16 April 2026
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Imdylltra (tarlatamab)
Treatment of pulmonary neuroendocrine carcinoma
EU/3/23/2876

Sponsor: Amgen Europe B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Tarlatamab
Other name(s)	-
International Non-Proprietary Name	Tarlatamab
Tradename	Imdylltra
Initial orphan condition	Treatment of small cell lung cancer
Amended orphan condition (at time of review of criteria for orphan designation)	Treatment of pulmonary neuroendocrine carcinoma
Sponsor's details:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda Noord-Brabant Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Amgen Europe B.V.
COMP opinion	7 December 2023
EC decision	12 January 2024
EC registration number	EU/3/23/2876
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Eva Skovlund / Robert Porszasz
Applicant	Amgen Europe B.V.
Application submission	27 June 2025
Procedure start	17 July 2025
Procedure number	EMA/H/C/006451
Invented name	Imdylltra
Proposed therapeutic indication	Imdylltra is indicated as monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. Further information on Imdylltra can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/imdylltra
CHMP opinion	26 March 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Maria Elisabeth Kalland / Brigitte Schwarzer-Daum
Sponsor's report submission	16 December 2025
COMP discussion and adoption of list of questions	17-18 March 2026
Oral explanation cancelled by the COMP	14 April 2026
COMP opinion	16 April 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2024 was based on the following grounds:

The sponsor Amgen Europe B.V. submitted on 13 July 2023 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing tarlatamab for treatment of small cell lung cancer (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing tarlatamab was considered justified based on non-clinical data in models of the condition showing an inhibition of tumour growth, in combination with clinical data demonstrating a tumour response in patients affected by the condition and whose disease progressed after two prior lines of treatment;
- the condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a poor 5-year overall survival;
- the condition was estimated to be affecting approximately 1.3 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tarlatamab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in relapsed or refractory patients with small cell lung cancer who had progressed after two prior lines of treatment including atezolizumab and durvalumab, and who responded to treatment with the proposed product. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing tarlatamab as an orphan medicinal product for the orphan condition: treatment of small cell lung cancer.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Small-cell lung cancer (SCLC) is an aggressive neuroendocrine carcinoma known for its poor differentiation, high metastatic potential, and poor prognosis. Representing about 15% of all lung cancers, it is strongly associated with tobacco exposure, with up to 9 in 10 cases caused by smoking (Wéber et al. 2023). While environmental factors have been suggested as additional risk factors, evidence remains limited (Rudin et al., 2021). Genetic mutations, particularly the loss of function in tumour suppressor genes (TP53 and RB1) and MYC oncogene amplification, drive its aggressiveness, leading to rapid tumour growth, poor genomic stability, and replication stress (Rudin et al., 2021; Saltos et al., 2020). Pathophysiologically, SCLC is characterized by high metastatic potential and resistance to apoptosis, often associated with paraneoplastic syndromes. It overexpresses VEGF, which promotes angiogenesis and contributes to its poor prognosis (Montanino et al., 2021). Histologically, SCLC appears as irregular masses in the central lung, with distinctive features such as cytoplasmic globules and the Azzopardi effect (Raso et al., 2021).

The World Health Organization (WHO) classifies SCLC as a "small cell carcinoma" within the neuroendocrine carcinoma category. In 2022, the WHO classification of Epithelial Neuroendocrine Neoplasms by anatomic site grouped SCLC and Large Cell Neuroendocrine Carcinoma (LCNEC) under the broader category of "Pulmonary Neuroendocrine Carcinoma. The tumour-node-metastasis (TNM) staging system further classifies SCLC into "limited stage" (LS), "extensive stage" (ES), and "recurrent," based on tumour size, lymph node involvement, and distant metastasis (Arriola et al., 2022; Dingemans et al., 2021). In addition to the TNM staging system, the Veterans Administration Lung Study Group (VALG) staging system is used due to its simplicity and clinical utility. According to the European Society for Medical Oncology (ESMO) guidelines, SCLC is divided into two histological subtypes: pure SCLC (P-SCLC) and combined SCLC (C-SCLC), with the latter involving additional non-small cell lung cancer (NSCLC) components (Li et al., 2022).

Clinically, SCLC typically presents with centrally located tumours in the major airways and extensive metastatic spread. Patients often remain asymptomatic until advanced disease stages due to the rapid growth of the tumour. If symptoms are present, they are typically recent and may include cough, dyspnoea, haemoptysis, wheezing, upper body oedema, and laryngeal nerve compression leading to vocal cord paralysis (Rudin et al., 2021). The 2021 ESMO guidelines recommend a diagnostic approach involving smoking history, physical examination, blood tests, and imaging studies (Dingemans et al., 2021).

The approved therapeutic indication "Imdylltra is indicated as monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy" falls within the scope of the designated orphan condition "pulmonary neuroendocrine carcinoma".

SCLC is recognized as a distinct subtype of lung cancer characterized by its rapid progression, unique genetic alterations, and specific clinical and histopathological features. The COMP now considers both Small Cell Lung Carcinoma (SCLC) and Large Cell Neuroendocrine Carcinoma (LCNEC) of the lung as poorly differentiated neuroendocrine carcinomas (NECs). Consequently, new applications for orphan designation will be grouped under the broader category of "Pulmonary Neuroendocrine Carcinoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by a positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

SCLC remains the most lethal lung cancer subtype and is characterized by aggressive growth and early metastasis to distant sites, resulting in most patients being diagnosed with extensive-stage disease (ES-SCLC). The median overall survival (OS) for SCLC is less than two years (i.e., 18.4 months), despite available treatments (Jones et al., 2020). Patients with limited stage (LS) SCLC, have a slightly better prognosis, with a 5-year OS rate of 20-25%, whereas patients with extensive stage (ES) have a 5-year OS rate of only 2% (Arriola et al., 2022; Tsiouprou et al., 2019). Stage II and III SCLC patients also have an increased risk of death compared to patients with Stage I (Zeng et al., 2021). SCLC is known to be chronically debilitating due to paraneoplastic syndromes.

