Single Technology Appraisal

Tarlatamab for extensive-stage small-cell lung cancer after 2 or more treatments [ID6364]
Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tarlatamab for extensive-stage small-cell lung cancer after 2 or more treatments [ID6364]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Amgen

2. **Consultee and commentator comments on the Draft Guidance** from:
   - Roy Castle Lung Cancer Foundation

3. **External Assessment Group critique of company response to the DG**

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

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Tarlatamab for treating advanced small-cell lung cancer after 2 or more treatments [ID6364]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 18 February 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Amgen Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Summary	Amgen thank the Committee for its careful consideration of the company's submission and stakeholder comments. Whilst disappointed with the draft recommendation not to recommend tarlatamab as a treatment for previously treated SCLC, Amgen welcomes the opportunity to address outstanding Committee uncertainty. Furthermore, Amgen reiterate the urgent need for an effective treatment for patients with third-line extensive-stage SCLC, who currently face extremely limited treatment options consisting of chemotherapies with limited survival benefit over best supportive care, and accompanied by toxicities and increasing resistance of SCLC tumours to chemotherapy as the condition progresses. As highlighted in the patient organisation submission, a diagnosis of a disease as aggressive as SCLC is devastating; in addition to the extremely poor prognosis for patients with SCLC which gets progressively worse following each line of treatment, SCLC greatly impacts patient quality-of-life (QoL). The small number of patients who reach third-line treatment would benefit greatly from a safe and tolerable treatment that is able to significantly extend life and improve QoL, as tarlatamab has been shown to do. The principal source of uncertainty for the Committee relates to the limited length of follow-up available from the DeLLphi-301 trial. The original company submission was based on the June 2023 data cut-off (DCO) of the DeLLphi-301 trial. Since then, additional data have become available including long-term follow-up (LTFU) information from October 2023, January 2024 and May 2024 DCOs. Efficacy outcomes (response, progression-free survival [PFS] and overall survival [OS]), duration of therapy, and safety data are presented from the October 2023 DCO. These data have been included in the updated base case and scenario analyses as part of this response, as this was the latest formal DCO with data for key outcomes available, which therefore ensured consistency across presented outcomes. Results of the January 2024 (response, PFS) and May 2024 DCOs (OS only) were presented by Sands *et al.* at the World Conference on Lung Cancer (WCLC) in September 2024 and are included in the reference pack provided alongside this response.[1] LTFU data show consistent outcomes across the October 2023, January 2024, and May 2024 outcomes, with tarlatamab showing response, PFS, OS far above any previously reported for a population of patients receiving third-line treatment for SCLC. Data from these additional DCOs serve to address this area of uncertainty. Given that the October 2023 DCO contains the most comprehensive set of outcomes with LTFU data, these data have been presented in full in Appendix 1, and have been incorporated into the updated base case indirect treatment comparison (ITC) analyses, which in turn inform the updated economic model. The results of these updated ITC analyses yield the same conclusion as in the original

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	company submission: tarlatamab significantly improves survival outcomes compared with current standard of care (SoC). In addition to incorporating the latest complete set of efficacy data in the ITC and cost-effectiveness model, in response to Committee comments, Amgen have provided a number of new analyses to reduce remaining uncertainty around the cost-effectiveness estimates: • The choice of parametric survival curves is now informed solely by best statistical fit, with models chosen separately for each treatment arm • An alternative source of real-world evidence (RWE), the US-based Flatiron database, has been used to inform an additional ITC analysis for consideration by the Committee • Alternative methods of estimating SoC progression-free survival (PFS) have been explored, using the hazard ratio (HR) between PFS and TTD in the DeLLphi-301 trial • A scenario analysis using utility values from the DeLLphi-301 matched to the patient characteristics of the UK Cancer Analysis Service (CAS) has been presented • A weighted approach to adverse event (AE) costs has been used Alongside these responses, the company have additionally provided a revised base case taking into account the Committee's preferred assumptions. A summary of the changes made to the base case cost-effectiveness analyses is presented in Appendix 2, alongside updated results. These changes from the company's previous base case analysis result in consistent cost-effectiveness estimates, with a small decrease in incremental cost-effectiveness ratio (ICER), with the 1.7 severity modifier criterion still being met. Both the deterministic and probabilistic ICERs for tarlatamab (at its with-PAS price) in comparison with SoC now fall under NICE's threshold of £30,000 per quality-adjusted life year (QALY), and scenario analyses have been presented using different assumptions and sources of data, which consistently result in ICERs under NICE's threshold. These results, informed by more mature DeLLphi-301 trial data, therefore address the Committee's concerns regarding the limited length of follow-up available from the DeLLphi-301 trial and demonstrate tarlatamab to be a cost-effective use of National Health Service (NHS) resource.
1	**An updated data cut of the DeLLphi-301 trial has been presented, further supporting that tarlatamab is associated with a durable response and PFS and OS benefits**

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The Committee noted that the relatively short follow up times in the original June 2023 data cut meant that there was uncertainty in the estimates of the clinical efficacy of tarlatamab. Since the original submission, additional data have become available including long-term follow-up (LTFU) information from October 2023, January 2024 and May 2024 DCOs (Table 1). Detailed results from a later data cut (October 2023 which was not previously available ahead of submission) are now presented in Appendix 1 below, with a summary of results provided in this response.

Table 1: Data available from DeLLphi-301 datacuts

DCO	Median follow-up (months)			
	ORR	DOR	PFS	OS
June 2023	[redacted]		[redacted]	10.6
October 2023	[redacted]		[redacted]	[redacted]
January 2024	16.6	15.1	16.4	NA[a]
May 2024	NA[a]	NA[a]	NA[a]	20.7

Abbreviations: DCO: data cutoff, DOR: duration of response, NA: not available; ORR: overall response rate, OS: overall survival, PFS: progression-free survival.
Sources: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* 2023;[3] Sands *et al.* 2024.[3]

Median follow up time for patients at the October 2023 DCO of the DeLLphi-301 trial was 13.6 months for PFS, and 13.8 months for OS,[4] which represents an additional 3.9 months of follow-up for PFS, and 3.2 months for OS as compared with the original June 2023 data cut.[3] The latest LTFU data from the May 2024 DCO is associated with a median follow-up of 20.7 months, however, given that the October 2023 DCO contains the most comprehensive set of outcomes with LTFU data,[4] data from this DCO has been used in the updated base case, to ensure consistency across presented outcomes, and when adjusting TTD and OS for post-progression use (see Section B.2.9.3 of company submission). Efficacy results at LTFU (October 2023 DCO) for PFS and OS were generally consistent with those from the primary analysis (June 2023 DCO) (estimated median PFS: 4.3 months versus 4.9 months; estimated median OS: 14.3 months versus 15.2 months).

Furthermore, objective response (OR) was unchanged, with 40% (40/99) of patients achieving either confirmed complete response (CR) or partial response (PR). This included one patient whose confirmed PR improved to CR. However, amongst the 40 responders, [redacted] patients ([redacted]%), [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%) had a DOR of at least 6, 9 and 12 months, respectively. This

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	demonstrates DOR has improved as compared with the June 2023 data cut ([redacted]%, [redacted]% and [redacted]%, respectively).[3] These updated efficacy results address the Committee's concerns regarding the limited follow up time, showing consistent results to those presented in the original company submission. These results are further corroborated by data from the January 2024 and May 2024 DCOs subsequently presented by Sands *et al*. at WCLC 2024. Of note, median follow up for OS was 20.7 months in the May 2024 DCO, with median OS reached at 15.2 months, which was consistent with the previously estimated median OS of 15.2 months in the October 2023 DCO informing this response. Together, these latest efficacy results robustly demonstrate the long-term effectiveness of tarlatamab, significantly reducing the Committee's uncertainty relating to follow-up times.
2	**Safety data from the October 2023 DCO of the DeLLphi-301 trial was consistent with those in the primary analysis (June 2023)** In the 10 mg target dose group across Part 1 and Part 2, 96 patients (97.0%) had at least 1 adverse event at the June 2023 DCO, and [redacted] patients ([redacted]) had at least 1 AE at the October 2023 DCO.[3] Grade ≥3 adverse events were reported for 57 patients (57.6%) at the June 2023 DCO, which were considered treatment-related for 29.3% of patients, compared to [redacted] patients ([redacted]%) at the October 2023 DCO, which were considered treatment-related for [redacted]% of patients.[3, 5] Furthermore, the most frequently reported treatment-related TEAEs remained the same between DCOs. At the October 2023 DCO, CRS was reported in [redacted]% of patients, pyrexia in [redacted]%, decreased appetite in [redacted]%, dysgeusia in [redacted]%, fatigue in [redacted]% and anaemia in [redacted]%.[5] Overall, no new safety signals were highlighted in the October 2023 DCO. Of particular note, the number of patients with unresolved Grade ≥2 ICANS decreased from the June 2023 to the October 2023 DCO ([redacted] patients [[redacted]%] versus [redacted] patients [[redacted]%]).[5] Additionally, [redacted] patients had unresolved Grade ≥2 CRS events at the end of either DCO. The Kaplan-Meier median time to resolution of Grade ≥2 CRS events at the October 2023 DOC was [redacted] days, and the median time to resolution of Grade ≥2 ICANS events was [redacted] days, both consistent with durations reported in the June 2023 DCO.[2] More recent safety results from the January 2024 DCO show a median resolution of (all-Grade) ICANS events of 33 days.[1]

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	Detailed safety results from the October 2023 DCO of the DeLLphi-301 trial are presented in Appendix 1. **Risk minimisation plan and medical training** The Committee concluded that tarlatamab has serious side effects, which will need healthcare staff training and capacity planning to monitor and manage. To support healthcare staff with monitoring and management of serious side effects of tarlatamab, Amgen has a risk minimisation plan (RMP) in place; this includes the distribution of risk minimisation materials (RMMs). The RMMs consist of a patient alert card and a healthcare professional guide. The RMP, RMMs, and the distribution plan have been reviewed by the (Medicines & Healthcare Products Regulatory Agency) MHRA. In addition, Amgen will reactively offer robust training via the medical science liaisons (MSLs) on monitoring and management of the serious side effects, CRS and ICANS, for relevant healthcare staff at healthcare organisations that request this training when using or considering the use of tarlatamab.
3	**The MAICs for OS and PFS have been updated to include the latest data from DeLLphi-301; results of these MAICs inform OS and PFS for SoC in the base case economic analysis. Adjustment for covariates using means and variance for continuous covariates, rather than means only, has also been explored.** Given the availability of a later data cut for the DeLLphi-301 trial, the company MAIC has been updated to include the latest available data informing the efficacy of tarlatamab relative to SoC. The results of this updated MAIC analysis using the DeLLphi-301 October 2023 DCO, as the latest LTFU data cut that provides a comprehensive set of outcomes, show both PFS and OS that are broadly similar to the previous analysis: in the base case, the HR for OS between tarlatamab and SoC decreased from [redacted] to [redacted], indicating greater OS benefit for tarlatamab compared with SoC when using the latest data cut. As was the case in the original company submission, the OS analysis was adjusted for post-progression treatment with tarlatamab in the DeLLphi-301 trial (see Section B.2.9.3). The PFS HR remained unchanged at [redacted]. Kaplan-Meier (KM) plots for tarlatamab and SoC are shown below for PFS (Figure 1) and OS (Figure 2), and a summary of hazard ratios (HRs) is provided in Table 2 below.

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Figure 1: Kaplan-Meier curves of PFS for tarlatamab vs. available treatment options (CAS)

Abbreviations: CAS: Cancer Analysis Service; PFS: progression-free survival.

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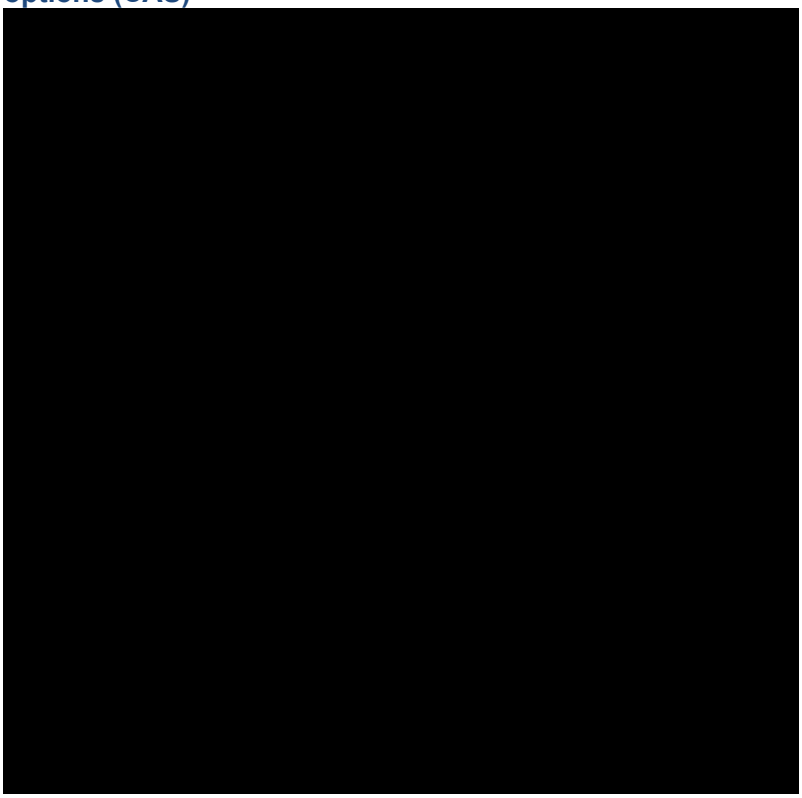
Figure 2: Kaplan-Meier curves of OS for tarlatamab vs. available treatment options (CAS)



Abbreviations: CAS: Cancer Analysis Service; OS: overall survival; TRT: treatment.

