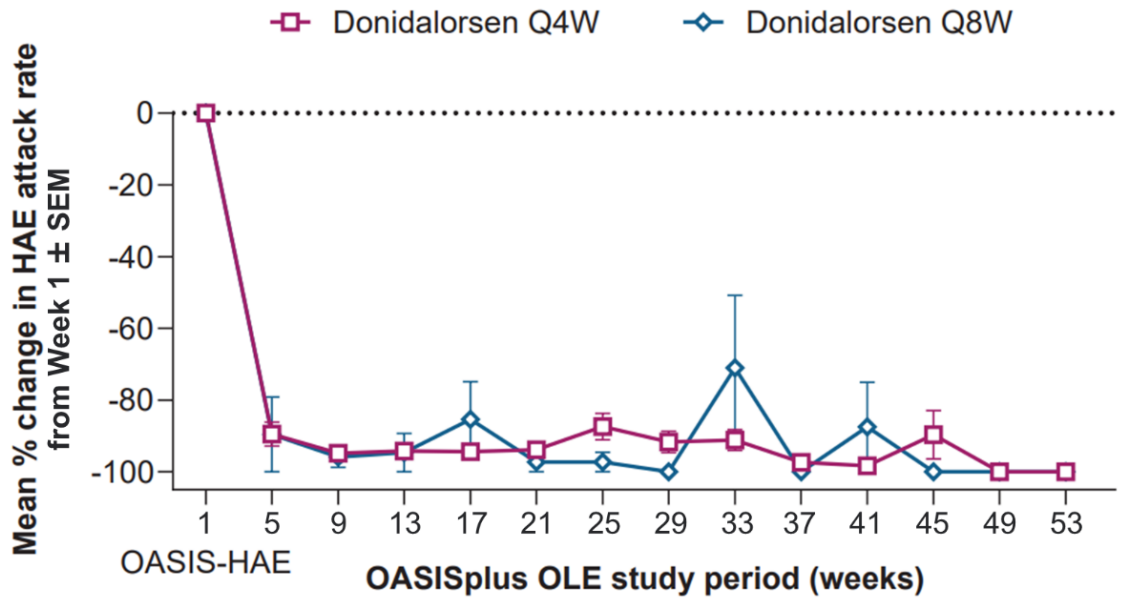
Time-normalised HAE attacks	Placebo (N=22)	Donidalorsen 80 mg 4-weekly (Q4W) (N=45)	Donidalorsen 80 mg 8-weekly (Q8W) (N=23)
Run-in (screening) period HAE attack rate			
Mean (SD)	2.90 (1.66)	3.61 (2.24)	3.18 (2.15)
Time-normalised HAE attack rate from Week 5 to Week 25			
Mean (SD)	[redacted]	[redacted]	[redacted]
Poisson Regression			
Least square mean rate (95% CI)	2.25 (1.59, 3.18)	0.30 (0.15, 0.58)	0.90 (0.53, 1.52)
Model adjusted mean rate ratio (95% CI)	-	[redacted]	[redacted]
P-value	-	<0.001	0.004
Percent difference relative to placebo (95% CI)	-	-87% (-93.8%, -71.9%)	-60% (-78.8%, -25.2%)

CI: confidence interval; FAS: full analysis set; HAE: hereditary angioedema; Q4W: once every 4 weeks, Q8W: once every 8 weeks; SD: standard deviation