Although 20% to 30% of patients with limited stage can be cured with chemotherapy and radiation therapy, treatment is rarely curative in extensive stage, with over half of patients relapsing within 6 months after first line chemo immunotherapy (Cheng et al, 2025; Cheng et al, 2024b; Cheng et al, 2022; Wang et al, 2022; Paz-Ares et al, 2019; Horn et al, 2018). Since the orphan designation in 2024, there have been no significant changes in the chronically debilitating or life-threatening nature of the condition. While new treatments, such as serplulimab and durvalumab, have been approved, these have not fundamentally improved the long-term prognosis for ES-SCLC. Over 90% of patients relapse within two years, and the median OS for second-line treatment remains around 6–8 months.

The COMP considers that the condition remains chronically debilitating and life threatening due to its rapid progression, development of widespread metastases, and poor prognosis.

Number of people affected or at risk

At the time of the orphan designation in 2024, the COMP concluded that the condition was estimated to be affecting approximately 1.3 in 10,000 persons in the European Union (EU). To estimate the current prevalence of SCLC in the 27 member states of the EU and the three European Economic Area (EEA) countries (EU27+) population, the sponsor applied a multi-step approach combining a systematic literature review with searches of epidemiological databases and cancer registries.

A systematic literature review was conducted in PubMed following PRISMA methodology (Liberati et al., 2009). Of 313 records identified, 11 publications were assessed in detail; however, none reported population-based prevalence estimates for SCLC in EU countries. Consequently, no studies were retained for prevalence estimation.

In the absence of direct literature data, the sponsor relied on cancer registries and epidemiological databases. A limited number of registries reported SCLC-specific prevalence, including the Netherlands Cancer Registry (1.41 per 10,000), the National Cancer Registry Ireland (1.08 per 10,000), and Orphanet (1.2 per 10,000). Where SCLC-specific data were not available, prevalence was estimated indirectly from lung cancer prevalence by applying an approximate proportion of 15% for SCLC, based

on published literature (Rudin et al., 2021; Saltos et al., 2020). Population denominators were obtained from sources such as the United Nations World Population Prospects and NORDCAN.

Using this approach, additional estimates were derived from several registries and databases, including the European Cancer Information System (ECIS), GLOBOCAN, and national registries (Table 1). Reported or indirectly calculated SCLC prevalence ranged from approximately 1.08 to 4.26 per 10,000 persons, with EU-level estimates (e.g., ECIS: 2.49 per 10,000; GLOBOCAN: 1.34 per 10,000) falling within this range.

Geographic variability was noted, with Denmark reporting the highest prevalence (4.26 per 10,000) and Ireland the lowest (1.08 per 10,000). Such variations may reflect differences in registry practices, diagnostic criteria, or population demographics. Sensitivity analyses suggest that changes in the assumed proportion of SCLC among lung cancers (e.g., 10–20%) could shift prevalence estimates. However, all estimates remain below the orphan designation threshold of 5 per 10,000 persons.

The sponsor acknowledged several limitations, including the use of combined tracheal and lung cancer codes, variability in registry practices, reliance on indirect estimates, and the impact of the aggressive disease course and short survival of SCLC on prevalence estimates. Potential effects of COVID-19 on cancer diagnosis rates were also noted.

Table 1. Complete Prevalence of SCLC: Data Extracted from Cancer Registries or Reports.

Registry or Database	**Country**	**Year**	**Case Definition (ICD-10 / ICD-O - 3 codes)**	**SCLC Prevalence (per 10,000)**	**Prevalence Duration[d]**	**Reference**
European Cancer Information System	EU 27	2020	C339, C34	2.49[c]	20 yrs	European Cancer Information System, 2025
	EU-27 + Norway, Iceland[b]	2020	C339, C34	2.49[c]	20 yrs	
Netherlands Cancer Registry	Netherlands	2022	C34; ICD-0-3 8041-8045	1.41	20 yrs	Netherlands Cancer Registry, 2023
Czech Republic Cancer Registry	Czech Republic	2023	C34	2.16[c]	33 yrs	Krejčí et al. Portal of Cancer Epidemiology in the Czech Republic. 2024
Slovenia Cancer Registry	Slovenia	2021	C33-C34	3.18[c]	60 yrs	Slovenian Cancer Registry, 2022
Robert Koch Institute (RKI)	Germany	2019	C33-C34	2.97[c]	20 yrs	German Centre for Cancer Registry Data, 2022

NORDCAN	Nordic Countries[a]	2023	C33-C34	2.82[c]	Total	NORDCAN, 2025
	Denmark			4.26[c]	Total	
	Sweden			2.32[c]	Total	
	Norway			3.15[c]	Total	
	Finland			1.93[c]	Total	
	Iceland			1.97[c]	Total	
GLOBOCAN	EU 27	2023	C33-C34	1.34[c]	5 yrs	Ferlay et al, 2024
	EU-27 + Norway, Iceland[b]	2022	C33-C34	1.33[c]	5 yrs	
National Cancer Registry Ireland	Ireland	2022	C34; ICD-0-3 8041-8045	1.08	28 yrs	National Cancer Registry Ireland, 2024
Orphanet	EU	NA	C34.9	1.2	NA	Orphanet, 2025

COMP discussion

The committee broadly agrees with the methodology proposed by the sponsor, including the use of registry data and indirect estimation approaches in the absence of directly reported SCLC prevalence data. However, the COMP acknowledges the inherent limitations of these methods, such as reliance on assumptions regarding SCLC proportions and variability across data sources.

Taking into account the range of estimates identified and the relative robustness and EU-specific coverage of the underlying data, the committee initially considered the estimate derived from the ECIS as the most appropriate, corresponding to a prevalence estimate of approximately 2.5 per 10,000 persons in the EU27+ population. However, this estimate is based on indirect calculations using extended prevalence duration periods (e.g., up to 20 years) and an assumed proportion of SCLC among all lung cancers. This approach inherently reflects the longer survival associated with non-small cell lung cancer (NSCLC) and does not adequately account for the aggressive clinical course and short survival typical of SCLC. Consequently, applying a fixed proportion of SCLC to a long-duration prevalence pool may lead to an overestimation of SCLC prevalence.

Directly reported SCLC-specific prevalence data from national cancer registries and rare disease databases consistently provide lower and more homogeneous estimates, generally ranging from approximately 1.1 to 1.4 per 10,000 persons. These data are considered more representative of the underlying disease epidemiology, as they are not influenced by assumptions regarding SCLC proportions or by the inclusion of long-term survivors of other lung cancer subtypes.

