

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**EAG's critique of the company's response to the draft  
guidance document**

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## TABLE OF CONTENTS

1	INTRODUCTION .....	5
2	CRITIQUE OF THE COMPANY'S RESPONSE TO THE DRAFT GUIDANCE DOCUMENT .....	6
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 .....	6
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).....	8
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. ....	9
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 .....	10
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. ....	13
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.....	14
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.....	15
2.8	Comment 8: A weighted approach to calculating the costs of AEs has been adopted in the updated base case analysis.....	16
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.....	16
3	VALIDATION OF THE COMPANY'S REVISED COST EFFECTIVENESS RESULTS.	17
4	EAG ANALYSES .....	18

4.1	EAG’s preferred assumptions .....	18
4.2	Scenario analysis conducted in the EAG’s base case .....	18
5	EAG CONCLUSION .....	20
6	REFERENCES .....	21

## LIST OF TABLES

Table 1	DeLLphi-301 trial OS and PFS results available from different data-cuts.....	7
Table 2	DeLLphi-301 trial CRS and ICANS adverse event data available from different data-cuts .....	8
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 .....	12
Table 4	Choice of survival curve in the company’s DG response and the EAG original and revised preferred assumptions .....	14
Table 5	Health state utility values (unadjusted versus MAIC-adjusted) .....	15
Table 6	Changes to the company’s base case: cumulative impact (deterministic) with PAS for tarlatamab.....	17
Table 7	EAG’s preferred assumptions - cumulative impact (deterministic) with PAS for tarlatamab.....	18
Table 8	EAG’s scenario analyses (deterministic) with PAS for tarlatamab .....	19

## LIST OF ABBREVIATIONS

<b>AIC</b>	Akaike information criterion
<b>CAS</b>	Cancer Analysis System
<b>CI</b>	Confidence interval
<b>CRS</b>	Cytokine release syndrome
<b>CS</b>	Company submission
<b>DCO</b>	Data cut-off
<b>EAG</b>	External Assessment Group
<b>ECOG</b>	Eastern Cooperative Oncology Group
<b>ESS</b>	Effective sample size
<b>HRG</b>	Healthcare Resource Group
<b>ICANS</b>	Immune effector cell-associated neurotoxicity syndrome
<b>ICER</b>	Incremental cost-effectiveness ratio
<b>ITC</b>	Indirect treatment comparison
<b>MAIC</b>	Matching-adjusted indirect comparison
<b>MHRA</b>	Medicines and Healthcare Products Regulatory Agency
<b>NHS</b>	National Health Service
<b>NICE</b>	National Institute for Health and Care Excellence
<b>OS</b>	Overall survival
<b>PFS</b>	Progression-free survival
<b>PS</b>	Performance status
<b>PSW</b>	Propensity score weighting
<b>QALY</b>	Quality-adjusted life year
<b>SCLC</b>	Small-cell lung cancer
<b>SOC</b>	Standard of care
<b>TNM</b>	Tumour-node-metastases
<b>TTD</b>	Time-to-treatment discontinuation
<b>UK</b>	United Kingdom
<b>US</b>	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 19<sup>th</sup> 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)<sup>1</sup> 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.<sup>2</sup> 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 ■ months. The committee commented that the follow-up times for OS and PFS were relatively short (draft guidance consultation document section 4.3).<sup>2</sup> 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).<sup>2</sup>

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
<b>OS</b>				
Number of patients who received at least 1 dose of tarlatamab	99	█	NA	99
Median follow-up months (95% CI) <sup>a</sup>	█	█	NA	20.7
Median OS (KM) months (95% CI) <sup>a</sup>	14.3 (10.8, NE)	█	NA	15.2 (10.8, NE)
<b>PFS <sup>b</sup></b>				
Number of patients who received at least 1 dose of tarlatamab	99	█	99	NA
Median follow-up months (95% CI) <sup>a</sup>	█	█	16.4	NA
Median PFS (KM) months (95% CI) <sup>a</sup>	4.9 (2.9, 6.7)	█	4.3 (3.0, 5.6) <sup>c</sup>	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.

<sup>a</sup> 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.

<sup>b</sup> As assessed by blinded independent central review.

<sup>c</sup> 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.<sup>2</sup>

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 <sup>1</sup> abstract DCO unclear
CRS	49.5%	█%	56.8%
Immune effector cell-associated neurotoxicity syndrome	7.1%	█%	NR

Source: EAG compiled table from information in company response to draft guidance document and Sands et al. 2024.<sup>1</sup>

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.

█ 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  $\geq 2$  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  $\geq 2$  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 = ■■■). 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 = ■■■).

#### **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.

■ 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<sup>3</sup> includes ■■■■■  
■■■■■  
■■■■■

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.

■ The confidential MAIC report submitted with the CS states that ■■■■■  
■■■■■



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

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.

<sup>a</sup> 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=█) 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	█	█	█	█
Post-progression	█	█	█	█

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	██████	████	-
	Tarlatamab	██████	████	£34,958
+ Adverse event costs: EAG recalculated.	SOC	██████	████	-
	Tarlatamab	██████	████	£37,341
+ OS: Tarlatamab Exponential, SOC gamma.	SOC	██████	████	-
	Tarlatamab	██████	████	£30,745
+ PFS: Tarlatamab Lognormal, SOC Gen. gamma.	SOC	██████	████	-
	Tarlatamab	██████	████	£30,469
+TTD: Tarlatamab Exponential, SOC Gen. gamma.	SOC	██████	████	-
	Tarlatamab	██████	████	£28,449
Revised company base case results	SOC	██████	████	-
	Tarlatamab	██████	████	£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	██████	██	-
	Tarlatamab	██████	██	£28,449
+ OS: Tarlatamab gamma, SOC gamma	SOC	██████	██	-
	Tarlatamab	██████	██	£28,584
+ TTD: Tarlatamab Gen. gamma, SOC Gen. gamma.	SOC	██████	██	-
	Tarlatamab	██████	██	£31,439
+ Quality of life: MAIC-adjusted utilities from DeLLphi-301 trial.	SOC	██████	██	-
	Tarlatamab	██████	██	£31,437
Revised EAG base case results	SOC	██████	██	
	Tarlatamab	██████	██	£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	██████	███	-
	Tarlatamab	██████	███	£31,437
OS: Tarlatamab exponential, SOC gamma	SOC	██████	███	-
	Tarlatamab	██████	███	£31,286
TTD: Tarlatamab exponential, SOC Generalised gamma.	SOC	██████	███	-
	Tarlatamab	██████	███	£28,581
Quality of life: ITT utilities from DeLLphi-301 trial.	SOC	██████	███	-
	Tarlatamab	██████	███	£31,439
Flatiron PSW analysis (with severity multiplier of 1.2)	SOC	██████	███	
	Tarlatamab	██████	███	£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)<sup>1</sup> 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.