Key clinical trial results – OASISplus

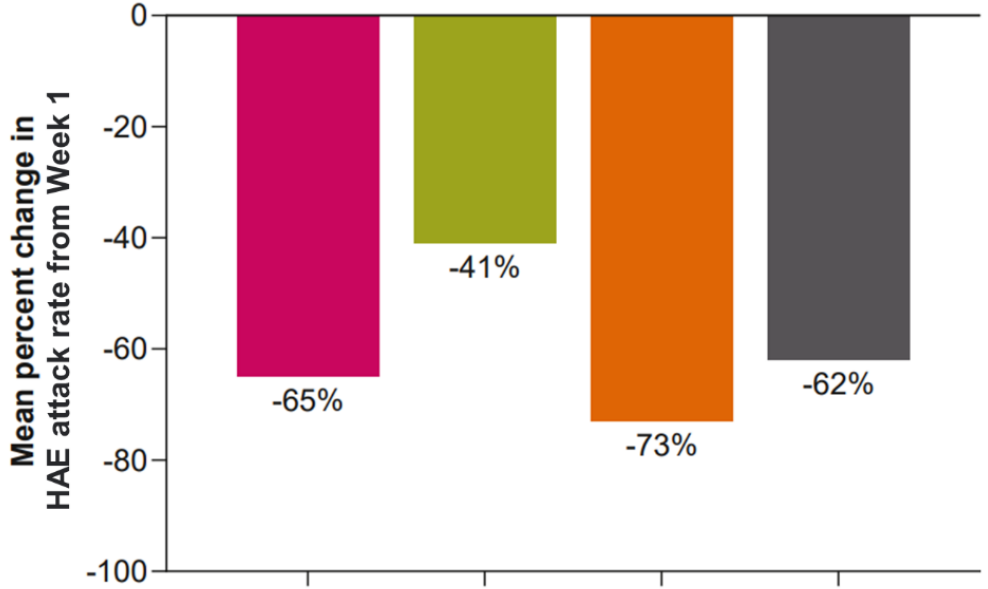
Donidalorsen significantly reduces attack rates compared with placebo

Figure: Investigator-confirmed OLE cohort HAE attack rate (per month)



Donidalorsen Q4W, n =	69	69	69	68	68	57	50	43	38	26	16	13	8	5
Donidalorsen Q8W, n =	14	14	14	14	14	11	9	9	8	6	4	3	2	2

Figure: Switch cohort, mean percentage change in time-normalised HAE attack rate (per month)



Prior LTP:	Lanadelumab	C1INH	Berotralstat	Total
n =	31	22	11	64
Week 1, mean ± SD =	0.69 ± 1.09	0.61 ± 0.96	1.80 ± 1.92	0.85 ± 1.28
Week 17 (donidalorsen Q4W), mean ± SD =	0.24 ± 0.33	0.36 ± 0.69	0.48 ± 0.53	0.33 ± 0.51

Abbreviations: CI: confidence interval; FAS: full analysis set; HAE: hereditary angioedema; Q4W: once every 4 weeks, Q8W: once every 8 weeks; SD: standard deviation