Considering the consistency of SCLC-specific data, the aggressive nature of the disease, and the methodological limitations of indirect prevalence-based approaches, the committee concludes that a more conservative prevalence estimate in the range of approximately 1.3 to 1.6 per 10,000 persons in the EU27+ population is more appropriate. Consequently, the COMP accepted that the same conclusion as for the initial orphan designation is supported by the data provided, confirming that SCLC affects approximately 1.3 in 10,000 persons in the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Several products have been authorised for the treatment of ES-SCLC. The sponsor provided a list of medicinal products authorised for the treatment of SCLC and outlined the treatment landscape for patients with ES-SCLC.

Treatment for ES-SCLC is generally palliative, with therapies aimed at prolonging survival and reducing symptoms associated with the disease. First-line treatment for ES-SCLC typically consists of platinum-based chemotherapy (cisplatin or carboplatin) in combination with etoposide, with or without immune checkpoint inhibitors such as atezolizumab (Tecentriq) or durvalumab (Imfinzi). While this regimen achieves response rates of 60–70%, resistance and relapse almost always occur, with median OS of approximately 12–13 months (Horn et al., 2018; Paz-Ares et al., 2019). More than 90% of patients relapse within 2 years, resulting in poor long-term outcomes (Faivre-Finn et al., 2017; Horn et al., 2018).

Tarlatamab (Imdylltra) is positioned as monotherapy for the treatment of adult patients with ES-SCLC who require systemic therapy following disease progression on or after first-line platinum-based chemotherapy. Accordingly, the product is intended for use in the second-line treatment setting or beyond. Relevant comparators are the authorised systemic therapies used in the second-line setting after progression on first-line platinum-based chemotherapy. An overview of medicinal products authorised for the treatment of relapsed ES-SCLC in the EU, along with an assessment of whether they are considered satisfactory treatment methods relevant to the discussion of the significant benefit of tarlatamab in SCLC, is presented in Table 2 below.

Second-line treatment in SCLC is generally determined by the treatment-free interval (TFI) following first-line platinum-based chemotherapy and by the patient's performance status (Dingemans et al., 2021) (Table 3 and Figure 1). Patients who relapse after initial therapy are typically classified as having platinum-sensitive disease (TFI ≥3 months) or platinum-resistant disease (TFI <3 months). Response rates to second-line chemotherapy are reported to be approximately 20–30% in platinum-sensitive patients and around 15% in platinum-resistant patients.

Second-line treatment options for relapsed ES-SCLC are limited, and prognosis remains poor. The only medicine specifically licensed in the EU for second-line treatment of SCLC is topotecan, which is approved for use in patients with relapsed SCLC when re-treatment with the first-line regimen is not considered appropriate. Topotecan is therefore considered a satisfactory method for the target patient population of tarlatamab.

In addition, anthracycline-based chemotherapy regimens, particularly the combination of cyclophosphamide, doxorubicin (or epirubicin), and vincristine (CAV), have historically been used in the treatment of relapsed SCLC. These regimens are described in clinical guidelines as alternative second-line treatment options. Although these agents are not specifically authorised as a fixed combination for second-line SCLC in the EU, they have broader indications that include SCLC and are therefore considered satisfactory methods for the target patient population. The CAV regimen is also recognised in clinical practice.

Lurbinectedin is recommended in ESMO guidelines for platinum-resistant relapse but is not approved in the EU for SCLC patients. Platinum–etoposide rechallenge (carboplatin or cisplatin plus etoposide) is also not a satisfactory method for the entire proposed indication, as it is only applicable to platinum-sensitive relapse and does not cover the broader population defined for tarlatamab.

Immunotherapy agents such as atezolizumab (Tecentriq), durvalumab (Imfinzi), serplulimab (Hetronifly), and tislelizumab (Tevimbra) are authorised in combination with platinum–etoposide for first-line treatment of adult patients with ES-SCLC. These medicines are not indicated for treatment after progression on first-line platinum-based chemotherapy and therefore do not represent satisfactory methods for the target patient population of tarlatamab in the second-line setting.

In summary, the relevant authorised comparators for tarlatamab in the second-line treatment of ES-SCLC are topotecan and anthracycline-based regimens such as cyclophosphamide–doxorubicin–vincristine (CAV). These methods are considered satisfactory as they align with the proposed indication for tarlatamab. Other medicines, including the approved immunotherapy agents atezolizumab, durvalumab, serplulimab, and tislelizumab, as well as lurbinectedin, are either indicated for first-line treatment or not approved in the EU for SCLC and are therefore not considered satisfactory methods relevant for a discussion on the significant benefit of tarlatamab in the target patient population.

Table 2. Overview of medicinal products authorised for treatment of relapsed ES-SCLC in the EU

Active substance (Product name)	**SCLC indication per SmPC**	**Consideration regarding Satisfactory methods**
Chemotherapeutic agents		
Carboplatin	Carboplatin is indicated for the treatment of small cell carcinoma of the lung	NO Carboplatin/Cisplatin plus Etoposide is indicated for extensive-stage as first line treatment in SCLC for immunotherapy-ineligible patients, and four to 6 cycles are recommended (*Ref 26/27/32 ESMO guidelines*). Carboplatin/Cisplatin plus Etoposide is also recommended as platinum rechallenge in Platinum-sensitive relapse (>3 months TFI). In this case, it would be a second line treatment (*Ref 68,69 ESMO guidelines*). However, 1) Imdylltra is indicated as monotherapy for the treatment of adult patients with ES-SCLC), who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy therefore positioning it a second line treatment, and 2) platinum–etoposide rechallenge (carboplatin or cisplatin plus etoposide) is not a satisfactory method for the entire proposed indication, as it is only applicable to patients with platinum-sensitive relapse and therefore does not cover the broader population defined in the proposed indication for Imdylltra.
Cisplatin	Cisplatin is intended for the treatment of advanced or metastasised small cell lung carcinoma. Cisplatin can be used as monotherapy and in combination therapy	
Etoposide	Etoposide is indicated in combination with other approved chemotherapeutic agents for the treatment of small-cell lung cancer in adults	