The results of the latest MAIC analysis, updated to include more mature survival data from the DeLLphi-301 trial, were consistent with those obtained from the original company MAIC: tarlatamab shows statistically significant PFS and OS benefits over current SoC. These updated MAIC results have been incorporated into the company's updated economic analysis, the results of which are presented in Appendix 2. Given the increase in tarlatamab OS in the updated MAIC analysis, this resulted in a decrease in the incremental cost-effectiveness ratio (ICER) for tarlatamab versus SoC.

In addition to suggesting an ITC update to include more mature survival data, the Committee concluded that re-analysis of the original company MAIC, adjusting for means and variance of the continuous covariates of age and time from diagnosis, would be beneficial to decision making. For this reason, Amgen have conducted a scenario analysis on the latest company MAIC using this methodology, details of which are presented in Appendix 4, with results presented in Appendix 3.

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A summary of the updated company base case MAIC inclusive of the October 2023 DeLLphi-301 trial data are shown in Table 2, alongside the same MAIC with variance adjustment.

Table 2: Summary of updated MAIC analysis results

	ESS	HR (95% CI)	p-value	Median tarlatamab (months)	Median SoC (months)
PFS					
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	
MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAIC variance adjustment	[redacted]	[redacted]	[redacted]	[redacted]	
OS					
Unadjusted		[redacted]	[redacted]	[redacted]	
MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAIC variance adjustment	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; NE: not estimable; OS: overall survival; PFS: progression-free survival; SoC: standard of care.

As shown in Table 2 above, the adjustment of continuous variables using means and variance produced only minor differences in survival estimates compared with the base case company MAIC. As such, no material differences in cost-effectiveness results were expected when using the variance adjustment, and these were not explored further in the cost-effectiveness model (CEM).

4

An alternative source of real-world evidence (RWE), the US-based Flatiron database, has been used to inform an additional ITC analysis utilising a propensity score weighting (PSW) approach, for consideration by the Committee

The Flatiron ITC addresses key limitations in the CAS MAIC which the Committee raised, including the small effective sample size (ESS) and TTD used as a proxy for PFS in the CAS MAIC. Specifically, the Flatiron ITC utilises

patient-level data adjustment to achieve cohort balance while maintaining reasonable ESS for assessing treatment effects. Additionally, it offers a thorough evaluation of indirect treatment effects by leveraging validated real-world progression-free survival (rwPFS) and real-world overall response rate (rwORR) data from Flatiron, specifically for currently available treatment options for SCLC previously treated with at least two therapies. Given these strengths, the company consider that this study provides valuable additional evidence for the Committee's decision-making process in this appraisal.

The Flatiron Health Research Database is a longitudinal database of electronic health records (EHR), comprising de-identified patient-level structured and unstructured data from approximately 280 community oncology practices and several academic cancer centres in the US.

Individual patient-level data (IPD) were leveraged for tarlatamab from the DeLLphi-301 trial (n=97) and an external control arm was constructed using IPD from the Flatiron database (n=184) for the population of interest: patients receiving treatment for SCLC previously treated with at least two prior therapies. After applying key eligibility criteria from the DeLLphi-301 trial to the Flatiron IPD and adjusting for relevant baseline confounders (i.e., weighting the Flatiron external control to be similar to the tarlatamab group), tarlatamab was associated with improved OS relative to physicians' choice of therapy (HR: [redacted]; 95% CI: [redacted] to [redacted]) (Table 3).

Given the availability of rwPFS data from the Flatiron database, a direct comparison of PFS outcomes for tarlatamab and SoC was possible, using the same PSW adjustment methods as for OS. Results of this comparison show a statistically significant improvement in PFS associated with tarlatamab compared with SoC (HR: [redacted]; 95% CI: [redacted] to [redacted]) (Table 2).

Table 3: ITC results for tarlatamab vs available treatment options in the Flatiron study, unadjusted and adjusted for relevant covariates

ITC results for tarlatamab vs available treatment options	OS		PFS		TTD	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression free survival; TTD: time to treatment discontinuation. As was done for the base case CAS MAIC, OS data from the DeLLphi-301 trial were adjusted for post-progression treatment with tarlatamab, using a method published by Latimer et al.[6] HRs from the Flatiron ITC were consistent with (HR=[redacted]) and without (HR=[redacted]) this adjustment, indicating the Flatiron ITC analysis to be robust to adjustment for post-progression treatment with tarlatamab. Further methodological details of the Flatiron ITC, along with results from the exploratory endpoints, are presented in Appendix 5. Economic results from the scenario analysis utilising the Flatiron ITC results are presented in Appendix 3, which also fall below the willingness to pay threshold of £30,000 per QALY.
5	**Parametric curves used for PFS and OS extrapolations have been selected separately for each treatment, such that they are most appropriate for the updated data cut, produce plausible extrapolations, and do not imply proportional hazards.** In the original company submission, the exponential distribution was selected for tarlatamab OS, the log-normal distribution was selected for tarlatamab PFS and the exponential distribution was used to model TTD. The exponential and log-normal distributions were used to model OS and TTD, respectively, in the SoC arm; in the absence of TTD data from the UK CAS study, TTD was used as a proxy for PFS. The exponential model was the statistical best fit for tarlatamab OS and was therefore selected. The exponential model was also chosen for SoC, in line with the NICE preference for using the same model across both treatments, as outlined in NICE Decision Support Unit (DSU) technical support document (TSD) 14 and due to the non-differential QALYs estimated for the SOC group across different models.[7] However, Amgen agree with the Committee that selecting exponential model for the SoC group is inadvertently assuming proportional hazards, and thus the base case extrapolation for SoC has been updated to the statistical best fit model – gamma for OS and generalised gamma for TTD. No changes to the updated base case ITC impacted the reference SoC curve and resulting parametric extrapolations. Therefore, the goodness-of-fit statistics for SoC remain as per those previously presented in Section B.3.3 of the original company submission. The best-fitting statistical models remained unchanged for tarlatamab when updated October 2023 DeLLphi-301 data were used, and were therefore retained in the company's updated base case. Goodness-of-fit statistics based on Akaike

information criterion (AIC), Bayesian information criterion (BIC) are presented for tarlatamab OS and PFS in Table 4 and Table 5 below.

The base case OS and TTD extrapolations for SoC have been updated to be selected based on best statistical fit, rather than on the tarlatamab OS and TTD extrapolations.

Table 4: AIC and BIC for tarlatamab OS parametric models using the October 2023 DCO (MAIC-adjusted)

Model selection	AIC	BIC
Exponential	**111.95**	**114.52**
Weibull	113.94	119.09
Lognormal	112.83	117.98
Log-logistic	113.47	118.62
Gompertz	113.61	118.76
Generalised gamma	114.25	121.98
Gamma	113.95	119.10

Bold indicates base case extrapolation.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO: data cut-off; OS: overall survival.

Table 5: AIC and BIC for tarlatamab PFS parametric models using the October 2023 DCO

Model selection	AIC	BIC
Exponential	158.65	161.23
Weibull	160.42	165.57
Lognormal	**157.61**	**162.76**
Log-logistic	158.58	163.73
Gompertz	159.10	164.24
Generalised gamma	158.26	165.99
Gamma	160.59	165.74

Bold indicates base case extrapolation.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO: data cut-off; PFS: progression-free survival.

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6	**Alternative methods of estimating PFS in the SoC arm have been explored, derived from the HR between PFS and TTD in the DeLLphi-301 trial** As noted in response 5 above, SoC PFS data were not available from the UK CAS study. As such, SoC PFS was assumed equal to TTD in the original company submission, a common assumption in oncology, given the usual requirements to stop treatment upon disease progression. However, clinical experts commented that patients may stop SoC treatments prior to progression, given toxicity associated with multiple rounds of chemotherapy. The Committee additionally highlighted a notable difference between PFS and TTD in the DeLLphi-301 trial, and thus considered the approach of assuming equal PFS and TTD for SoC to be uncertain. Therefore, the Committee suggested the HR between PFS and TTD observed in the DeLLphi-301 trial be applied to SoC TTD to estimate SoC PFS. Amgen consider this approach to be unsuitable for several reasons. Survival outcomes for SoC are extremely poor, especially given most patients will be receiving treatment on which they previously failed. For this reason, any differences observed between TTD and PFS are likely to be small, as PFS beyond the point of discontinuation is likely to be extremely short. Furthermore, as noted above, tarlatamab has an entirely novel mechanism of action, targeting a separate biological target than the chemotherapies constituting SoC. Accordingly, response to treatment with tarlatamab is deeper and longer-lasting than any previously reported for conventional third-line SCLC treatments. For this reason, it does not hold reasonable clinical face validity to adopt a modelling approach which assumes that the difference between TTD and PFS observed in the DeLLphi-301 trial for tarlatamab to be applicable to SoC. Additionally, it is important to note that the adverse event profiles differ between tarlatamab and chemotherapy. Patients treated with chemotherapy often experience haematological AEs, such as anaemia, neutropenia, and thrombocytopenia, which can lead to treatment discontinuation or delays. In contrast, these AEs occur at a much lower rate with tarlatamab, potentially resulting in a different relationship between TTD and PFS between tarlatamab (more progression-driven) and SoC chemotherapies (mix of toxicity and progression driven discontinuation). As such, the application of a HR derived from TTD and PFS seen in the DeLLphi-301 trial has not been incorporated in the updated company base case analysis as it is considered clinically and biologically implausible to do so. Instead, a scenario analysis was performed where the ratio of PFS to TTD was calculated from the tarlatamab extrapolations on a per-cycle basis. This ratio was

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<table>
<tr><td></td><td>then applied to the SoC TTD curve to generate an estimate of PFS, which assumes that the ratio of the TTD and PFS curves for tarlatamab is applicable to that of SoC. The results of this analysis are shown in Appendix 3. In this scenario analysis, the conclusion of cost-effectiveness of tarlatamab versus SoC at a willingness-to-pay threshold of £30,000 per ICER gained remained unchanged.</td></tr>
<tr><td>7</td><td>A scenario analysis has been conducted in which health state utility values are derived from the DeLLphi-301 trial, adjusted for the characteristics of the UK CAS study population.

In response to a Committee request, Amgen have provided the MAIC-adjusted utility values from the DeLLphi-301 trial, presented in Table 6 below.

Table 6: Health state utility values (unadjusted versus MAIC-adjusted)
<table>
<tr><th rowspan="2">Health state</th><th colspan="2">Unadjusted</th><th colspan="2">MAIC-adjusted</th></tr>
<tr><th>Mean</th><th>SE</th><th>Mean</th><th>SE</th></tr>
<tr><td>Pre-progression</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Post-progression</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: MAIC: matching-adjusted indirect treatment comparison; SE: standard error

As shown in Table 6 above, whilst pre-treatment and pre-progression utility values are largely unchanged by MAIC adjustment, the post-progression utility values increase slightly upon adjustment.

Amgen note that the increase in post progression utility may stem from the drop in the ESS after weighting of the DeLLphi-301 cohort, compounded with a higher amount of missing EQ-5D data during the post-progression phase. For this reason, Amgen consider the MAIC-adjusted trial utility values to be less robust and less valid than the unweighted utility estimates and thus have not incorporated these into the revised economic base case analysis. Despite this, a scenario analysis using these adjusted utility values has been provided for completeness (see Appendix 3). In this scenario analysis, the ICER for tarlatamab compared with SoC decreased slightly, meaning that the company base approach to utilities can be considered conservative.</td></tr>
<tr><td>8</td><td>A weighted approach to calculating the costs of AEs has been adopted in the updated base case analysis

In response to the Committee’s preference for the external assessment group’s (EAG) approach of using a weighted average across all available severities of adverse event levels to calculate the costs associated with AEs, this approach has been incorporated into the company’s revised base case (see Appendix 2).</td></tr>
</table>

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Tarlatamab for treating advanced small-cell lung cancer after 2 or more treatments [ID6364]

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9	**The company's conclusion that application of the 1.7x severity modifier is appropriate remains unchanged in the updated economic model and reflects the devastatingly poor outcomes associated with current treatment for third-line ES-SCLC.** The company's updated base case (see Appendix 2) results in no change to the estimates of total QALYs for SoC which inform the QALY shortfall calculations. As such, proportional QALY shortfall in this population remains above NICE's threshold of 0.95, above which a severity modifier of 1.7 is applied. As such, in line with the ingoing company submission, total QALYs for both treatments are multiplied by 1.7 in the updated base case analysis. Given the extremely short life expectancy and devastating impact on patient QoL of ES-SCLC at this stage, this adjustment is justified in order to account for this severity.

Insert extra rows as needed

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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Tarlatamab for treating advanced small-cell lung cancer after 2 or more treatments [ID6364]

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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 during our consultations 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.