Network meta-analysis – company

NMA shows wide credible intervals reflecting uncertainty

Figure: Network of evidence for company NMA

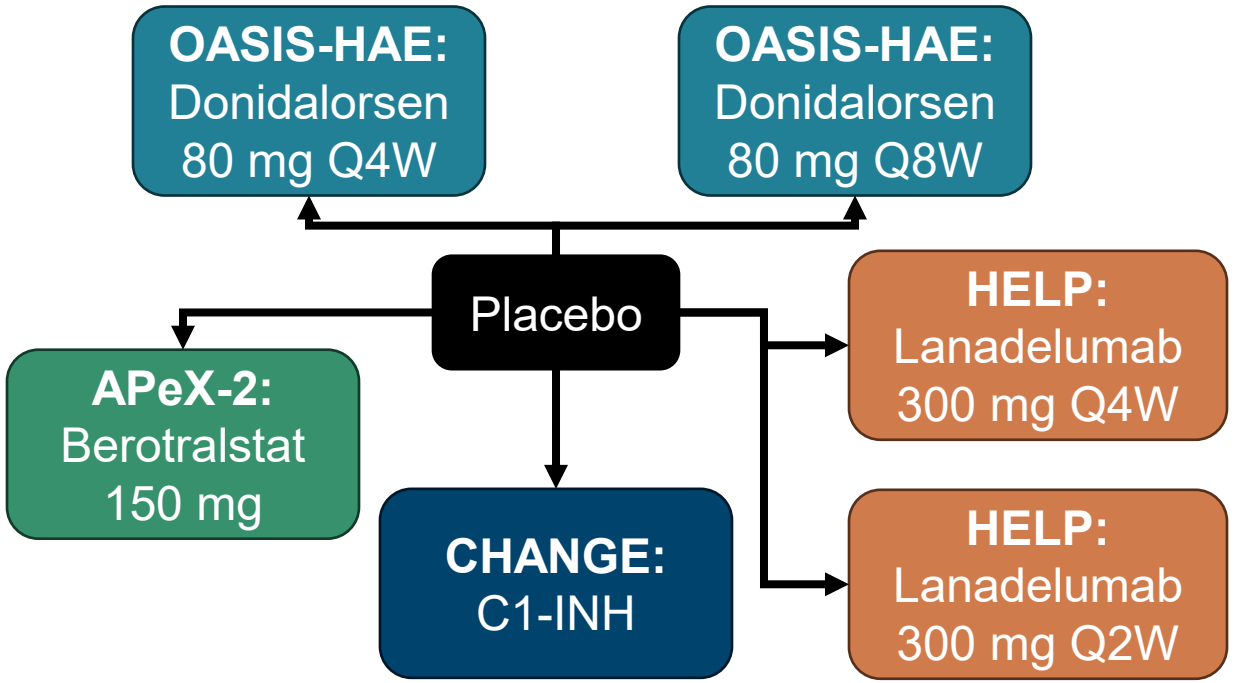


Table: Median rate ratios from company NMA for mean number of HAE attacks per month

Treatment	Median rate ratio (95% CrI)
Berotralstat	[redacted]
C1-INH (Cinryze)	[redacted]
Donidalorsen Q8W	[redacted]
Lanadelumab Q2W	[redacted]
Lanadelumab Q4W	[redacted]
Placebo	[redacted]

*95% credible interval does not include 1, so considered statistically meaningful

Company

- Point estimates for donidalorsen more favourable vs berotralstat, lanadelumab Q4W, C1-INH and placebo. Less favourable vs lanadelumab Q2W and garadacimab (see next slide for garadacimab)
- Credible intervals wide across comparators, frequently crossed 1, indicating considerable uncertainty in relative effects – no statistically significant differences between treatments could be concluded

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Abbreviations: C1-INH: C1-esterase inhibitor; CrI: credible interval; HAE: hereditary angioedema; NMA: network meta-analysis; Q2W: once every 2 weeks; Q4W: once every 4 weeks, Q8W: once every 8 weeks