Topotecan	Topotecan monotherapy is indicated for the treatment of patients with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate	YES Topotecan is licensed in the EU for use as second-line therapy in SCLC and is therefore considered satisfactory for the target population of tarlatamab.
Cyclophosphamide	Cyclophosphamide may be used alone or in combination with other chemotherapeutic agents, depending on the indication. Cyclophosphamide is indicated in the treatment of small cell lung cancer	YES In second line, anthracycline-based regimes were commonly used, including cyclophosphamide plus doxorubicin and vincristine (CAV). Ref 65 ESMO guidelines: Von Pawel J, Schiller JH, shepherd FA, et al. Topotecan vs cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent SCLC
Doxorubicin	Doxorubicin hydrochloride is indicated for the treatment of small-cell lung cancer (SCLC)	YES In second line, anthracycline-based regimes were commonly used, including cyclophosphamide plus doxorubicin and vincristine (CAV). Ref 65 ESMO guidelines: Von Pawel J, Schiller JH, shepherd FA, et al. Topotecan vs cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent SCLC
Epirubicin	Epirubicin is used in the treatment of a range of neoplastic conditions including small cell lung cancer	YES Development in second line, anthracycline-based regimes were commonly used, including cyclophosphamide plus doxorubicin and vincristine (CAV). Epirubicin used instead of doxorubicin *Ref 65 ESMO guidelines:* Von Pawel J, Schiller JH, shepherd FA, et al. Topotecan vs cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent SCLC

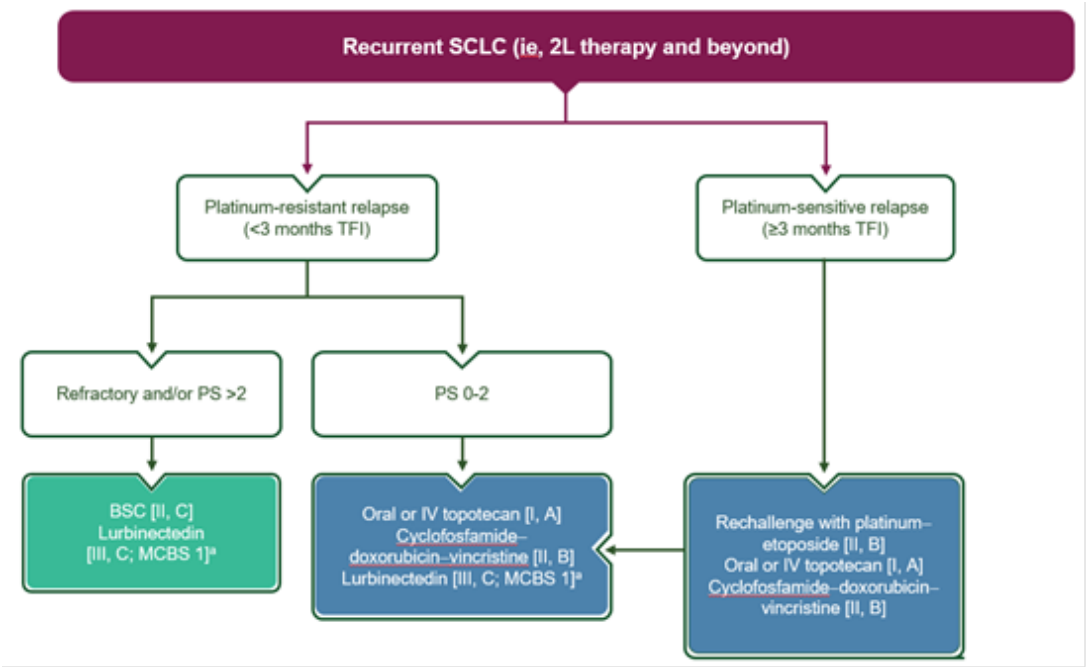
Vincristine	Vincristine sulphate is used primarily as a component of various chemotherapeutic regimens for the treatment of acute leukaemia. It has also been used in conjunction with other oncolytic drugs in the treatment of Hodgkin's Disease, all forms of lymphoma, Wilm's tumour, sarcomas and tumours of the breast, brain and lung.	YES In second line, anthracycline-based regimes were commonly used, including cyclophosphamide plus doxorubicin and vincristine (CAV). Ref 65 ESMO guidelines: Von Pawel J, Schiller JH, shepherd FA, et al. Topotecan vs cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent SCLC

Table 3. ESMO Guidelines Summary for Extensive-stage SCLC

Population	ESMO Guideline Recommendations	Level of Evidence and Grades of Recommendation[a]
2L+ ES SCLC		
Patients with platinum-sensitive relapse (CFI ³ 3 months)	Rechallenge with 1L platinum plus etoposide	II, B
Patients with platinum-resistant (CFI < 3 months) or platinum-sensitive (CFI ³ 3 months) relapse	Oral or IV topotecan	I, A
	CAV	II, B
Patients with platinum-resistant relapse (CFI < 3 months)	Lurbinectedin	III, C
Patients with platinum-refractory SCLC (not responding or progressing during chemotherapy)	Poor prognosis and participation in a clinical trial or BSC is recommended	II, C

[a] Adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System (details are available in Dingemans et al, 2021b.
1L = first-line; 2L = second-line; BSC = best supportive care; CAV = cyclophosphamide, doxorubicin, and vincristine; CFI = chemotherapy-free interval; ES = extensive stage; ESMO = European Society for Medical Oncology; IV = intravenous; PCI = prophylactic cranial irradiation; PD-L1 = programmed death ligand 1; PS = performance status; SCLC = small cell lung cancer

Figure 1. Treatment Algorithm for SCLC in Patients with Recurrent SCLC (Second-line)



Purple = general categories or stratification; blue = systemic anticancer therapy; turquoise = combination of treatments or other systemic treatments; white = other aspects of management. [a] The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. 2L = second-line; BSC = best supportive care; ESMO = European Society for Medical Oncology; IV = intravenous; MCBS = ESMO-Magnitude of Clinical Benefit Scale; PS = performance status; SCLC = small cell lung cancer; TFI = treatment-free interval; Source: Dingemans et al, 2021a

Significant benefit

The sponsor did not seek protocol assistance from EMA to discuss the approach for justifying significant benefit over existing methods of treatment for patients with relapsed SCLC after platinum-based first-line chemotherapy. The sponsor explained that this was because tarlatamab had not yet received orphan designation at the time the pivotal study (Study 20210004, DeLLphi-304) was designed.