Appendices

1. Latest DeLLphi-301 DCO

Clinical effectiveness results of the relevant studies

The clinical effectiveness results reported in this appendix are from the June 2023 and October 2023 DCOs. The definitions of all clinical outcomes and efficacy analysis sets presented below are as previously defined for the June 2023 DCO (see Sections B.2.3.2 and B.2.4 of Document B of the original Company submission). Summary results from the January 2024 and May 2024 DCOs presented in Sands et al. are also discussed where relevant.[1]

Primary endpoint (objective response) for Part 1 and Part 2

For the 99 patients in the blinded independent central review (BICR) Full Analysis Set for Part 1 and Part 2 receiving the 10 mg target dose, the overall response rate (ORR) remained unchanged in the October 2023 DCO as compared with the June 2023 DCO (ORR: [redacted]% [97.5% CI: [redacted]%, [redacted]%]).[3] However, one patient with a partial response at the June 2023 DCO had a complete response in the October 2023 DCO; a total of [redacted] patients [[redacted]%] had a confirmed CR and [redacted] patients [[redacted]%] had a confirmed PR at the October 2023 DCO.[5] These results are consistent with updated response data from the January 2024 DCO presented by Sands et al.,[1] which also showed an ORR of 40.4%, which included [redacted] CR from the October 2023 DCO.

A side-by-side comparison between objective response for patients in the 10 mg target dose group at the June 2023 and October 2023 DCOs is presented in Table 7 below.

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Table 7: Objective response as assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2; 10 mg dose)

	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
Best overall response[a], n (%)		
Confirmed complete response	1 (1.0)	[redacted]
Confirmed partial response	39 (39.4)	[redacted]
Stable disease	30 (30.3)	[redacted]
Progressive disease	19 (19.2)	[redacted]
Not evaluable	2 (2.0)	[redacted]
No post-baseline scan	8 (8.1)	[redacted]
Objective response rate		
n (%)	40 (40.4)	[redacted]
97.5% CI[b]	(29.4, 52.2)	[redacted]
Disease control rate		
n (%)	70 (70.7)	[redacted]
95% CI[b]	(60.7, 79.4)	[redacted]
Any tumour shrinkage, n (%)		
Yes[c]	[redacted]	[redacted]
At least 30% tumour shrinkage[d]	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing	[redacted]	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose
[a] Assessment of disease response was determined based on RECIST 1.1 guidelines. [B] Exact confidence interval was calculated using the Clopper Pearson method.[c] Includes patients who had any tumour shrinkage in the target lesions at post-baseline assessment. [D] Includes patients who had at least 30% tumour shrinkage in the target lesions at post-baseline assessment.
Abbreviations: BICR: blinded independent central review; DCO: data cut-off; RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* 2023;[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

Secondary endpoints

Duration of response

Duration of response (DOR) among confirmed responders in the 10 mg target dose group for the June 2023 and October 2023 DCO is presented in Table 8. The median follow-up time of response was [redacted] months at the June 2023 DCO and [redacted] months for the October 2023 DCO.[2, 5]

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Of the 40 responders in the 10 mg target dose group, 23 patients (57.5%) and 10 patients (25.0%) had a DOR of at least 6 and 9 months, respectively, at the June 2023 DCO, which increased to [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%) at the October 2023 DCO.[3] Furthermore, at the June 2023 DCO, 22 of 40 responders (55.0%) in the 10 mg target dose group still had an ongoing response (on treatment without disease progression or death), including [redacted] patients ([redacted]%) whose responses reached at least 6 months.[2, 3] At the October 2023 DCO, [redacted] of [redacted] responders ([redacted]%) in the 10 mg target dose group still had an ongoing response (on treatment without disease progression or death), including one additional patient whose response reached at least 6 months, increasing the total to [redacted] patients ([redacted]%).[5]

Furthermore, at the January 2024 DCO, median DOR was 9.7 months (95% CI, 6.9, NE) with 17/40 (43%) of responses ongoing at the data cut off.[1]

Table 8: Duration of response among confirmed responders as assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2; 10 mg dose)

Duration of response	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
Number of confirmed responders	40	[redacted]
Patient status		
Events, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
On study without disease progression or death	[redacted]	[redacted]
No evaluable post-baseline disease assessment	[redacted]	[redacted]
Missed 2 or more consecutive assessments	[redacted]	[redacted]
Started new anti-cancer therapy	[redacted]	[redacted]
Withdrawal of consent from study	[redacted]	[redacted]
Decision by sponsor	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Completed study without disease progression or death	[redacted]	[redacted]
Duration of response (KM) (months)[a]		
25th percentile (95% CI)	4.4 (2.8, 7.1)	[redacted]
Median (95% CI)	NE (5.9, NE)	[redacted]
75th percentile (95% CI)	NE (NE, NE)	[redacted]
Min, Max (+ for censored)	[redacted]	[redacted]
Follow-up time for DOR (KM) (months)[a]		

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25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Min, Max (+ for censored)	[redacted]	[redacted]
Kaplan-Meier estimate (%) (95% CI)[b]		
At 3 months	[redacted]	[redacted]
At 6 months	66.5 [redacted]	[redacted]
At 9 months	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]
Observed duration of response, n (%)		
≥3 months of observed DOR	35 (87.5)	[redacted]
On study without disease progression or death	[redacted]	[redacted]
≥ 6 months of observed DOR	23 (57.5)	[redacted]
On study without disease progression or death	[redacted]	[redacted]
≥ 9 months of observed DOR	10 (25.0)	[redacted]
On study without disease progression or death	[redacted]	[redacted]
≥12 months of observed DOR	[redacted]	[redacted]
On study without disease progression or death	[redacted]	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose
[A] Median and percentiles were estimated using Kaplan-Meier method and their 95% CI were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method. [B] 95% CIs were estimated using Kalbfleisch and Prentice (1980) method.
Abbreviations: BICR: blinded independent central review; DCO: data cut-off; DOR: duration of response; KM: Kaplan-Meier; min: minimum; NE: not estimable; RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* 2023;[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

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Disease control

Duration of disease control results for the June 2023 and October 2023 DCOs as assessed by BICR are provided in Table 9.

In the 10 mg target dose group, the median DoDC by BICR was 6.9 months (95% CI: 5.4, 9.7) at the June 2023 DCO, and also [redacted] months (95% CI: [redacted], [redacted]) at the October 2023 DCO.[3] The Kaplan-Meier estimate of duration of disease control at 6 months was [redacted]% (95% CI: [redacted]%, [redacted]%) at the June 2023 DCO, and [redacted]% (95% CI: [redacted]%, [redacted]%) at the October 2023 DCO.[2, 3, 5]

Table 9: Duration of disease control as assessed by BICR (BICR full analysis set for Part 1 and 2; 10 mg dose)

	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
Number of patients with a best overall response of CR, PR or stable disease	70	[redacted]
Patient status		
Event, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
On study without disease progression or death	[redacted]	[redacted]
No evaluable post-baseline disease assessment	[redacted]	[redacted]
Missed 2 or more consecutive assessments	[redacted]	[redacted]
Started new anti-cancer therapy	[redacted]	[redacted]
Withdrawal of consent from study	[redacted]	[redacted]
Decision by sponsor	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Completed study without disease progression or death	[redacted]	[redacted]
Duration of disease control (KM) (months)[a]		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	6.9 (5.4, 9.7)	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Min, max (+ for censored)	[redacted]	[redacted]
Follow-up time for DoDC (KM) (months)[a]		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]

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75th percentile (95% CI)	[redacted]	[redacted]
Min, max (+ for censored)	[redacted]	[redacted]
Kaplan-Meier estimate (%) (95% CI)[b]		
At 3 months	[redacted]	[redacted]
At 4 months	[redacted]	[redacted]
At 6 months	[redacted]	[redacted]
At 9 months	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose. [a] Median and percentiles were estimated using Kaplan-Meier method and their 95% CI were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method. [b] 95% CIs were estimated using Kalbfleisch and Prentice (1980) method.
Abbreviations: BICR: blinded independent central review; CR: complete response; DCO: data cut-off; DoDC: duration of disease control; KM: Kaplan-Meier; min: minimum; NE: not estimable; PR: partial response; RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* 2023;[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

Progression-free survival

PFS results, as assessed by BICR, for patients receiving the 10 mg target dose for both the June 2023 and October 2023 DCOs are presented in Table 10, with a KM plot of results for the October 2023 DCO presented in Figure 3. In the 10 mg target dose group, estimated median PFS by BICR at the June 2023 DCO was 4.9 months (95% CI: 2.9, 6.7), with a median follow-up time of [redacted] months, compared with [redacted] months (95% CI: [redacted], [redacted]) at the October 2023 DCO, with a median follow-up time of [redacted] months.[2, 3] The slight difference in estimated median, despite median PFS having been reached in the original DCO, is attributable to censored events close to the median timepoint in the original DCO becoming progression events in the later data cut.

A further [redacted] disease progression events were reported in the Oct 2023 DCO as compared with the June 2023 DCO (56 patients [56.6%] versus [redacted] patients [[redacted]%]), with no further death events in the analysis of PFS.[2, 3, 5]

Table 10: Progression-free survival as assessed by BICR (BICR Full Analysis set for Part 1 and 2; 10 mg dose)

	1->10 mg (N=99)	
	June 2023 DCO	**October 2023 DCO**
Number of patients who received at least 1 dose of tarlatamab	99	[redacted]
Patient status		
Events, n (%)	64 (64.6)	[redacted]
Death	8 (8.1)	[redacted]

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Disease progression	56 (56.6)	[redacted]
Censored, n (%)	35 (35.4)	[redacted]
On study without disease progression or death	25 (25.3)	[redacted]
No evaluable post-baseline disease assessment	2 (2.0)	[redacted]
Missed 2 or more consecutive assessments	3 (3.0)	[redacted]
Started new anti-cancer therapy	2 (2.0)	[redacted]
Withdrawal of consent from study	3 (3.0)	[redacted]
Decision by sponsor	0 (0.0)	[redacted]
Lost to follow-up	0 (0.0)	[redacted]
Completed study without disease progression or death	0 (0.0)	[redacted]
Progression-free survival (KM) (months)[a]		
25th percentile (95% CI)	2.4 (1.4, 2.8)	[redacted]
Median (95% CI)	4.9 (2.9, 6.7)	[redacted]
75th percentile (95% CI)	NE (7.1, NE)	[redacted]
Min, Max (+ for censored)	0.0+, 13.7+	[redacted]
Follow-up time of progression-free survival (KM) (months)[a]		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Min, Max (+ for censored)	[redacted]	[redacted]
Kaplan-Meier estimate (%) (95% CI)[b]		
At 3 months	58.8 (48.1, 68.1)	[redacted]
At 6 months	40.8 (30.6, 50.7)	[redacted]
At 9 months	28.5 (19.2, 38.6)	[redacted]
At 12 months	[redacted]	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose. [a] Median and quantiles were estimated using Kaplan-Meier method and 95% CI of median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method. [B] 95% Cis were estimated using Kalbfleisch and Prentice (1980) method.
Abbreviations: BICR: blinded independent central review; DCO: data cut-off; KM: Kaplan-Meier; min: minimum; NE: not estimable; RECIST: response evaluation criteria in solid tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* 2023;[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

Figure 3: KM plot for PFS as assessed by BICR (Safety Analysis Set; October 2023 DCO)

1 -> 10 mg = 1 mg step dose to 10 mg target dose.
Survival data are shown for the n=97 patients, excluding two patients who received tarlatamab as second-line therapy.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; KM: Kaplan-Meier; PFS: progression-free survival.
Source: Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

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Overall survival

In the 10 mg target dose group, estimated median OS was 14.3 months (95% CI: 10.8, NE) at the June 2023 DCO, with a median follow-up time of 10.6 months.[2, 3] In comparison, median OS was [redacted] months (95% CI: [redacted], [redacted]), with a median follow-up time of [redacted] months at the October 2023 DCO.[5] The Kaplan-Meier estimates for OS at 6 and 12 months were 73.4% and [redacted]%, respectively, for the June 2023 DCO, and [redacted]% and [redacted]%, respectively, for the October 2023 DCO.[2, 3, 5] An overview of OS results for patients in the 10 mg dose group for the June 2023 and October 2023 DCO is presented in Table 11. A KM plot for OS for the October 2023 DCO is presented in Figure 4.

Further LTFU OS data are available from a May 2024 DCO presented by Sands et al. at WCLC,[1] with median OS follow up of 20.7 months. Median OS was 15.2 months (95% CI: [redacted], [redacted]) and 12-month OS was 57.0%, consistent with results from the October 2023 DCO. Overlayed KM plots for OS from the June 2023, October 2023 and May 2024 DCOs are presented in Figure 5.