Network meta-analysis – EAG

EAG updated company NMA to include garadacimab

Figure: Network of evidence for EAG NMA

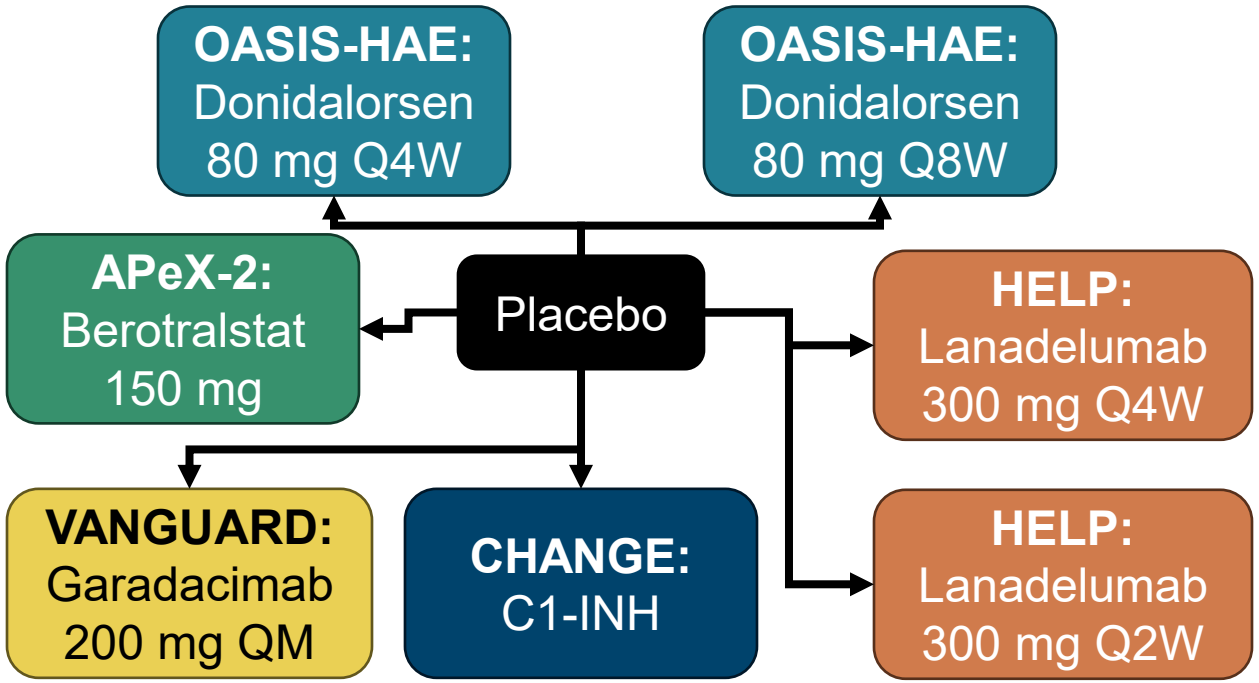

Table: Median rate ratios from EAG NMA for mean number of HAE attacks per month

Treatment	Median rate ratio (95% CrI)
Berotralstat	[redacted]
C1-INH (Cinryze)	[redacted]
Donidalorsen Q8W	[redacted]
Lanadelumab Q2W	[redacted]
Lanadelumab Q4W	[redacted]
Garadacimab	[redacted]
Placebo	[redacted]

*95% credible interval does not include 1, so considered statistically meaningful

TA1101

- Committee concluded that garadacimab has similar or better clinical effectiveness compared with berotralstat, C1-INHs or lanadelumab
- Committee noted that the company NMA was aligned with a recently published fixed-effect NMA (see here)

Abbreviations: C1-INH: C1-esterase inhibitor; CrI: credible interval; HAE: hereditary angioedema; NMA: network meta-analysis; Q2W: once every 2 weeks; Q4W: once every 4 weeks, Q8W: once every 8 weeks; QM: once monthly

Key issue: Exclusion of garadacimab as comparator (1)

Company exclude garadacimab as comparator despite positive NICE guidance

Background

- Garadacimab recommended by NICE in October 2025 (TA1101)

Company

- Garadacimab excluded because it is not established clinical practice, very limited use in NHS in UK
- Section 2.2.12 of NICE manual specifies that comparators should reflect established clinical practice
- If garadacimab is to be included, company shared NMA results for donidalorsen vs garadacimab (below)
- Argue that NMA results show no statistically significant difference between donidalorsen and garadacimab
- Thus, supporting company base case of equal efficacy between donidalorsen and all comparators

Table: Median rate ratios from donidalorsen Q4W and garadacimab RE NMA for mean number of HAE attacks per month – steady-state period

Treatment	Median rate ratio (95% CrI)
Garadacimab	[redacted]
Placebo	[redacted]

Table: Median rate ratios from donidalorsen Q4W and garadacimab RE NMA for mean number of HAE attacks per month – full trial period

Treatment	Median rate ratio (95% CrI)
Garadacimab	[redacted]
Placebo	[redacted]

Should garadacimab be included as a decision-making comparator?