Tarlatamab is a DLL3-targeted bispecific T-cell engager (BiTE) antibody construct designed to redirect cytotoxic T-cells to DLL3-expressing tumour cells, a feature commonly observed in SCLC. By engaging DLL3, tarlatamab facilitates T-cell-mediated tumour cell lysis, offering a novel mechanism of action distinct from existing treatment options.

The sponsor argues that tarlatamab provides a significant benefit over existing satisfactory methods for the treatment of patients with relapsed SCLC after platinum-based chemotherapy. The relevant existing therapies for comparison in the proposed indication are topotecan and the CAV regimen (cyclophosphamide, doxorubicin, vincristine). The comparison to topotecan is based on a direct comparison as part of the pivotal phase III study, while the comparison to the CAV regimen is based on an indirect comparison.

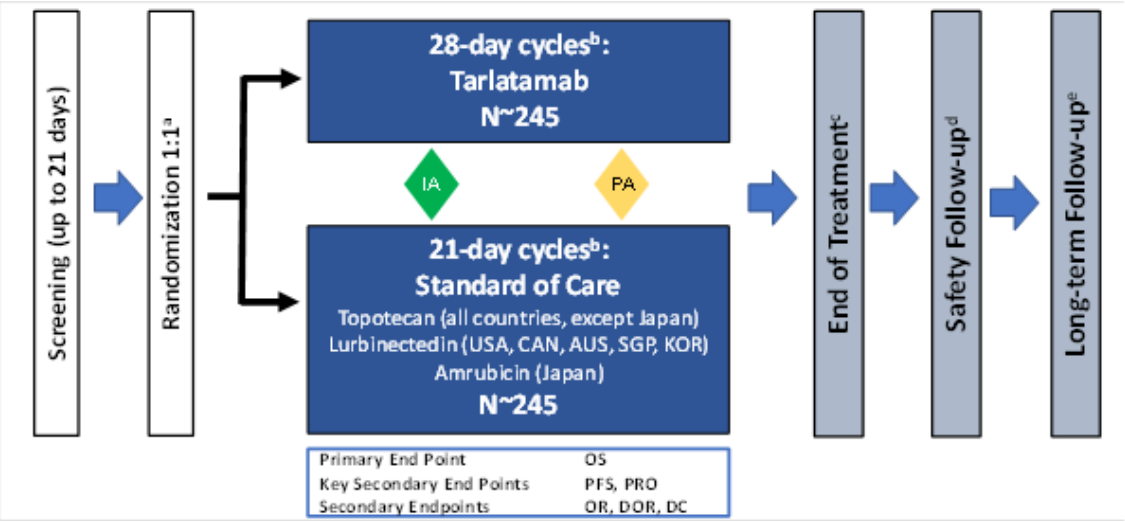
Direct comparison to topotecan

The sponsor's primary evidence for the claim of significant benefit is derived from the pivotal, global, randomised, open-label, multicenter phase III study 20210004 (also known as DeLLphi-304). This study provides the evidence required to support marketing authorization of the proposed indication, which targets adult patients with relapsed SCLC after platinum-based chemotherapy. The study enrolled 509 patients who were randomised 1:1 to receive tarlatamab (n=254) or standard-of-care (SOC) chemotherapy (n=255). SOC chemotherapy consisted of topotecan (185 patients), lurbinectedin (47 patients), or amrubicin (23 patients, exclusively used in Japan) (Figure 2). Randomisation was stratified by prior anti-PD-(L)1 exposure, platinum sensitivity (chemotherapy-free interval), presence of brain metastases, and SOC (topotecan/amrubicin vs. lurbinectedin).

The primary objective of the study was overall survival (OS), defined as the time from randomisation to death from any cause. Key secondary endpoints included progression-free survival (PFS) based on investigator assessment per RECIST 1.1 criteria and patient-reported outcomes (PROs) assessing disease-related symptoms, physical function, and quality of life. Secondary endpoints included other measures of efficacy, such as objective response rate (ORR), duration of response (DOR), and disease control rate (DCR). The data cut-off (DCO) date for the primary efficacy analysis was 29 January 2025.

Baseline demographics and disease characteristics were generally consistent between the tarlatamab and SOC groups. The median age of enrolled patients was 65 years (range: 20–86). Most patients were men (69.0%) and White (57.2%). Metastatic disease was present in 91.0% of cases, with brain metastases (44.8%) and liver metastases (35.2%) being common. Regarding performance status, 67.2% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1, while 32.8% had ECOG 0. Most patients were former or current smokers, consistent with smoking as a major risk factor for SCLC. Patients had a median of one prior line of therapy (range: 1–3), with 70.7% having received prior anti-PD-1 or PD-L1 therapy and 62.9% having undergone prior radiotherapy. In addition, 56.2% of patients had a chemotherapy-free interval (CFI) of ≥90 days.