Table 11: Analysis of overall survival (Safety Analysis Set)

	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
Number of patients who received at least 1 dose of tarlatamab	99	[redacted]
Patient status		
Events, n (%)	35 (35.4)	[redacted]
Death	35 (35.4)	[redacted]
Censored, n (%)	64 (64.6)	[redacted]
Alive at last follow-up	57 (57.6)	[redacted]
Withdrawal of consent from study	6 (6.1)	[redacted]
Decision by sponsor	0 (0.0)	[redacted]
Lost to follow-up	1 (1.0)	[redacted]
Completed study without death	0 (0.0)	[redacted]
Overall survival (KM) (months)[a]		
25th percentile (95% CI)	5.7 (4.7, 10.5)	[redacted]
Median (95% CI)	14.3 (10.8, NE)	[redacted]
75th percentile (95% CI)	NE (NE, NE)	[redacted]
Min, Max (+ for censored)	0.3+, 15.2+	[redacted]
Follow-up time (months)[a]		
25th percentile (95% CI)	8.0 (7.4, 9.0)	[redacted]
Median (95% CI)	10.6 (9.2, 11.5)	[redacted]

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75th percentile (95% CI)	12.5 (11.5, 13.9)	[redacted]
Min, Max (+ for censored)	0.3, 15.2	[redacted]
Kaplan-Meier estimate (%) (95% CI)[b]		
At 3 months	88.7 (80.5, 93.6)	[redacted]
At 6 months	73.4 (63.2, 81.2)	[redacted]
At 9 months	68.0 (57.1, 76.6)	[redacted]
At 12 months	[redacted]	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose. a Median and quantiles were estimated using Kaplan-Meier method and 95% CI of median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method. [B] 95% Cis were estimated using Kalbfleisch and Prentice (1980) method.
Abbreviations: DCO: data cut-off; KM: Kaplan-Meier; min: minimum; NE: not estimable.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* 2023;[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

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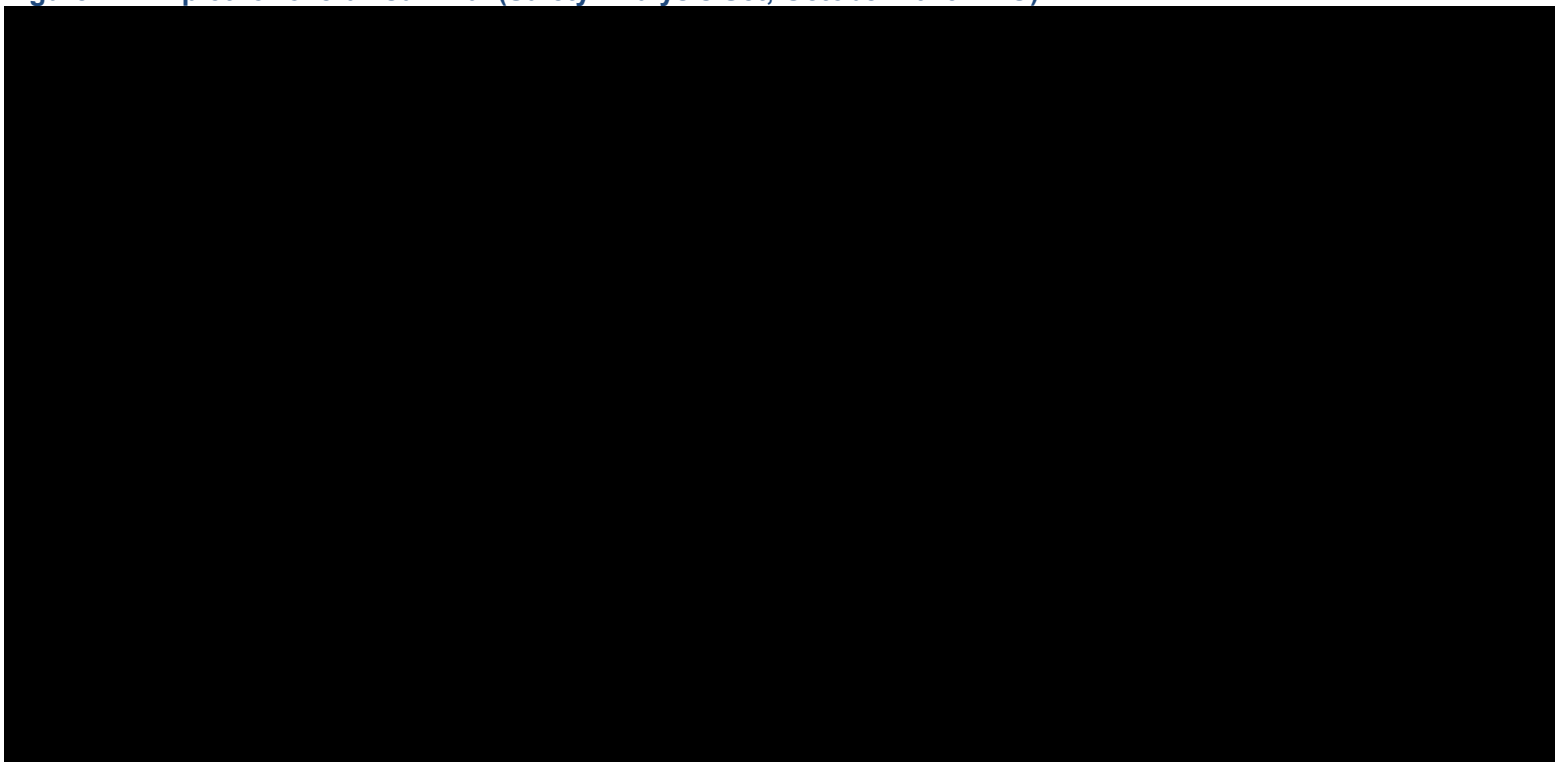
Figure 4: KM plot for overall survival (Safety Analysis Set; October 2023 DCO)



1 -> 10 mg = 1 mg step dose to 10 mg target dose.
Survival data are shown for the n=97 patients, excluding two patients who received tarlatamab as second-line therapy.
Abbreviations: CI: confidence interval; DCO; data cut-off; KM: Kaplan-Meier; NE: not evaluable; OS: overall survival.
Source: Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

Figure 5: KM plot for overall survival (Safety Analysis Set; June 2023, October 2023, May 2024 DCOs)

1 -> 10 mg = 1 mg step dose to 10 mg target dose.
Survival data are shown for the n=97 patients, excluding two patients who received tarlatamab as second-line therapy.
Abbreviations: DCO; data cut-off; KM: Kaplan-Meier; OS: overall survival.

Adverse reactions

Summary of the safety of tarlatamab

A summary of treatment-emergent adverse events (TEAEs) for tarlatamab in patients in the 10 mg target dose group in DeLLphi-301 for the June 2023 and October 2023 DCOs is presented in Table 12. In the 10 mg target dose group across Part 1 and Part 2, 96 patients (97.0%) had at least 1 adverse event at the June 2023 DCO, and [redacted] patients had at least 1 AE at the October 2023 DCO.[3] Grade ≥3 adverse events were reported for 57 patients (57.6%) at the June 2023 DCO, which were considered treatment-related for 29.3% of patients, compared to [redacted] patients ([redacted]%) at the October 2023 DCO, which were considered treatment-related for [redacted]% of patients.[3, 5]

Serious adverse events (SAEs) were reported for [redacted] patients ([redacted]%) in the 10 mg target dose group for both DCOs, with SAEs considered by the investigator to be related to tarlatamab reported for [redacted]% of all patients.[3, 5] AEs that led to discontinuation of investigational product were reported for [redacted] patients ([redacted]%) at both DCOs.[3] Fatal AEs were reported for 3 patients (3.0%) at the June 2023 DCO, and for [redacted] patients ([redacted]%) at the October 2023 DCO, none of which were considered by the investigator to be related to tarlatamab at either DCO.[5]

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Table 12: Summary of incidence of treatment-emergent adverse events (Safety Analysis Set; 10 mg Parts 1 and 2)

Treatment-emergent adverse events, n (%)	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
All treatment-emergent adverse events	96 (97.0)	[redacted]
Grade ≥2	86 (86.9)	[redacted]
Grade ≥3	57 (57.6)	[redacted]
Grade ≥4	16 (16.2)	[redacted]
Serious adverse events	58 (58.6)	[redacted]
Leading to dose interruption and/or reduction of tarlatamab	31 (31.3)	[redacted]
Leading to discontinuation of tarlatamab	7 (7.1)	[redacted]
Serious	[redacted]	[redacted]
Nonserious	[redacted]	[redacted]
Fatal adverse events	3 (3.0)	[redacted]

1 -> 10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: DCO: data cut-off.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* (2023);[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

Extent of exposure

An overview of exposure to tarlatamab in the 10 mg target dose group at the June 2023 and October 2023 DCO is provided in Table 13 below.

In the 10 mg target dose group (Part 1 and Part 2), patients were treated with tarlatamab for a median of [redacted] weeks (range: [redacted] to [redacted]) at the June 2023 DCO, with [redacted]% and [redacted]% of patients receiving ≥6 and ≥9 months of treatment, respectively. For the October 2023 DCO, patients were treated with tarlatamab for a median of [redacted] weeks (range: [redacted] to [redacted]), with [redacted]% and [redacted]% of patients receiving ≥6 and ≥9 months of treatment, respectively.[5] The median relative dose intensity was [redacted]% at both DCOs.[5]

Table 13: Exposure to tarlatamab (Safety Analysis Set; 10 mg Parts 1 and 2)

	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
Number of doses per patient		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Cumulative dose (mg)		

n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Relative dose intensity (%)[a]		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Treatment duration (weeks)		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Treatment duration (months), n (%)		
≥3	[redacted]	[redacted]
≥6	[redacted]	[redacted]
≥9	[redacted]	[redacted]
≥12	[redacted]	[redacted]

1 -> 10 mg = 1 mg step dose to 10 mg target dose. [a] Relative dose intensity (%) = (Actual cumulative dose / Planned cumulative dose) x 100.
Abbreviations: DCO: data cut-off; IP: investigational product; min: minimum.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* (2023);[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

Treatment-related treatment-emergent adverse events

Treatment-related adverse events were reported for 89 patients (89.9%) in the 10 mg target dose group in Part 1 and Part 2 at the June 2023 DCO, and for [redacted] ([redacted]%) at the October 2023 DCO.[3, 5] An overview of treatment-related TEAEs at both DCOs is provided in Table 14 below. Overall, the most frequently reported treatment-related TEAEs remained the same between DCOs. At the October 2023 DCO, CRS was reported in [redacted]% of patients, pyrexia in [redacted]%, decreased appetite in [redacted]%, dysgeusia in [redacted]%, fatigue in [redacted]% and anaemia in [redacted]%.[5] Overall, no new safety signals were highlighted in the October 2023 DCO.

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Table 14: Treatment-related treatment-emergent adverse events by preferred term for >5% of patients overall (Safety Analysis Set; 10 mg Parts 1 and 2)

Preferred Term, n (%)	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
Number of patients reporting treatment-related treatment-emergent adverse events	89 (89.9)	[redacted]
Cytokine release syndrome	49 (49.5)	[redacted]
Pyrexia	34 (34.3)	[redacted]
Decreased appetite	21 (21.2)	[redacted]
Dysgeusia	20 (20.2)	[redacted]
Asthenia	14 (14.1)	[redacted]
Fatigue	14 (14.1)	[redacted]
Anaemia	16 (16.2)	[redacted]
Constipation	12 (12.1)	[redacted]
Pruritus	7 (7.1)	[redacted]
Nausea	8 (8.1)	[redacted]
Alanine aminotransferase increased	9 (9.1)	[redacted]
Aspartate aminotransferase increased	7 (7.1)	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Taste disorder	8 (8.1)	[redacted]
Vomiting	5 (5.1)	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Blood creatinine increased	5 (5.1)	[redacted]
Thrombocytopenia	4 (4.0)	[redacted]
Immune effector cell-associated neurotoxicity syndrome	2 (2.0)	[redacted]

1 -> 10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: DCO: data cut-off.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* (2023);[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

Serious adverse events

The frequencies of SAEs (grade ≥3) in patients in DeLLphi-301 for the June 2023 and October 2023 DCOs are presented in Table 15. Grade ≥3 adverse events were reported for 57 patients (57.6%) in the 10 mg target dose group in Part 1 and Part 2 at the June 2023 DCO, and for [redacted] patients ([redacted]) at the October 2023 DCO.[3] The most frequently reported Grade ≥3 AEs by preferred term in this target dose group at the June 2023 DCO were anaemia ([redacted]%), lymphocyte count decreased ([redacted]%), lymphopenia ([redacted]%), fatigue ([redacted]%) and hyponatremia ([redacted]%).[2] Similarly, the most frequently reported Grade ≥3 AEs by preferred term at the October

2023 DCO were anaemia ([redacted]), lymphocyte count decreased ([redacted]), lymphopenia ([redacted]), hyponatremia ([redacted]), fatigue ([redacted]), asthenia ([redacted]) and neutrophil count decreased ([redacted]).[5]

Table 15: Treatment-emergent grade 3 or higher adverse events for >2% of patients overall in either DCO (Safety Analysis Set; 10 mg Parts 1 and 2)

System Organ Class Preferred Term, n (%)	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
Number of patients with grade ≥3 treatment-emergent adverse events	57 (57.6)	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Device-related infection	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]

1 ->10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: DCO: data cut-off.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* (2023);[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

Deaths

Patient incidence of fatal treatment-emergent adverse events by system organ class and preferred term in DeLLphi-301 for the 10 mg target dose group at the June 2023 and October 2023 DCOs is presented in Table 16. Fatal adverse events were reported for 3 patients (3.0%) in the 10 mg target dose group in Part 1 and Part 2 at the June 2023 DCO, compared with [redacted] patients ([redacted]) at the October 2023 DCO.[3, 5] [redacted] fatal adverse events

by preferred term were reported for more than 1 patient in the 10 mg target dose group in Part 1 and Part 2 in either DCO.[2, 5]

Table 16: Patient incidence of fatal treatment-emergent adverse events by system organ class and preferred term (Safety Analysis Set; 10 mg Parts 1 and 2)

System Organ Class Preferred Term, n (%)	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
Number of patients with fatal treatment-emergent adverse events	3 (3.0)	[redacted]
Cardiac disorders	[redacted]	[redacted]
Cardio-respiratory arrest	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Hepatic failure	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Coronavirus infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Aspiration	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Respiratory acidosis	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]

1 -> 10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: DCO: data cut-off; NR: not reported.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* (2023);[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

Adverse events of special interest

Patient incidences for AEs of interest are summarised for the 10 mg target dose group in Table 17 below. The proportion of patients experiencing a CRS event remained consistent across both DCOs (49.5% versus [redacted]), with [redacted] Grade 3 or above CRS events (AMQ narrow search) reported in the October 2023 DCO. Furthermore, [redacted] patients had unresolved Grade ≥2 CRS events at the end of either DCO, and the median duration of resolved CRS AEs was consistent across both DCOs ([redacted] days at both DCOs).[5]

Similarly, the proportion of patients experiencing ICANS events also remained consistent across both DCOs (7.1% versus [redacted]%).[3, 5] Furthermore, the number of patients with unresolved Grade ≥2 ICANS decreased from the June 2023 to the October 2023 DCO ([redacted] patients [[redacted]%] versus [redacted] patients [[redacted]%]).[5] The median duration of ICANS AEs was also unchanged from the original DCO, at [redacted] days.[5] However, these estimates were based on a limited number of resolution events. More recent data from the January 2024 DCO show median

resolution of (all-Grade) ICANS events of [redacted] days.[1] As with previous DCOs, ICANS were limited to Grade 1 or 2 severity.