CrI: credible interval; HAE: hereditary angioedema; NMA: network meta-analysis; Q4W: once every 4 weeks; RE: random effects

Key issue: Exclusion of garadacimab as comparator (2)

Company exclude garadacimab as comparator despite positive NICE guidance

EAG

- Garadacimab has positive NICE guidance, should be included as a relevant comparator (NICE manual)
- Experts say garadacimab is expected to be used in the same treatment line and setting as donidalorsen
- Implementation is underway in routine practice and garadacimab is expected to have a large market share
- Additional analysis from company is pairwise NMA, full NMA including garadacimab would be more helpful
- Pairwise NMA maintains wide credible intervals seen in company and EAG NMAs
  - Absence of statistically meaningful difference reflects imprecise estimates, not equivalent efficacy
- Company choice of 'steady-state' analysis (weeks 5 to 25) as primary analysis potentially selective
  - Garadacimab reaches steady state period earlier than donidalorsen
  - May exclude clinically relevant treatment effects occurring in early treatment period for garadacimab
  - Full trial point estimate is [redacted] to garadacimab than steady-state estimate
- No cost-utility analyses including garadacimab provided by the company

Clinical experts

- Garadacimab not currently commonly used, but will be in the very near future
- Will be used mainly for people with ≥ 2 attacks per month, and a proportion with ≥ 8 attacks per month

Should garadacimab be included as a decision-making comparator?

Abbreviations: NMA: network meta-analysis

Key issue: Use of other treatments in trial

Androgens and tranexamic acid are not typically used in HAE trials

Company

- Only [redacted] continued receiving androgens during treatment in OASIS-HAE (placebo: n=[redacted], donidalorsen Q4W: n=[redacted], donidalorsen Q8W: n=[redacted]) and only [redacted] received tranexamic acid
- Sensitivity analyses have not been performed excluding these people

EAG

- Androgens have been widely used as long-term prophylaxis treatment for HAE patients in many countries
- Use of androgens and tranexamic acid during a prophylaxis trial is clinically unusual, as both agents are recognised to reduce HAE attack frequency and are typically excluded with a defined washout period
- EAG expert said inclusion of these therapies may confound the treatment effect, trials typically exclude these treatments and have a significant washout period to ensure no influence on efficacy results
- EAG unable to adjust results to remove these treatments due to lack of patient data

Clinical experts

- Unusual to include androgens and tranexamic acid in HAE LTP trials
- But not a significant concern as usage of androgens is similar in placebo and donidalorsen Q4W arms

Is the use of other treatments in OASIS-HAE a concern?
If so, how should this be considered in decision-making?

HAE: hereditary angioedema; LTP: long-term prophylaxis; Q4W: once every 4 weeks; Q8W: once every 8 weeks

Additional issue: Baseline characteristics in OASIS-HAE

Baseline characteristics showed some differences across arms

Company

- Baseline characteristics are broadly well matched across cohorts
- However, given the relatively small sample sizes some variation is expected

EAG

- Study had small treatment groups (placebo n=22; donidalorsen Q4W n=45; donidalorsen Q8W n=23), so baseline differences may have a disproportionate effect on estimates of treatment effect
- Mean run-in attack rates were higher for donidalorsen (3.61 Q4W, 3.18 Q8W) vs placebo (2.90)
- Donidalorsen Q4W had a higher mean number of attacks in 12 months prior to enrolment than placebo
- Differences indicate that people in the donidalorsen arms entered the study with a higher disease burden
- EAG used pooled baseline attack rate from people with ≥ 2 attacks per month for all LTPs
  - No change in company cost comparison base case, ICER marginally improves in cost-utility scenario
- Effect of differing baseline attack rates between donidalorsen and placebo / other treatments unknown
- Adolescents were limited (placebo = 0, donidalorsen Q4W = 4 / Q8W = 3, restricting conclusions in group
- Proportion of males in placebo arm was 63.6% with only 36.4% of females – EAG expert highlighted this could be unexpected as more females may suffer HAE attacks due to hormonal differences

Is evidence from OASIS-HAE suitable for decision-making?