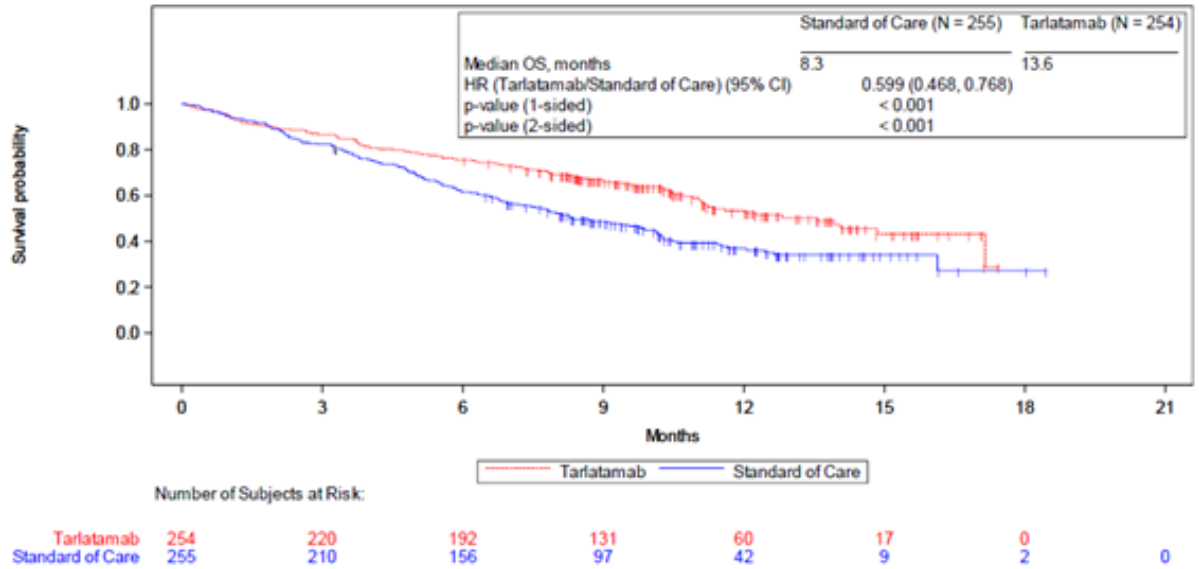
Figure 2. DeLLphi-304 study schema



AUS = Australia; CAN = Canada; CFI = chemotherapy-free interval; DC = disease control; DOR = duration of response; IA = interim analysis; KOR = Korea; N = number of subjects; OR = objective response; OS = overall survival; PA = primary analysis; PD-L(1) = programmed cell death (ligand) 1; PFS = progression free survival; PRO = patient-reported outcomes; SFU = safety follow-up; SGP = Singapore; SOC = standard of care;
[a] Stratified by: prior anti-PD-(L)1 exposure, CFI, presence (previous or current) of brain metastases (yes or no), and SOC.
[b] Subjects receive study treatment until disease progression, unacceptable toxicity, withdrawal of consent, death, or end of study as determined by the sponsor (whichever occurs first).
[c] End of Treatment visit occurs at the time the decision is made to discontinue study treatment and prior to start of new anti-cancer treatment.
[d] Safety Follow-up visit occurs approximately 60 (☐5) days after last study treatment administration.
[e] Long-term follow-up for survival occurs approximately every 12 weeks (± 14 days) after the SFU visit, or last imaging visit, whichever is later, for up to 3 years from last subject enrolled, or 1 year from the subject's last dose of study treatment, whichever is later.

Tarlatamab demonstrated a statistically significant improvement in OS compared with SOC chemotherapy. Median OS was 13.6 months with tarlatamab versus 8.3 months with SOC, corresponding to a hazard ratio (HR) of 0.60 (95% CI: 0.47–0.77; p<0.001) (Figure 3). This represents a 40% reduction in the risk of death compared with the comparator treatments.

Figure 3. Kaplan-Meier plot for overall survival (ITT Analysis Set)



IVRS=interactive voice response system; N=Number of subjects in the analysis set
Censor indicated by vertical bar |
The survival curves and median overall survival are estimated using Kaplan-Meier method
Hazard ratio and 95% CI are estimated using a stratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
This stratified analysis is based on IVRS data
P-value is calculated using a stratified log-rank test
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025
Source: Figure 14-4.2.3 eCTD 5.3.5.1

Tarlatamab also showed a statistically significant improvement in PFS, with a median PFS of 4.2 months versus 3.2 months with SOC (HR 0.72; 95% CI: 0.59–0.88; p<0.001), corresponding to a 28% reduction in the risk of disease progression or death (Table 4). Additional efficacy outcomes supported these findings. The ORR was 35.0% with tarlatamab compared with 20.4% with SOC, and the median DOR was 6.9 months versus 5.5 months, respectively. A higher proportion of responses with tarlatamab were durable, with 46.1% of responders maintaining response for ≥6 months compared with 26.9% in the SOC arm, and 13.5% versus 1.9%, respectively, maintaining response for ≥12 months. At the time of analysis, 47% of responses in the tarlatamab arm remained ongoing, compared with 15% in the SOC arm.

The sponsor further reports that PROs demonstrated improvements in dyspnoea and cough at 18 weeks compared with SOC chemotherapy. These findings are presented as additional evidence of clinical benefit beyond traditional efficacy endpoints.

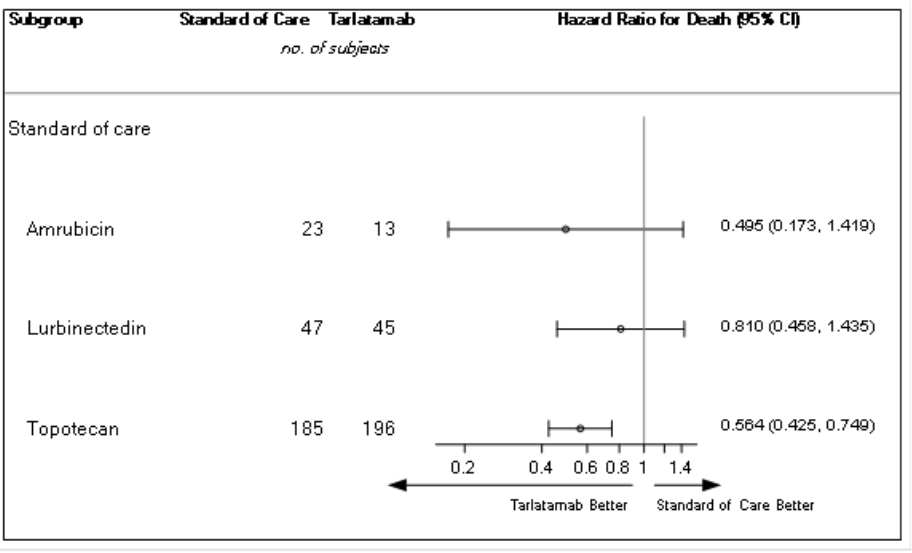
Table 4. Efficacy results for patients with SCLC in 20210004