Table 17: Summary of patient incidence of treatment-emergent adverse events of interest (Safety Analysis Set; 10 mg Parts 1 and 2)

Event of Interest, n (%)	1->10 mg (N=99)	
	June 2023 DCO	October 2023 DCO
Cytokine release syndrome (AMQ narrow search)		
All treatment-emergent adverse events	49 (49.5)	[redacted]
Grade ≥2	[redacted]	[redacted]
Grade ≥3	0 (0.0)	[redacted]
Immune effector cell associated neurotoxicity syndrome and associated neurological events (AMQ broad search)		
All treatment-emergent adverse events	7 (7.1)	[redacted]
Grade ≥2	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]
Neurological events (nervous system disorders [SOC] + psychiatric disorders [SOC])		
All treatment-emergent adverse events	[redacted]	[redacted]
Grade ≥2	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]
Neutropenia (AMQ narrow search)		
All treatment-emergent adverse events	[redacted]	[redacted]
Grade ≥2	[redacted]	[redacted]
Grade ≥3	6 (6.1)	[redacted]

1 ->10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: AMQ: Amgen MedDRA query; DCO: data cut-off; SOC: system organ class
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[2] Ahn *et al.* (2023);[3] Amgen Data on File. DeLLphi-301 Clinical Data Package (2nd October 2023 DCO).[5]

2. Updated base case economic results

In line with Committee comments following discussions in the appraisal committee meeting, the revised base case incorporates the following changes:

- Incorporation of EAG corrections suggested in the EAG report, including use of weighted AE costs
- Incorporation of updated MAIC results for tarlatamab incorporating the latest October 2023 DCO from the DeLLphi-301 trial
- Updated parametric model selections for OS and PFS to the best-fitting models as per AIC:

- Tarlatamab parametric models
  - OS: Exponential
  - PFS: Log-normal
- SOC parametric models
  - OS: Gamma
  - PFS: Generalised gamma (using TTD as a proxy as per the model base case)

The updated base case results incorporating the above changes are presented below in Table 18. Results of scenario analyses described in the body of the draft guidance response are presented in Appendix 3. For all analyses, the 1.7x disease severity modifier is met and applied, with the exception of the Flatiron analysis, where the improved QALYs in the SOC arm mean that only the 1.2x disease severity modifier is met; for this scenario alone, the incremental QALYs are multiplied by 1.2.

In line with the conclusions of the base case results presented in the original company submission, the revised base case results presented in Table 18 demonstrate the cost-effectiveness of tarlatamab versus SoC at a willingness-to-pay threshold of £30,000, with an ICER of £28,449.13/QALY gained.

Table 18: Updated base case results (with same PAS as in the original submission)

Treatment	Total discounted Costs (£)	Total discounted LYs	Total discounted QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£ per LY)	ICER (£ per QALY)
SOC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,213.69	£28,449.13

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year.

3. Scenario analysis results

Results from the requested scenario analyses utilising the ratio between PFS and TTD from the tarlatamab parametric model extrapolations to estimate PFS from TTD in the SOC arm and using MAIC-adjusted utility values are presented in Table 19 and Table 20, respectively.

Table 19: Scenario utilising ratio between PFS and TTD from the tarlatamab parametric model extrapolations to estimate PFS from TTD in the SOC arm

Treatment	Total discounted Costs (£)	Total discounted LYs	Total discounted QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£ per LY)	ICER (£ per QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,213.74	£28,474.11

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year.

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Table 20: Scenario results utilising MAIC-adjusted utility values

Treatment	Total discounted Costs (£)	Total discounted LYs	Total discounted QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£ per LY)	ICER (£ per QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,213.69	£28,444.18

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year; MAIC: matching-adjusted indirect comparison; SoC: standard of care.

Additionally, a scenario analysis was conducted using the results of Flatiron PSW analysis presented in Appendix 5. The Flatiron analysis utilises different parametric curve selections based on statistical goodness-of-fit and clinician feedback; the selections are as follows:

- OS: Log-logistic
- PFS: Generalised gamma
- TTD: Exponential

For each outcome, the same parametric curves were used for tarlatamab and SoC. As noted in the main body of the draft guidance response, PFS data are available from the Flatiron database, so it was possible to model PFS directly for SoC in this analysis.

The results of the scenario analysis in which data from the Flatiron PSW analysis are considered are presented in Table 19. These results indicate tarlatamab to be cost-effective versus SoC, with the ICER marginally lower than the revised base case ICER (£28,449.13 versus £26,304.74, respectively).

The main reason for the marginally lower ICER in the Flatiron scenario analysis compared to the revised base case is that the best fitting OS parametric curve for tarlatamab in the Flatiron analysis was the log-logistic curve, which assumes long-term survival benefits, compared to the revised base case in which the best fitting OS parametric curve was the exponential curve, which assumes a constant hazard over time.

Table 21: Scenario using Flatiron PSW analysis results

Treatment	Total discounted Costs (£)	Total discounted LYs	Total discounted QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£ per LY)	ICER (£ per QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,787.71	£26,304.74

Results shown include a x1.2 severity modifier applied to total QALYs.
Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; PSW: propensity-score weighting; QALY: quality-adjusted life year; SoC: standard of care.

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4. Variance-adjusted MAIC

In response to NICE's draft guidance, Amgen has updated the MAIC of DeLLphi-301 vs UK CAS where both means and variances (standard deviations) were matched for the continuous covariates, including "age at diagnosis" and "time from diagnosis to line initiation". The mean and variance adjusted MAIC was carried out following the approach outlined in Phillippo et al.[8] All analyses outlined below are based on the October 2023 DCO for the DeLLphi-301 trial (see Appendix 1).

Updated MAIC weights for the variance adjusted MAIC and baseline characteristics before and after weighting are shown in Figure 6 and Table 22, respectively. Since standard deviations were well balanced for the two continuous variables prior to weighting, the ESS only marginally decreased for the updated mean-and-variance adjusted MAIC analyses from [redacted] (Amgen base case) to [redacted] (variance adjusted MAIC).

Figure 6: Weight distribution after matching

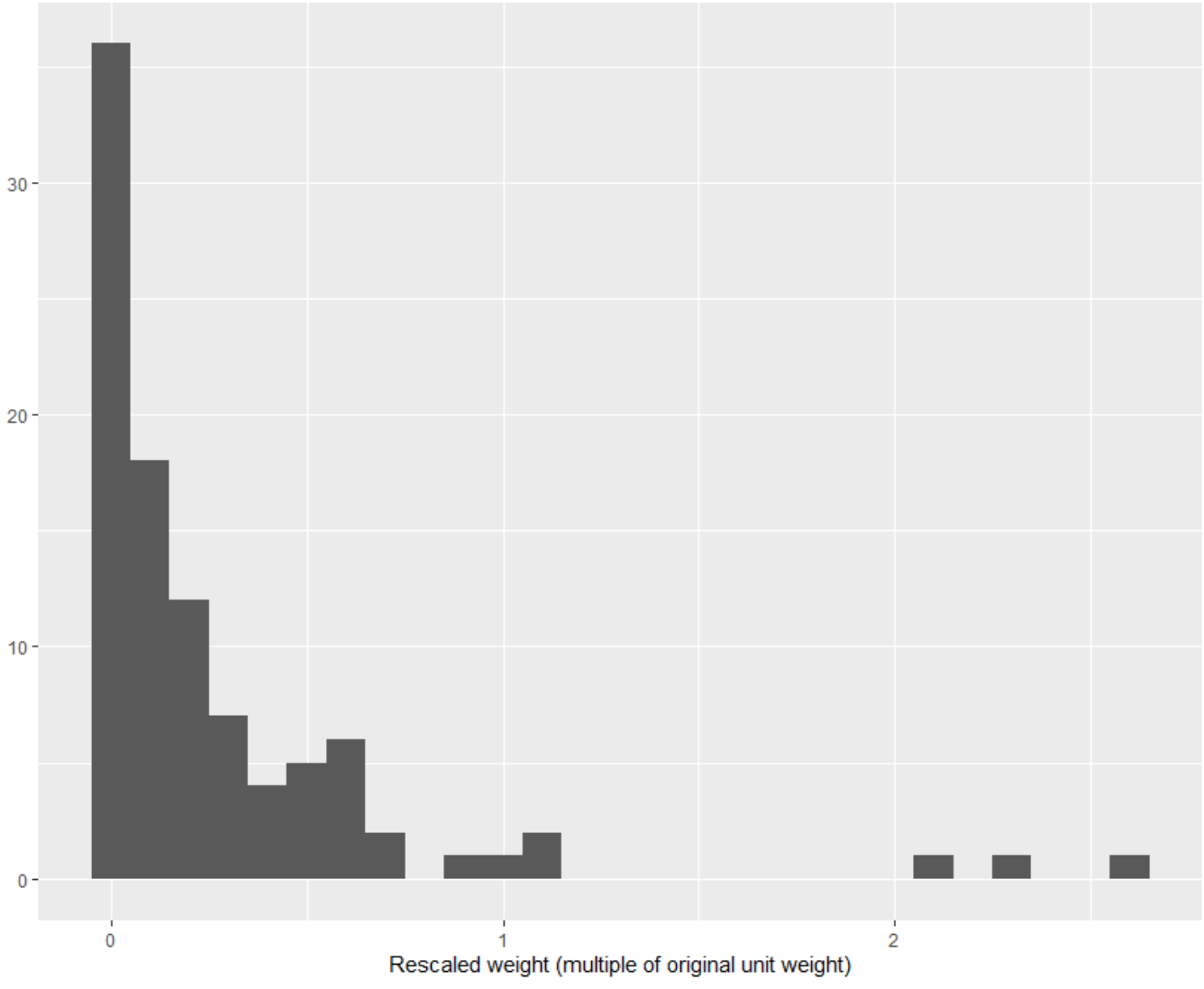

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Table 22: Baseline characteristics for tarlatamab and available treatment options (CAS) groups before and after matching

Prognostic variables	Tarlatamab, before matching N = 97	Available treatment options (CAS) n = 540	Tarlatamab, after matching ESS = [redacted]
Age at index (years) - mean (SD)	63.5 (8.7)	64.1 (9.0)	64.1 (9.0)
Sex (female %)	26.8%	55.0%	55.0%
ECOG PS 0 at index	25.8%	20.0%	20.0%
ECOG PS 1 at index	74.2%	80.0%	80.0%
Presence of brain metastases*	22.7%	5.0%	5.0%
Presence of liver metastases*	38.1%	10.0%	10.0%
Platinum resistant (CFI <90 days) after 1L treatment	26.8%	10.0%	10.0%
Platinum sensitive (CFI 90 to <180 days) after 1L treatment	22.7%	20.0%	20.0%
Platinum sensitive (CFI ≥180 days) after 1L treatment**	50.5%	70.0%	70.0%
Disease stage – ES at initial diagnosis	78.4%	85.0%	85.0%
Time from diagnosis to index (days) – mean (SD)	590.5 (304.4)	629.5 (304.4)	629.5 (304.4)

*Presence of brain and liver metastases were assessed at index in DeLLphi-301 but prior to 1L initiation in CAS.
**In DeLLphi-301, some patients had missing data for disease stage at diagnosis and CFI. For disease stage, it was assumed that all patients with missing data had ES disease. For CFI, it was assumed that all patients with missing data had a CFI longer than 180 days.
Note: To preserve patient anonymity, masking rules were applied to outputs from CAS study. All numbers above 10 were rounded to the nearest 10, percentages were presented rounded to the nearest 5%, and minimum and maximum were replaced with 5th and 95th percentiles.
Abbreviations: 1L: first line; CAS: Cancer Analysis System; CFI: chemotherapy-free interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ES: extensive stage; ESS: effective sample size; SD: standard deviation.

Similar to the base case MAIC analysis, the results of this scenario indicate significantly better OS and PFS in the tarlatamab group relative to the available treatment options group, with an OS HR of [redacted] ([redacted], [redacted]) [base case MAIC: [redacted] ([redacted], [redacted])] and a PFS HR of [redacted] ([redacted], [redacted]) [base case MAIC: [redacted] ([redacted], [redacted])]. KM plots for OS and PFS are shown in Figure 7 and Figure 8, respectively.