Abbreviations: LTP: long-term prophylaxis; Q4W: once every 4 weeks; Q8W: once every 8 weeks

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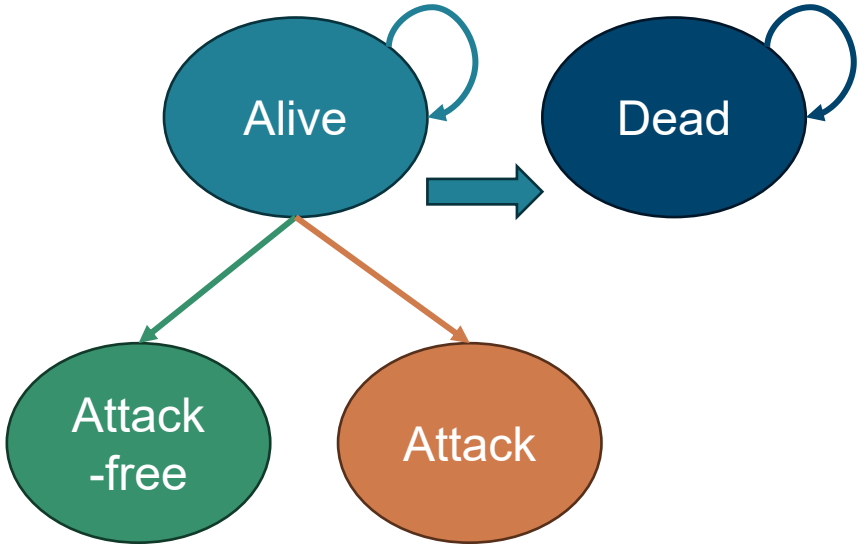
Company model



Model feature	Chosen values
Structure	Markov model
Time horizon	Lifetime (63 years)
Cycle length	28 days
Discount rate	3.5% for costs and outcomes
Population	People with HAE and ≥ 2 attacks per month
Treatment effect	Baseline attack rate per week: 0.73 (≥ 2 attacks per month) 2.00 (≥ 8 attacks per month)
Treatment waning	Lifetime
Economic evaluation	Cost comparison base case – equal efficacy for treatments (cost-utility scenario)
Utilities	None included in cost-comparison base case Patient and carer utility included in cost-utility scenario based on Nordenfelt et al. (2014)
Costs	BNF costs, NHS reference costs, PSSRU costs

Abbreviations: BNF: British National Formulary; HAE: hereditary angioedema; PSSRU: personal social services research unit

Key issue: Equal efficacy across treatments

Company assumes equal efficacy across treatments due to wide NMA results

Company

- Base case is a cost comparison – assumes equal efficacy across all treatments in the model
- Appropriate because NMA results (wide and overlapping credible intervals) show no statistically significant difference between donidalorsen and comparator LTPs, indicating similar efficacy and QoL benefits
- Experts validated approach, say it is reasonable to assume all treatments can demonstrate equal efficacy

EAG

- Wide and overlapping credible intervals reflects limited precision rather than evidence of equivalence
- Non-inferiority was not assessed, and no margins were prespecified to justify collapsing treatment effects
- Interpretation is further complicated by heterogeneity in study design, patient populations, and baseline characteristics across trials, as well as the sparse network anchored only by the placebo arm of each trial

Clinical experts

- Donidalorsen outcomes are broadly consistent with berotralstat, lanadelumab, C1-INH and garadacimab
- Donidalorsen likely better than berotralstat and lanadelumab, and equivalent efficacy to garadacimab

Is equal efficacy justified based on the mechanism of action of treatments?
How should the relative treatment effects across treatments be modelled?