Efficacy parameter	IMDYLLTRA (N = 254)	Standard of care (N = 255)
Overall survival (OS)		
Deaths (%)	111 (43.7)	152 (59.6)
Median[a] in months (95% CI)	13.6 (11.1, NE)	8.3 (7.0, 10.2)
Hazard ratio[b] (95% CI)	0.60 (0.47, 0.77)	
p-value (stratified log-rank)	< 0.001	
Progression-free survival (PFS)[c]		
Events (%)	191 (75.2)	205 (80.4)
Median[a] in months (95% CI)	4.2 (3.0, 4.4)	3.2 (2.9, 4.2)
Hazard ratio[b] (95% CI)	0.72 (0.59, 0.88)	
p-value (stratified log-rank)	< 0.001	
Overall response rate (ORR)[c]		
ORR, % (95% CI)	35.0 (29.2, 41.3)	20.4 (15.6, 25.9)
Complete response, n (%)	3 (1.2)	0 (0.0)
Partial response, n (%)	86 (33.9)	52 (20.4)
Duration of response (DOR)[c]		
Median[a] in months (95% CI) Min, Max (+ for censored)	6.9 (4.5, 12.4) 1.9, 15.3+	5.5 (4.2, 5.7) 1.3+, 12.5+
Responders with duration ≥ 6 months[d], %	46.1	26.9
Responders with duration ≥ 12 months[d], %	13.5	1.9

a per Kaplan-Meier estimates.
b Hazard ratio based on the stratified Cox proportional hazard model.
c PFS, ORR, DOR based on investigator assessment per RECIST v1.1.
d Based on observed duration of response. + Denotes ongoing response.
At the time of analysis, 47% (42/89) of patients randomised to IMDYLLTRA and 15% (8/52) of patients randomised to SOC had ongoing responses.
CI = Confidence interval

Subgroup analyses presented by the sponsor indicate that the OS benefit of tarlatamab was generally consistent across multiple patient subgroups, including age, sex, race, prior exposure to PD-1/PD-L1 inhibitors, CFI (<90 days or ≥90 days), presence or absence of brain or liver metastases, and across different SOC comparators. Post hoc analyses suggested that the survival benefit of tarlatamab was observed regardless of the specific chemotherapy used in the control arm (topotecan, lurbinectedin, or amrubicin; Figure 4).

Figure 4. Forest Plot of Standard of Care Subgroup Analysis of Overall Survival (ITT Analysis Set)



N = Number of subjects in the analysis set; NE = not estimable
Hazard ratios and 95% CIs are estimated using Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025
Program: /userdata/stat/amg757/onc/20210004/analysis/pa_posthoc/figures/f-eff-forest-os-sub-soc.sas
Output: f14-04-006-401-eff-forest-os-sub-soc.rtf (Date Generated: 16MAY25 02:45) Source Data: pa_adam.adsl, pa_adam.adtte

Comparison to CAV regimen

The sponsor argues that tarlatamab provides a significant benefit over the CAV regimen based on improved efficacy. While CAV was not included as a comparator in the pivotal study 20210004, the sponsor relies on published evidence to support an indirect comparison. Specifically, reference is made to a randomised, multicenter phase III study (von Pawel et al., 1999), which evaluated topotecan (n = 107) versus CAV (n = 104) in patients with recurrent SCLC (relapse ≥ 60 days after first-line therapy) and demonstrated comparable efficacy between CAV and topotecan, including similar median OS (approximately six months), time to progression, and ORRs (Table 5). Based on this equivalence, the sponsor extrapolates the demonstrated superiority of tarlatamab over topotecan in study 20210004 to CAV, inferring a clinically meaningful benefit versus this regimen.

In addition, the sponsor highlights that real-world evidence indicates that topotecan remains the most frequently used second-line treatment in Europe, regardless of platinum sensitivity (Reguart et al., 2024). The inclusion of topotecan in the SOC arm of study 20210004 is therefore considered representative of current clinical practice in the EU.

The sponsor concludes that tarlatamab provides clinically meaningful improvements in survival outcomes and response rates compared with currently available therapies, as well as improvements in selected PROs (e.g. cough and dyspnoea) and a manageable safety profile. This conclusion is primarily supported by direct comparative evidence of tarlatamab versus topotecan, supplemented by naïve indirect comparisons with CAV (without a quantitative analysis). On this basis, the sponsor considers that tarlatamab confers a significant benefit over existing satisfactory methods for the treatment of adult patients with SCLC who experience disease progression following platinum-based chemotherapy.

Table 5. Summary of Significant Benefit of Tarlatamab over CAV

Therapy (per ESMO 2021 guideline)	Level of evidence / grade	Key outcomes (historical data)	Comparator in DeLLphi-304?	Observed / inferred benefit of tarlatamab
Topotecan (oral or IV)	I, A	Median OS ~7–8 mo; ORR 17–24%; PFS 3 mo (von Pawel 1999; Eckardt 2007)	Yes	Direct comparison; topotecan included in SOC arm: OS 13.6 vs. 8.3 mo (HR 0.60); ORR 35% vs. 20.4%; PFS 4.2 vs. 3.2 mo. Subgroup analyses show consistent OS benefit of tarlatamab vs. topotecan.
CAV (cyclophosphamide + doxorubicin + vincristine)	II, B	Median OS ~6 mo; ORR 18% (von Pawel 1999)	No	Indirect comparison: CAV has similar efficacy to topotecan. Since tarlatamab is superior to topotecan, significant clinical benefit is inferred.

COMP discussion and conclusion

The direct comparison of tarlatamab to topotecan in study 20210004 is considered sufficient to support the claim of significant benefit of tarlatamab over topotecan in the target patient population. The outcomes of the pivotal study, along with supportive studies, demonstrate that tarlatamab, provides statistically significant and clinically relevant improvements in OS compared to SOC, including topotecan, in patients with ES-SCLC who have progressed on or after first-line treatment with platinum-based chemotherapy. These findings are further supported by improvements in PFS and ORR. PRO data also indicate improvements, particularly in symptoms such as cough and dyspnoea. However, the robustness of the PRO analyses is questioned due to the open-label study design.

The extrapolation of the efficacy of topotecan to the CAV regimen is subject to important uncertainties and is not considered sufficiently substantiated. In particular, the assumption of equivalence between CAV and topotecan, based on the data from the phase III study published by von Pawel and colleagues 25 years ago (1999), lacks a robust foundation for indirect inference of superiority without a formal quantitative analysis. Furthermore, no indirect treatment comparison or network meta-analysis has been provided to support this claim.

To adequately support the extrapolation, a methodologically sound indirect comparison is required, including comprehensive reporting of the analytical framework, justification of key assumptions, and an assessment of their validity. The modelling approach should be clearly described, and the potential impact of any assumption violations should be explored through sensitivity analyses. Furthermore, the limitations inherent to such analyses should be explicitly discussed. In the absence of such evidence, the claimed significant benefit of tarlatamab over the CAV regimen currently remains insufficiently demonstrated.