Table 23: Adjusted and unadjusted MAIC results tarlatamab vs available treatment options

	ESS	HR (95% CI)	p-value	Median (months) Tarlatamab	Median (months) available treatment options
Overall survival					
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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MAIC base case	[redacted]	[redacted]	[redacted]	[redacted]	
MAIC variance adjustment	[redacted]	[redacted]	[redacted]	[redacted]	
Progression-free survival					
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	
MAIC base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAIC variance adjustment	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; SE: standard error.

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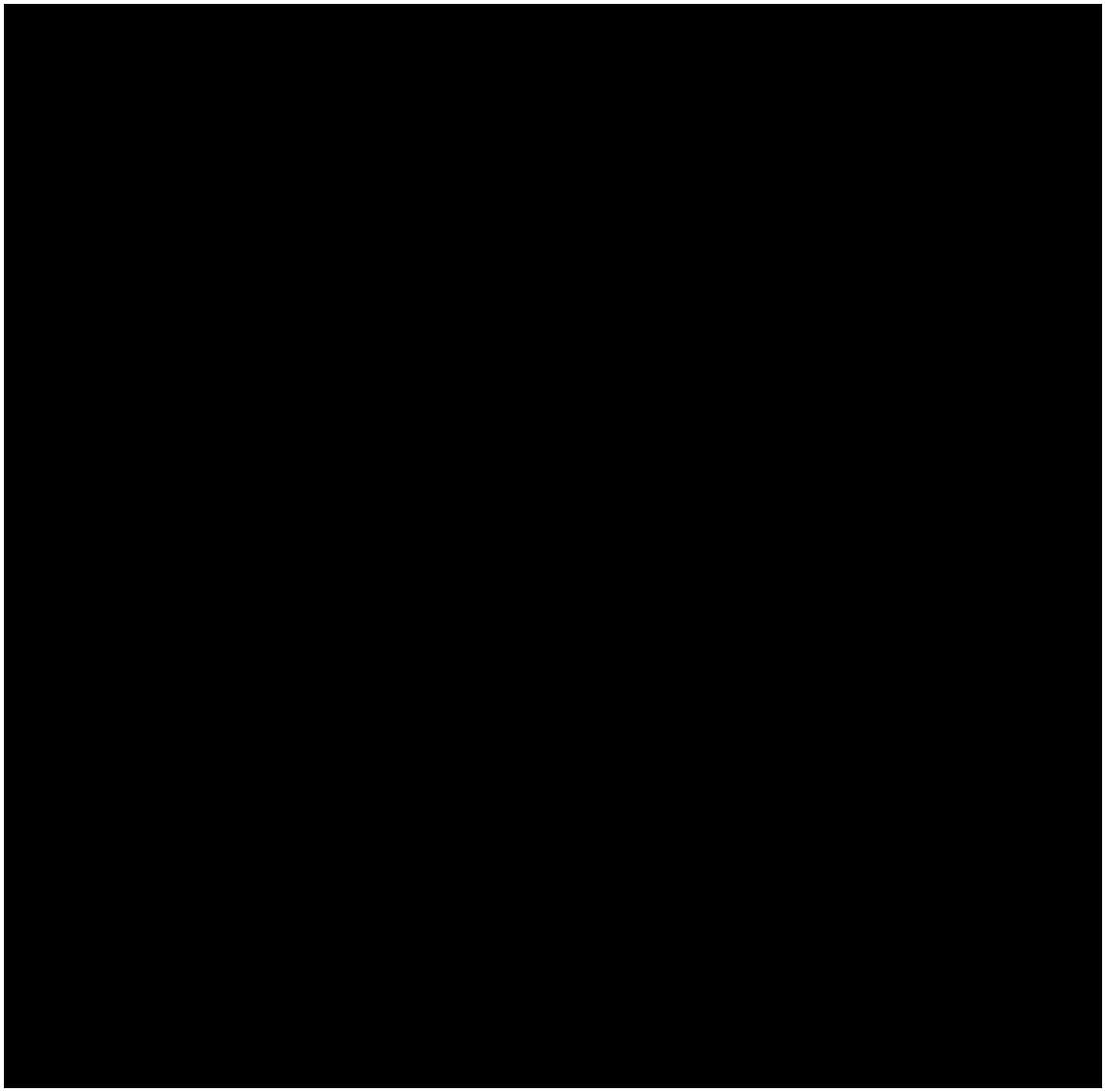
Figure 7: KM curves of weighted and unweighted OS for tarlatamab vs. available treatment options (MAIC variance adjustment)



Abbreviations: KM: Kaplan-Meier; OS: overall survival.

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Figure 8: KM curves of weighted and unweighted PFS for tarlatamab vs. available treatment options MAIC variance adjustment)

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Adjusting for post-progression tarlatamab use

Table 24 shows results for OS adjusted for post-progression tarlatamab use, which indicate significantly better OS in the tarlatamab group compared to available treatment options, regardless of MAIC weights.

Table 24: Adjusted and unadjusted MAIC results tarlatamab vs available treatment options

	ESS	HR (95% CI)	p-value	Median (months) Tarlatamab	Median (months) available treatment options
Overall survival - censoring OS for post-progression tarlatamab use					
MAIC unadjusted					
MAIC base case					

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		[redacted]		[redacted]	
MAIC variance adjustment	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; SE: standard error.

5. Flatiron ITC Methodology and exploratory outcome results

Flatiron Study

The Flatiron Health Research Database is a longitudinal database of EHR, comprising de-identified patient-level structured and unstructured data from approximately 280 community oncology practices and several academic cancer centres in the US.

Patients included in the dataset were diagnosed with SCLC on or after January 1st 2013, had failed their first-line platinum-based regimen and received at least two additional lines of therapy (LOTs), with initiation of second-line therapy between 1st January 2018 and 30th April 2021.

The Flatiron ITC was finalised after the initial submission and addresses key limitations in the CAS MAIC. Specifically, it utilises patient-level data adjustment to achieve cohort balance while maintaining reasonable ESS for assessing treatment effects. Additionally, it offers a thorough evaluation of indirect treatment effects by leveraging validated) and real-world overall response rate rwORR data from Flatiron. Given these strengths, the Company believes this study provides valuable evidence for the committee's decision-making process in this appraisal.

The ITC methodology and results are presented below. The economic results of a scenario analysis in which these Flatiron-informed ITC data are considered in the economic model are presented above in Appendix 3.

Methodology

A patient-level ITC was conducted to estimate relative treatment effects of tarlatamab versus comparator therapies among patients with relapsed or refractory SCLC who had progressed or recurred following one platinum-based regimen and at least one other LOT. A target trial framework was used to emulate a hypothetical randomised controlled trial of tarlatamab versus comparator therapies in 3L+ settings for SCLC.

Adjusting for prognostic factors

Prognostic factors for outcomes in SCLC were previously identified through a multi-step approach, incorporating literature review, empirical analyses of available data, and expert input. In the main analysis, confounding variables considered to be of high and medium importance were adjusted, including: age, ECOG PS, TNM disease stage, number of previous LOTs at index, chemotherapy-free interval after 1L therapy, sex, presence of brain metastases, smoking status and time from SCLC diagnosis to index.

Standardised mortality ratio (SMR) weighting was then used to reweight patients so that the distributions of baseline characteristics of patients treated with comparator therapies matched that of patients treated with tarlatamab.

Outcome analyses

Efficacy outcomes including OS, TTD, TTNTD, PFS, ORR, OS adjusted for post-progression use of tarlatamab, and TTD adjusted for post-progression use of tarlatamab were compared between the tarlatamab and comparator therapies cohorts before and after PS weighting. For OS, TTD, TTNTD, PFS, OS adjusted for post-progression use of tarlatamab, and TTD adjusted for post-progression use of tarlatamab, comparisons were conducted using unweighted and weighted Kaplan-Meier analyses and log rank tests. The method of adjustment for post-progression treatment with tarlatamab was a two-stage adjustment described by Latimer et al.[6]

The outcomes included in the scenario analysis using the Flatiron ITC (i.e. OS, PFS and TTD) are presented in response 4 above. Additional analyses of TTNTD and ORR were conducted, and the results presented in Table 25 below.

HRs comparing tarlatamab vs. comparator therapies were estimated before and after weighting using unweighted and weighted Cox proportional hazards models, respectively.

For ORR, the proportion of patients achieving complete response (CR) or partial response (PR) were summarised and compared between the tarlatamab and comparator therapies cohorts before and after weighting. Odds ratios (ORs) were estimated before and after weighting using unweighted and weighted logistic regression models, respectively.

Exploratory endpoint results

TTNTD and ORR results from the PSW analysis informed by Flatiron data are presented in Table 25. The results are consistent with those presented in the company base case, showing statistically significantly improved PFS outcomes, driven by greater response to treatment.

Table 25: PSW results for tarlatamab vs available treatment options in the Flatiron study (exploratory endpoints)

ITC results for tarlatamab vs available treatment options	TTNTD		ORR	
	HR (95% CI)	p-value	OR (95% CI)	p-value
Before weighting	[redacted]	[redacted]	[redacted]	[redacted]
After weighting	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; MAIC: matching-adjusted indirect treatment comparison; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

NICE National Institute for Health and Care Excellence

Tarlatamab for treating advanced small-cell lung cancer after 2 or more treatments [ID6364]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 18 February 2025. Please submit via NICE Docs.

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Response to the National Institute for Health and Care Excellence's Draft Guidance Consultation Document - Tarlatamab for treating advanced small-cell lung cancer after 2 or more treatments [ID6364]

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are disappointed that the Committee's preliminary decision is not to recommend Tarlatamab in this indication.

- Extensive small cell lung cancer is an aggressive disease, with very few advances in treatment over decades. The outcome from current standard treatment, for this patient group, is woefully poor. There is massive unmet need.

- Tarlatamab is a new type of immunotherapy drug known as a bispecific T-cell engager, or BiTE. As such, it is a novel and innovative treatment in this disease.

- We note the uncertainty highlighted in this preliminary decision. Namely, that, although the clinical trial evidence shows that Tarlatamab increases both the length of time before the cancer progresses and how long they live, Tarlatamab was not directly compared with chemotherapy. There are currently, however, no approved therapies after 2 lines of treatment in small cell lung cancer and we understand that many patients do not receive active anti-cancer treatment in this circumstance.

- The Committee may be aware that we sought opinion on this appraisal, in a short survey of our online patient community. We received 10 responses from those with experience of small cell lung cancer, having asked about the acceptability of accepting treatment, which would require a stay in hospital to monitor side effects for a new treatment. 3 would be willing to spend up to 5 days in hospital, if it offered them an extra treatment option. 6 would want to know more, before making the decision and only one would not accept a treatment, which meant additional days in hospital. So, in general, there is acceptability.

- Tarlatamab is shown to be of benefit in the management of patients with previously treated advanced SCLC.

- We therefore, urge the Committee to reconsider their decision. This is a group of patients who do not have time to wait.

Roy Castle Lung Cancer Foundation
February 2025

CONFIDENTIAL UNTIL PUBLISHED

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

EAG's critique of the company's response to the draft guidance document

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Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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[redacted]

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LIST OF ABBREVIATIONS

AIC	Akaike information criterion
CAS	Cancer Analysis System
CI	Confidence interval
CRS	Cytokine release syndrome
CS	Company submission
DCO	Data cut-off
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
ESS	Effective sample size
HRG	Healthcare Resource Group
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PFS	Progression-free survival
PS	Performance status
PSW	Propensity score weighting
QALY	Quality-adjusted life year
SCLC	Small-cell lung cancer
SOC	Standard of care
TNM	Tumour-node-metastases
TTD	Time-to-treatment discontinuation
UK	United Kingdom
US	United States

1 INTRODUCTION

This document is the External Assessment Group's (EAG's) critique of the response by the company, Amgen Ltd, to the National Institute for Health and Care Excellence's (NICE's) draft guidance document (issue date January 2025) for the technology appraisal of tarlatamab for extensive-stage small-cell lung cancer after two or more treatments (ID6364). The EAG received the company's draft guidance form, associated documents and updated and revised model on 19th February 2025.

The company's draft guidance response contains the following documents:

- The draft guidance response form.
- An updated and revised version of the company's economic model.

The company notes in their draft guidance response form that further data-cuts from the DeLLphi-301 trial of tarlatamab have become available, and evidence from the October 2023, January 2024 and May 2024 data-cuts is provided in the response. The company states that results from the January 2024 and May 2024 data-cut offs were presented at the World Conference on Lung Cancer in September 2024 by Sands et al. (2024)[1] and the company provided the conference abstract with their draft guidance response.

In this report we present the following:

- Our critique of the company's response to NICE's draft guidance on tarlatamab for extensive-stage small-cell lung cancer after two or more treatments and the company's new evidence (section 2).
- A validation of the company's revised cost-effectiveness results (section 3).
- The results of the EAG base case and scenario analyses (section 4).