Abbreviations: C1-INH: C1-esterase inhibitor; LTP: long-term prophylaxis; NMA; network meta-analysis; QoL: quality of life

Key issue: Berotralstat stopping rule

Company does not model berotralstat stopping rule due to equal efficacy

Background

- TA738: berotralstat should be stopped if attacks per month do not reduce by at least 50% after 3 months

Company

- Stopping rule not included in model as it is inconsistent with equal efficacy assumption in model
- Treatment discontinuation is assumed to be equal across all treatments
- So, including the stopping rule would remove treatment costs for patients who do not respond to berotralstat but would not recognise the associated poorer health outcomes
- Assumption is in favour of berotralstat by assuming a better clinical profile than expected

EAG

- Previous appraisals have identified the stopping rule as a key driver of cost effectiveness
- EAG implemented a berotralstat stopping rule in its base-case cost-utility analysis, which does not assume equal efficacy across long-term prophylaxis treatments – the ICER impact is large

Should the berotralstat stopping rule be included in modelling?

Abbreviations: ICER: incremental cost-effectiveness ratio

Additional issue: Extrapolation of long-term attack rates

Company uses average attack rate for the long-term, EAG questions other ways

Company

- Weekly attack rates are calculated for the first 24 weeks, in line with the duration of the OASIS-HAE trial
- The attack rate beyond Week 25 is the average attack rate from the timepoint at which the treatment has reached maximum effect, until the end of the trial period
  - This is week 5 for donidalorsen based on steady-state definition taken from the OASIS-HAE trial
- Cost comparison base case assumes equal HAE attack rate per cycle for all treatments

EAG

- Company did not explore alternative approaches to address uncertainty in long-term extrapolation, such as zero-inflated or Poisson regression models that account for the high proportion of attack-free periods in HAE
- TA738 and TA1101 show that long-term extrapolation assumptions can materially affect the ICER
- EAG unable to explore issue due to the lack of individual patient data

Clinical experts

- Extrapolation of the trial data using average attack rate from week 5 to 25 seems plausible

How should long-term attack rates be modelled?

Abbreviations: HAE: hereditary angioedema

Other key assumptions

Model feature	Assumption
Baseline attack rate	• Equal baseline attack rate assumed for all patients irrespective of treatment received • ≥ 2 attacks per month: attack rate of 0.725 per week which is the mean run-in period HAE attack rate in the placebo arm of the OASIS-HAE trial • ≥ 8 attacks per month: attack rate of 2 attacks per week was used, in line with reimbursement criteria for lanadelumab
Treatment dosing in model	• Switching for lanadelumab from 2 to 4-weekly dosing modelled at 45% at 12 months (TA606) • However, EAG experts suggested variable switching in practice, so EAG scenario with 45% switching at 3 months was explored
Disutility per administration	• Company used utility decrements per annual injection: −0.0003 for IV and −0.0002 for SC • EAG agree with principle, but disutility should vary with route **and** frequency of injections • No consensus on best implementation as disutility over multiple injections is not additive
Carer disutilities	• Carer disutility not included or accepted in TA606 and TA738 • But it was accepted by committee in TA1101: a carer disutility of 0.0123 for every 0.1 decrement in patient utility • Company uses the same approach in this appraisal – and EAG agrees

Does the committee consider these other key assumptions appropriate?

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Abbreviations: HAE: hereditary angioedema; SC: subcutaneous

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Relative treatment effect	Equal efficacy (cost comparison)	NMA point estimates (cost utility)
Comparators	Excludes garadacimab	Includes garadacimab
Baseline attack rates	From OASIS-HAE	Pooled across treatments
Berotralstat stopping rule	Excluded due to equal efficacy	Included

Abbreviation: NMA: network meta-analysis

Cost-effectiveness results

Cost-effectiveness results are confidential and will be presented in Part 2 of this meeting

≥ 2 attacks per month	Company base case	EAG base case
Donidalorsen vs berotralstat	Cost comparison so no ICERs	ICERs above normal cost-effectiveness range
Donidalorsen vs garadacimab	-	

≥ 8 attacks per month	Company base case	EAG base case
Donidalorsen vs lanadelumab	Cost comparison so no ICERs	ICERs within normal cost-effectiveness range
Donidalorsen vs C1-INH		
Donidalorsen vs garadacimab	-	ICERs above normal cost-effectiveness range