2 CRITIQUE OF THE COMPANY'S RESPONSE TO THE DRAFT GUIDANCE DOCUMENT

2.1 Comment 1: An updated data cut of the DeLLphi-301 trial has been presented, further supporting that tarlatamab is associated with a durable response and PFS and OS benefits

In section 4.3 of the draft guidance for tarlatamab, it was noted by the committee that the DeLLphi-301 trial suggested a potential for tarlatamab to be clinically effective, but the results from the trial were uncertain.[2] In their original company submission (CS), the company presented DeLLphi-301 trial results from a June 2023 data-cut, in which median follow-up for overall survival (OS) was 10.6 months and median follow-up for progression-free survival (PFS) was [redacted] months. The committee commented that the follow-up times for OS and PFS were relatively short (draft guidance consultation document section 4.3).[2] The draft guidance specified that economic model analyses could be conducted using updated OS and PFS data from the most recent DeLLphi-301 data-cut (sections 4.8, 4.13 and 4.14 of the draft guidance consultation document).[2]

In their response to the draft guidance document, the company reports that additional data are available from data-cuts of the DeLLphi-301 trial dated October 2023, January 2024 and May 2024. The company use the data from the October 2023 data-cut in their economic model updated base case in their response to the draft guidance, because they considered it to contain the most comprehensive set of outcomes and thus this would help ensure consistency across outcomes when adjusting time-to-treatment discontinuation (TTD) and OS for post-progression use of tarlatamab. The company focus on presenting results from the October 2023 data-cut in Appendix 1 of their response but discuss results from the January 2024 and May 2024 data-cuts where considered relevant. Results for objective response, duration of response, disease control, PFS, OS, and adverse reactions are presented for the 99 participants who received tarlatamab 10 mg in both Parts 1 and 2 of the DeLLphi-301 trial (i.e. the blinded independent central review Full Analysis Set). We focus on the updated OS and PFS results here, as the OS and PFS outcomes inform the company's economic model. Adverse event results from the trial also inform the model, but these are discussed in section 2.2.

We summarise the OS and PFS results available from each data cut of the DeLLphi-301 trial in Table 1. We agree with the company's assertion that these longer-term follow-up data show clinical effectiveness results that are consistent with those obtained from the June

2023 data-cut presented in the company's original CS. We additionally note that overlaid KM plot estimates from the June 2023, October 2023 and May 2024 data-cuts for OS shown in Figure 5 of the company's response document show generally similar participant survival trajectories between the data cuts.

Table 1 DeLLphi-301 trial OS and PFS results available from different data-cuts

Outcome	June 2023 DCO (Original CS)	October 2023 DCO (ACM1 response model)	January 2024 DCO	May 2024 DCO
OS				
Number of patients who received at least 1 dose of tarlatamab	99	[redacted]	NA	99
Median follow-up months (95% CI) [a]	[redacted]	[redacted]	NA	20.7
Median OS (KM) months (95% CI) [a]	14.3 (10.8, NE)	[redacted]	NA	15.2 (10.8, NE)
PFS [b]				
Number of patients who received at least 1 dose of tarlatamab	99	[redacted]	99	NA
Median follow-up months (95% CI) [a]	[redacted]	[redacted]	16.4	NA
Median PFS (KM) months (95% CI) [a]	4.9 (2.9, 6.7)	[redacted]	4.3 (3.0, 5.6) [c]	NA

Source: Company response to draft guidance document Table 1 and Appendix 1, including Tables 10 and 11.
ACM1, Appraisal Committee meeting 1; CI, confidence interval; CS, company submission; DCO, data cut-off, NA, not available; NE, not estimable; OS, overall survival; PFS, progression-free survival.
[a] Median and quantiles were estimated using Kaplan-Meier method and 95% CI of median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method.
[b] As assessed by blinded independent central review.
[c] Not reported in the company's response to the draft guidance document, but results reported in Sands et al. (2024) and, although not explicitly stated in Sands et al., the EAG has determined from information in the company's response to the draft guidance document that this result appears to be from the January 2024 data cut-off.

2.2 Comment 2: Safety data from the October 2023 DCO of the DeLLphi-301 trial was consistent with those in the primary analysis (June 2023)

In section 4.6 of the draft guidance document, the committee expressed interest in seeing all further information available about adverse events from a more recent data cut of the DeLLphi-301 trial. Potentially serious adverse events associated with tarlatamab are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). The committee noted comments from the Cancer Drugs Fund lead that the more recent data-cut of the DeLLphi-301 trial showed that CRS happens during the initial weeks following starting treatment and that it resolves relatively quickly, but these data had not been available to the committee. The committee had also discussed that the serious side effects associated with tarlatamab would require training of healthcare staff and capacity planning around the monitoring and management of these adverse effects.[2]

In their response to the draft guidance consultation, the company provided updated adverse events data from the October 2023 data-cut of DeLLphi-301 and compared these to the adverse event findings from the June 2023 data-cut. Limited data are also presented in Sands et al. (2024) from a later data-cut than October 2023, however the specific date is unclear.

The EAG agrees with the company's conclusion that the data from the October 2023 data-cut do not indicate any new safety concerns.

The CRS and ICANS data are compared in Table 2 which shows that between the June 2023 data-cut and Sands et al. data-cut (unclear data cut-off [DCO] date) the rate of CRS has increased by approximately seven percentage points.

Table 2 DeLLphi-301 trial CRS and ICANS adverse event data available from different data-cuts

Outcome	June 2023 DCO (Original CS)	October 2023 DCO (ACM1 response model)	Sands et al. 2024 [1] abstract DCO unclear
CRS	49.5%	[redacted]%	56.8%
Immune effector cell-associated neurotoxicity syndrome	7.1%	[redacted]%	NR

Source: EAG compiled table from information in company response to draft guidance document and Sands et al. 2024.[1]
ACM1, Appraisal Committee meeting 1; CRS, cytokine release syndrome; CS, company submission; DCO, data cut-off, ICANS, immune effector cell-associated neurotoxicity syndrome; NR, not reported.

[redacted] participants experienced a grade ≥3 CRS or ICANS event at either the June 2023 or October 2023 data-cuts. Sands et al. (2024) notes that CRS events were primarily grade 1

or 2 and that no grade 4 or 5 events occurred, which suggests that by the time of the Sands et al. report there had been at least one grade 3 rated CRS event.

The company reports that [redacted] of the grade ≥2 CRS events experienced by participants remained unresolved at the end of either of the June 2023 and October 2024 data-cuts. The median duration of resolved CRS events was reported to be [redacted] days at both data-cuts.

At the October 2023 data-cut there was a reduction in number and rates of unresolved grade ≥2 ICANS events compared to the June 2023 data-cut ([redacted] patients [redacted%] in June 2023 versus [redacted] patients [redacted%] in October 2023). The median duration of the ICANS adverse events was reported to be [redacted] days at both data-cuts. The company point out that the latter figure is based on a small number of events and that the January 2024 data-cut shows a median time of [redacted] days for the resolution of ICANS events.

In relation to the committee's concerns about healthcare staff training and capacity to monitor and manage adverse events, the company state that they have a risk minimisation plan in place, including risk minimisation materials that will be distributed that include a patient alert card and a healthcare professional guide. The company state that the plan and materials have been reviewed by the Medicines and Healthcare Products Regulatory Agency (MHRA). The company also state that they will reactively offer training on the monitoring and management of CRS and ICANS where this is requested by healthcare organisations using tarlatamab.

In summary, the EAG agrees with the company's conclusion that adverse event rates were similar between the June 2023 and October 2023 data-cuts, however, we note that there was a slight increase in the rate of CRS at one of the data-cuts that took place after October 2023 compared to that reported from the June 2023 and October 2023 data-cuts. The company details steps that have taken to address the training of healthcare professionals and the monitoring and management of adverse events when using tarlatamab.

2.3 Comment 3: The MAICs for OS and PFS have been updated to include the latest data from DeLLphi-301; results of these MAICs inform OS and PFS for SoC in the base case economic analysis. Adjustment for covariates using means and variance for continuous covariates, rather than means only, has also been explored.

The results of the company base case matching-adjusted indirect comparison (MAIC) using the updated October 2023 DeLLphi-301 data-cut are consistent with those of the prior analysis. However, the issue of a large reduction in the effective sample size (ESS) remains,

reflecting the lack of overlap between the two populations (ESS = [redacted]). The additional analysis, matching on mean and variance, was successful and led to consistent results; albeit, we again observe a large reduction in the ESS, which, again, indicates a poor overlap between the DeLLphi-301 and UK Cancer Analysis System (CAS) study datasets, meaning the results could be unstable (ESS = [redacted]).

2.4 Comment 4: An alternative source of real-world evidence (RWE), the US-based Flatiron database, has been used to inform an additional ITC analysis utilising a propensity score weighting (PSW) approach, for consideration by the Committee

In section 4.5 of the draft guidance for tarlatamab, the committee noted the EAG's concern about the small ESS that resulted from the company's MAIC included in their original CS. The original MAIC compared tarlatamab using data from the DeLLphi-301 trial with an external control arm consisting of a standard of care single basket comparator, using data from the UK CAS study. The committee also expressed concerns about TTD being used as a proxy for PFS in the standard of care arm of the company's original MAIC analyses (draft guidance consultation document section 4.9); the company had taken this approach due to a lack of available PFS data from databases used in the UK CAS study. In their response to the draft guidance document, the company set out to address these points by conducting an additional indirect treatment comparison (ITC) using real-world evidence from the United States (US)-based Flatiron Health Research database that included patients with small-cell lung cancer (SCLC) who had previously been treated with at least three therapies (a platinum-based regimen and at least two other lines of therapy). An external control arm was constructed by identifying individual-patient level data from the Flatiron database that matched the population eligibility criteria for the DeLLphi-301 trial (patients with relapsed or refractory SCLC whose disease has progressed or recurred following one platinum-based regimen and at least one other line of therapy). The constructed external control arm (n=184) was then used in a patient-level ITC which used a propensity score weighting (PSW) approach. Standardised mortality ratio weighting was applied to reweight the external control participants across baseline characteristics so that the distribution of the characteristics matched that for the tarlatamab cohort. The covariates included in the analyses were: age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), tumour-node-metastases (TNM) disease stage, number of previous lines of therapy at index therapy, chemotherapy-free interval after first-line therapy, sex, presence of brain metastases, smoking status and time from SCLC diagnosis to index (we comment on how these compare to those used in the original MAIC analysis below). The outcomes analysed in the ITC included OS, PFS and TTD, among others. An analysis adjusting OS for post-

progression use of tarlatamab was also carried out. The OS, PFS and TTD results from the analyses were used in an economic model scenario analysis. It is unclear which DeLLphi-301 trial data-cut was used in the Flatiron ITC.

The EAG notes the following about the Flatiron ITC analyses:

- No information is provided in the company's response to the draft guidance about the specific therapies the patients in the US-based Flatiron database external control arm had received at third-line therapy+ and the proportions of patients receiving each therapy. Therefore, the extent to which the external control arm reflects standard of care at third-line+ therapy in National Health Service (NHS) clinical practice is uncertain.
- [redacted]The prognostic factors (covariates) included in the analyses differ to those included in the company's original MAIC base case analysis presented in the CS. For example, the Flatiron ITC includes age as a covariate (the timepoint at which this was captured is unclear), while the MAIC base case included age at diagnosis; smoking status is a covariate in the Flatiron ITC, but was omitted from the original MAIC base case; TNM stage is used in the Flatiron database, but extensive-stage disease at diagnosis was included as a covariate in the original MAIC base case (due to a lack of real-world data about disease-stage at initiation of third-line therapy); presence of liver metastases was included as a covariate in the original MAIC base case but not in the Flatiron ITC. The latter is notable, as our clinical experts advised us that they considered the presence of liver metastases to be one of the most important prognostic factors. Additionally, we note the confidential MAIC report submitted with the CS[3] includes [redacted]

  Some of the differences in the selection of covariates (e.g. inclusion of smoking and absence of liver metastases as covariates) may result in some uncertainty in the findings of the Flatiron ITC.
- The company did not provide information in their response about the distribution of weights for the PSW. Provision of a histogram of the weights attached to patients in the PSW would have been desirable, because it is uncertain how many patients have been removed from the analysis (attached zero weights) and whether the analyses are being driven by a small group of patients with high weights.
- [redacted]The confidential MAIC report submitted with the CS states that [redacted]

[redacted][3] If the same censoring rule was applied in the Flatiron ITC, this could potentially bias results in favour of tarlatamab.

We summarise the results of the Flatiron ITCs of OS, PFS and TTD in Table 3, comparing the results to those obtained from the company's corresponding original and updated MAIC analyses of OS and PFS (both of which utilised data from the UK CAS study, in which TTD was used as a proxy for PFS). The results of both the original and updated MAIC and Flatiron analyses of OS and PFS consistently favour tarlatamab over available treatment options, but the specific hazard ratios differed extensively between the two MAIC analyses (original CS and updated) and the Flatiron ITC analyses, particularly the PFS hazard ratios. It is unclear if the latter is due to the use of actual PFS data in the Flatiron ITC rather than the use of TTD as a proxy for PFS in the standard of care arm, as in the company's original and updated MAICs, or other factors. The company's economic model scenario analysis that used the Flatiron PSW analysis findings resulted in an incremental cost-effectiveness ratio (ICER) of £26,304.74 (NB. a 1.2 severity multiplier was applied). Kaplan Meier curves from the Flatiron ITC are not presented in the company's response nor revised and updated economic model, so the EAG is unable to check and comment on the company's choice of curves (the parametric curves selected are detailed in Appendix 5 of the company's response).

Table 3 ITC results from the company's original and updated MAIC base case and the company's Flatiron ITC of tarlatamab versus available treatment options

Outcome / analysis	ESS	HR (95% CI)	p-value
OS			
Original CS MAIC-unadjusted	N/A	[redacted]	<0.0001
Original CS MAIC-adjusted	[redacted]	[redacted]	0.001
Updated MAIC-unadjusted	N/A	[redacted]	[redacted]
Updated MAIC-adjusted [a]	[redacted]	[redacted]	[redacted]
Flatiron ITC-unadjusted	N/A	[redacted]	[redacted]
Flatiron ITC-adjusted	N/A	[redacted]	[redacted]
Flatiron ITC-adjusted and also adjusted for post-progression tarlatamab use	N/A	[redacted] (NR, NR)	NR
PFS			

Outcome / analysis	ESS	HR (95% CI)	p-value
Original CS MAIC-unadjusted	N/A	[redacted]	<0.0001
Original CS MAIC-adjusted	[redacted]	[redacted]	<0.0001
Updated MAIC-unadjusted	N/A	[redacted]	[redacted]
Updated MAIC-adjusted	[redacted]	[redacted]	[redacted]
Flatiron ITC-unadjusted	N/A	[redacted]	[redacted]
Flatiron ITC-adjusted	N/A	[redacted]	[redacted]
TTD			
Flatiron ITC-unadjusted	N/A	[redacted]	[redacted]
Flatiron ITC-adjusted	N/A	[redacted]	[redacted]

Source: Company's response to the draft guidance document, including Table 3, and CS Tables 19 and 20.
CI, confidence interval; CS, company submission; ESS, effective sample size; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; N/A, not applicable; NR, not reported; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation.
[a] This appears to include adjustment for post-progression tarlatamab use.

In summary, a strength of the company's ITC is the use of individual-patient level data for both the tarlatamab and standard of care cohorts, but due to the concerns about the Flatiron ITC noted above, the EAG suggests that the analysis leads to further uncertainty about the relative treatment effect of tarlatamab versus standard of care.

2.5 Comment 5: Parametric curves used for PFS and OS extrapolations have been selected separately for each treatment, such that they are most appropriate for the updated data cut, produce plausible extrapolations, and do not imply proportional hazards.

The exponential curve was used for both treatment arms in the company's original submission (for OS and TTD) and the EAG report (for PFS and TTD).

The NICE committee stated that analyses that used the exponential distribution to extrapolate outcomes for both tarlatamab and standard of care assumed proportional hazards between arms. This was because the exponential model assumed a constant hazard function. So, because the proportional hazards assumption did not hold, it was considered inappropriate to use the exponential curve for both arms. The committee acknowledged that there was a case for fitting different parametric curves to each arm rather than fitting an exponential curve to both treatment arms.

The company refit the parametric curves to their extended survival data, and stated that they chose the better fitting curve for each arm and avoided using the exponential curve for both arms.

The choice of curves by the company and the EAG are shown in Table 4.

Table 4 Choice of survival curve in the company's DG response and the EAG original and revised preferred assumptions

Company assumptions in DG response	EAG original preferred assumptions	EAG preferred assumptions in DG response
OS: Tarlatamab Exponential, SOC gamma.	OS: Tarlatamab gamma, SOC gamma.	OS: Tarlatamab gamma, SOC gamma.
PFS: Tarlatamab Lognormal, SOC Gen Gamma	PFS: Tarlatamab exponential, SOC exponential.	PFS: Tarlatamab Lognormal, SOC Gen gamma.
TTD: Tarlatamab Exponential, SOC Gen Gamma.	TTD: Tarlatamab Exponential, SOC Exponential	TTD: Tarlatamab Gen gamma, SOC Gen gamma.

DG, draft guidance; EAG, External Assessment Group; OS, overall survival; PFS, progression-free survival; SOC, standard of care, TTD, time-to-treatment discontinuation.

The EAG acknowledges the committee's comments on the use of the exponential curve. We also note that for PFS and OS changes to the curves has minimal impact on the ICER for the company's revised draft guidance base case.

For OS, we prefer to use the same curves for both arms and so prefer to use gamma for both arms, as the gamma is also a good fit for both treatment arms. For PFS, we agree with the company's chosen curves. For TTD, we note that the exponential does not provide a good fit visually and is the worst fit by Akaike information criterion (AIC), whilst the generalised gamma provides a much better fit, in our view. We therefore choose the generalised gamma for both treatment arms.

2.6 Comment 6: Alternative methods of estimating PFS in the standard of care arm have been explored, derived from the HR between PFS and TTD in the DeLLphi-301 trial

In the absence of PFS data for standard of care, the company assumed that PFS was equal to TTD in the original company submission. However, the NICE committee suggested that

the company provide additional analyses to explore different approaches to modelling PFS in the standard care arm, including but not limited to analyses adjusting TTD for the standard of care arm by the ratio between PFS and TTD that was reported in DeLLphi-301.

The company has conducted a scenario applying a hazard ratio derived from the TTD and PFS results from the DeLLphi-301 trial, as requested by the NICE committee. In this scenario (reported in Table 19 of the company's response) the ICER increases marginally from £28,449 to £28,474 per quality-adjusted life year (QALY).

The company maintain that the best approach is to assume that PFS is equal to TTD because of the poor progression-free survival for standard of care which would likely mean that any differences observed between TTD and PFS are likely to be small.

The EAG agree with the company's approach of assuming PFS to be equal to TTD for the reasons given by the company. We note that using the approach suggested by the committee has minimal effect on the ICER.

2.7 Comment 7: A scenario analysis has been conducted in which health state utility values are derived from the DeLLphi-301 trial, adjusted for the characteristics of the UK CAS study population.

In the original company base case, the company used utility values from the 10 mg target dose DeLLphi-301 trial population (n=97) for the progression-free and post-progression health states. The EAG noted that utility values from the population used in the MAIC (n=[redacted]) would be beneficial to explore, as this would better match the standard of care population. The committee requested that the company provide the MAIC-adjusted utility values from the DeLLphi-301 trial (section 4.14 of the draft guidance), which the company provided in their response.

Table 5 Health state utility values (unadjusted versus MAIC-adjusted)

Health state	Unadjusted		MAIC-adjusted	
	Mean	SE	Mean	SE
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]

Source: reproduced from Table 6 of the company's response to draft guidance
MAIC, matching-adjusted indirect treatment comparison; SE, standard error

The company consider the MAIC-adjusted utilities to be less robust and less valid in comparison to the original unadjusted utility values, and have not implemented them in the updated base case, instead opting to present them as a scenario analysis. Using the MAIC-

adjusted utilities decreases the ICER marginally; the company consider using the unadjusted utilities to be a conservative approach. The EAG considers the MAIC-adjusted utility values to be more appropriate given the standard of care population, and have included these utilities in the EAG base case (see section 4.1). The MAIC-adjusted and unadjusted utility values are shown in Table 5.

2.8 Comment 8: A weighted approach to calculating the costs of AEs has been adopted in the updated base case analysis

As discussed in section 4.11 of the committee draft guidance, for adverse events the company selected the most expensive Healthcare Resource Group (HRG) code in the cases where multiple HRG codes could apply. The EAG preferred to use a weighted average across all HRG codes per adverse event, to ensure that costs were not overestimated. The committee agreed with the EAG's approach and in section 4.13 of the draft guidance, the committee requested that the weighted average approach be used in the base case model. The company have implemented this appropriately in their updated base case.

2.9 Comment 9: The company's conclusion that application of the 1.7x severity modifier is appropriate remains unchanged in the updated economic model and reflects the devastatingly poor outcomes associated with current treatment for third-line ES-SCLC.

The company states that there is no change to the estimates of total QALYs for standard of care, which informs the QALY shortfall calculation, and therefore the QALY shortfall remains above NICE's threshold of 0.95, above which a severity modifier of 1.7 is applied. The EAG has checked the results in the model and agree with the company's statement above. We therefore also agree that a severity modifier of 1.7 should be applied, according to NICE guidelines.

3 VALIDATION OF THE COMPANY'S REVISED COST EFFECTIVENESS RESULTS

The changes to the company base case for their revised results are:

- Adverse event costs using weighted averages,
- OS: Tarlatamab exponential, SOC gamma,
- PFS: Tarlatamab lognormal, SOC generalised gamma,
- TTD: Tarlatamab exponential, SOC generalised gamma.

The new survival curves were fitted to the data from the October 2023 data-cut. The details of the individual changes to the company's base case results are shown in Table 6. The EAG confirm that no additional changes have been made to the company model.

Table 6 Changes to the company's base case: cumulative impact (deterministic) with PAS for tarlatamab

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
EAG corrected company base-case results	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£34,958
+ Adverse event costs: EAG recalculated.	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£37,341
+ OS: Tarlatamab Exponential, SOC gamma.	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£30,745
+ PFS: Tarlatamab Lognormal, SOC Gen. gamma.	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£30,469
+TTD: Tarlatamab Exponential, SOC Gen. gamma.	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£28,449
Revised company base case results	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£28,449

Source: EAG created table
EAG, evidence assessment group; OS, overall survival; PFS, progression-free survival; HRQoL, health-related quality of life; PD, progressed disease; SOC, standard of care; Gen, generalised. Severity multiplier of 1.7 applied to incremental QALYs.

4 EAG ANALYSES

4.1 EAG's preferred assumptions

The EAG's preferred assumptions (where different from the company's) are:

- OS: Tarlatamab gamma, SOC gamma,
- TTD: Tarlatamab generalised gamma, SOC generalised gamma,
- Quality of life: MAIC-adjusted utilities from DeLLphi-301 trial.

The results for the EAG's preferred assumptions increase the ICER to £31,437 per QALY.

Table 7 EAG's preferred assumptions - cumulative impact (deterministic) with PAS for tarlatamab

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
Revised company base case results	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£28,449
+ OS: Tarlatamab gamma, SOC gamma	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£28,584
+ TTD: Tarlatamab Gen. gamma, SOC Gen. gamma.	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£31,439
+ Quality of life: MAIC-adjusted utilities from DeLLphi-301 trial.	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£31,437
Revised EAG base case results	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£31,437

Source: EAG created table
EAG, evidence assessment group; Gen, generalised; HRQoL, health-related quality of life; OS, overall survival; PD, progressed disease; PFS, progression-free survival; SOC, standard of care. Severity multiplier of 1.7 applied to incremental QALYs.

4.2 Scenario analysis conducted in the EAG's base case

The EAG conducted scenario analyses on the EAG base case to show the effect of alternative assumptions. The results are shown in Table 8. The scenario results are most influenced by the choice of curves for time on treatment.

Table 8 EAG's scenario analyses (deterministic) with PAS for tarlatamab

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
EAG revised base case	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£31,437
OS: Tarlatamab exponential, SOC gamma	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£31,286
TTD: Tarlatamab exponential, SOC Generalised gamma.	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£28,581
Quality of life: ITT utilities from DeLLphi-301 trial.	SOC	[redacted]	[redacted]	-
	Tarlatamab	[redacted]	[redacted]	£31,439
Flatiron PSW analysis (with severity multiplier of 1.2)	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£26,214

Source: EAG created table
EAG, evidence assessment group; HRQoL, health-related quality of life; ITT, intention to treat; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PSW, propensity score weighting; SOC, standard of care.
Severity multiplier of 1.7 applied to incremental QALYs.

5 EAG CONCLUSION

Longer-term follow-up data from the October 2023 data-cut of the DeLLphi-301 trial provide results that are consistent with those from the June 2023 data-cut originally presented in the CS. The MAIC base case analysis that was updated with the October 2023 data resulted in similar hazard ratios for OS and PFS to the original MAIC base case analysis, and a scenario analysis exploring adjustment for covariates using means and variance for continuous covariates, rather than means only, resulted in similar OS and PFS results to the base case analysis. However, the issue of a small effective sample size remains, indicating that the results of the MAICs may be unreliable. The company's updated safety data from the October 2023 and later data-cuts suggest no new safety signals, but the EAG notes that a higher rate of CRS (56.8%) was reported in Sands et al. (2024)[1] from a data-cut (exact date unclear) later than October 2023. Using the Flatiron database as a source of real-world data in an ITC analysis comparing tarlatamab to available treatment options contributes, in the EAG's opinion, further uncertainty about the relative effectiveness of tarlatamab and standard of care. In particular, information was not provided in the company's response to draft guidance on the treatments participants from the Flatiron database received at third-line therapy+. Therefore it is unclear whether they reflect those used in NHS clinical practice.

The company revised and updated their economic model base case following draft guidance, as discussed in section 2. The EAG disagrees with some of the assumptions in the company's model. Our preferred assumptions include:

- OS: Tarlatamab gamma, SOC gamma,
- TTD: Tarlatamab generalised gamma, SOC generalised gamma,
- Quality of life: MAIC-adjusted utilities from DeLLphi-301 trial.

Incorporating the EAG preferred assumptions, the ICER increases to £31,437 per QALY for tarlatamab versus standard of care.

6 REFERENCES

1. Sands J, Cho BC, Ahn M-J, et al. Tarlatamab Sustained Clinical Benefit and Safety in Previously Treated SCLC: DeLLphi-301 Phase 2 Extended Follow-up *IASLC 2024 World Conference on Lung Cancer, 9th September 2024*; 2024.

2. National Institute for Health and Care Excellence. Draft guidance consultation: Tarlatamab for extensive-stage small-cell lung cancer after 2 or more treatments. NICE, 2025.

3. Analysis Group Inc (Amgen Data on File). Indirect treatment comparison of tarlatamab versus available treatment options in patients with relapsed or refractory small cell lung cancer after two prior lines of treatment, 2024.