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Abbreviations: C1-INH: C1-esterase inhibitor

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Key issues

Key issues for discussion	ICER impact	Slide
Exclusion of garadacimab as comparator	Large 	16
Use of other treatments in trial	Unknown 	18
Equal efficacy across treatments	Large 	22
Berotralstat stopping rule	Large 	23

Additional issues identified	ICER impact	Slide
Baseline characteristics in OASIS-HAE	Unknown 	19
Extrapolation of long-term attack rates	Unknown 	24
Trial generalisability to NHS practice	Unknown 	34

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Abbreviations: ICER, incremental-cost effectiveness ratio

Key questions for committee

Should garadacimab be included as a decision-making comparator?
Is evidence from OASIS-HAE suitable for decision-making?
Are there differences in baseline disease severity in OASIS-HAE? If so, how should this be considered in decision-making?
Is the OASIS-HAE trial generalisable to the NHS?
How should the relative treatment effects across treatments be modelled?
Should the berotralstat stopping rule be included in modelling?
How should long-term attack rates be modelled?
Does the committee consider other key assumptions appropriate (baseline attack rate, treatment dosing, disutility for patients and carers)?
What is the committee's preferred ICER?
What is the committee's preferred ICER threshold?
What is the committee's decision?

Abbreviations: HAE: hereditary angioedema

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Supplementary appendix

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Steady state period for treatments

Steady state refers to the point at which the concentration of a prophylactic drug in the body has stabilised.

This means the rate of drug administration equals the rate of elimination, producing a consistent therapeutic level.

Table: Steady state period for each treatment comparator and economic model assumptions

Treatment	Steady state period as defined in the clinical trial	Timepoint of full treatment effect used to extrapolate attack rate in the economic model
Donidalorsen	Days 35-175 (Weeks 5-25)	5 weeks
Berotralstat	Days 8-168	1 week
Lanadelumab	Days 70-182	10 weeks
C1-INH	Not reported	0 weeks

C1-INH: C1-esterase inhibitor

Findings of Walsh et al. 2025

Network Meta-Analysis of Pharmacological Therapies for Long-Term Prophylactic Treatment of Patients with Hereditary Angioedema

"The results of these NMAs show improved efficacy, QoL, and reduced rate of adverse events with garadacimab (200 mg once monthly), lanadelumab (300 mg every two or four weeks), subcutaneous C1INH (60 IU/kg twice weekly), and berotralstat (150 mg once daily) compared to placebo in the treatment of patients with HAE. For the primary outcome of time-normalized number of HAE attacks, garadacimab statistically significantly reduced the rate of attacks compared to lanadelumab Q4W and berotralstat. A similar statistically significant reduction was shown for HAE attacks treated with on-demand treatment. Garadacimab showed statistically significant reduction in the rate of moderate and/or severe HAE attacks compared to lanadelumab Q2W. Garadacimab also showed statistical improvements in change from baseline in AE-QoL total score as compared to berotralstat."

C1-INH: C1-esterase inhibitor; Q2W: every 2 weeks; QoL: quality of life

Additional issue: Trial generalisability to NHS practice

Company experts consider OASIS-HAE generalisable to UK, EAG disagrees

Company

- UK clinical experts in September 2025 considered the characteristics of the patient population of OASIS-HAE to be generalisable to the HAE patient population treated in the UK

EAG

- The trial population was predominantly White and recruited largely outside the UK, with limited representation of UK patients
- Differences in clinical practice patterns, access to on-demand therapy, and patient characteristics may limit the applicability of results to NHS settings
- Unknown impact on cost-effectiveness results

Clinical experts

- OASIS-HAE trial generally reflects UK practice
- Trials have been conducted in centres including the UK and in keeping with current clinical practice

Is the OASIS-HAE trial generalisable to the NHS?

HAE: hereditary angioedema