4. COMP list of issues

- Significant benefit

The sponsor states that the significant benefit of tarlatamab over the CAV regimen (cyclophosphamide, doxorubicin, vincristine) can be extrapolated based on its demonstrated superiority over topotecan and the established equivalence of CAV and topotecan. However, uncertainties regarding this extrapolation remain. The sponsor is therefore requested to substantiate the claim of significant benefit over CAV by providing a quantitative analysis, such as an indirect comparison or network meta-analysis, with a comprehensive description of the methodology, underlying assumptions, and limitations. In addition, the sponsor is requested to provide the absolute values for median overall survival and progression free survival in the subgroup analyses of patients randomised to either tarlatamab or topotecan.

Comments on sponsor's response to the COMP list of issues

In response to the request to substantiate the claim of significant benefit of tarlatamab over CAV, the sponsor submitted a broader comparative evidence package based on indirect treatment comparison methodologies. The response included both a network meta-analysis (NMA) and, for settings in which a connected evidence network could not be established, unanchored matching-adjusted indirect comparisons (MAICs). The sponsor also provided an extensive description of the study identification process, feasibility assessment, methodological approach, assumptions, sensitivity analyses, and limitations.

As discussed in the previous section, the phase 3 DeLLphi-304 study directly compared tarlatamab with selected second-line treatments commonly used in ES-SCLC, namely topotecan, lurbinectedin, and amrubicin, but did not directly include all comparators considered relevant in clinical practice across regions and patient subgroups. In particular, CAV remains a relevant treatment option, especially in patients with platinum-refractory or platinum-resistant disease, as well as in those not considered suitable for platinum rechallenge. On this basis, the sponsor sought to generate indirect comparative evidence versus CAV in order to support the significant benefit claim.

To identify relevant evidence, the sponsor performed a systematic literature review covering phase 2 to 4 studies in adults with SCLC progressing after one prior platinum-based regimen in line with health technology assessment (HTA) guidance, combining an updated search (October 2024) with an earlier review (April 2022). Searches were conducted in major bibliographic databases and supplemented by manual searches of grey literature and conference abstracts. From 961 unique records, 111 publications covering 93 unique studies met the prespecified inclusion criteria for the PICOS (Populations, Interventions, Comparators, Outcomes, and Study design) in second-line ES-SCLC. A subset of these studies was subsequently selected for indirect comparison analyses after application of further PICOS-based selection criteria. The sponsor reported that 8 randomised controlled trials were included in the NMA and 20 studies were considered eligible for MAIC feasibility assessment.

The sponsor stated that NMA was the preferred approach where feasible, as it preserves randomisation across a connected network and is generally considered the most robust form of indirect evidence synthesis. Based on feasibility assessments, the sponsor considered NMA feasible in the overall second-line ES-SCLC population and in the platinum-sensitive subgroup with CFI ≥ 90 days. However, for comparisons involving CAV in platinum-refractory/resistant populations (CFI < 90 days), the sponsor considered NMA infeasible due to lack of network connectivity and therefore performed unanchored MAIC analyses.

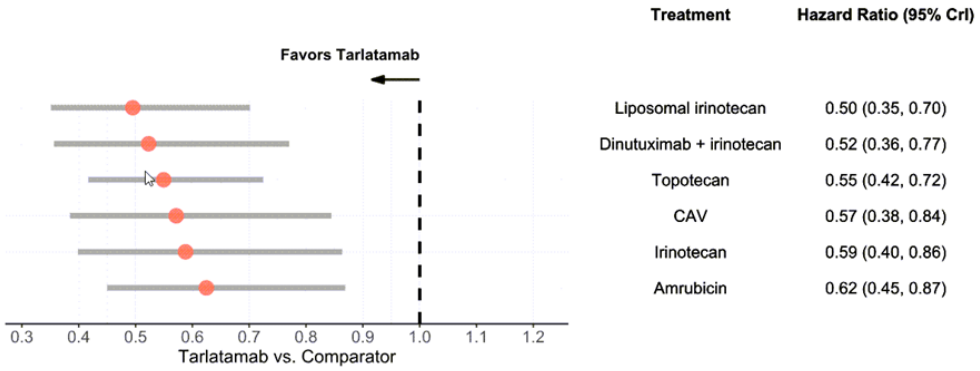
For the NMA, the sponsor used a Bayesian framework with fixed-effects models and evaluated outcomes including OS, PFS, ORR, and DCR. HRs were used for time-to-event endpoints and odds

ratios for binary outcomes. The sponsor described the studies included in the networks, the available outcome data, the response assessment methods across trials, and the assessment of the proportional hazards assumption. The response also outlined cross-trial heterogeneity and stated that separate analyses were prespecified for the overall second-line population and the platinum-sensitive subgroup in order to address differences in platinum sensitivity.

Evidence for CAV in the network was derived exclusively from the study published by von Pawel and colleagues (von Pawel et al., 1999), which applied a CFI cutoff of ≥ 60 days rather than ≥ 90 days. Since the study did not report the CFI distribution of enrolled patients, it was not possible to determine the proportion of patients with a CFI ≥ 90 days. Consequently, this trial was included in the overall second-line NMA, and a sensitivity analysis was conducted to incorporate it in the platinum-sensitive NMA, enabling the estimation of tarlatamab versus CAV in that subgroup (as von Pawel et al., 1999 remains the sole source of evidence for CAV).

In the overall second-line ES-SCLC population, tarlatamab showed a statistically significant reduction in the hazard of death compared to CAV, with an HR of 0.57 (95% credible interval [CrI]: 0.38, 0.84). Tarlatamab ranked first among all comparators on the SUCRA (surface under the cumulative ranking curve) plot (100.0%), whereas CAV ranked fourth (46.9%). A sensitivity analysis using propensity score-weighted HRs for tarlatamab versus topotecan from DeLLphi-304 yielded consistent estimates with the main NMA analyses. For response outcomes, tarlatamab was associated with significantly higher odds of achieving an overall response (odds ratio [OR]: 3.76, 95% CI: 1.67, 8.56) and a disease control (OR: 2.35, 95% CI: 1.17, 4.73) compared to CAV. No PFS comparison was possible between tarlatamab and CAV, as the study by von Pawel et al. (1999) did not report PFS data for CAV.

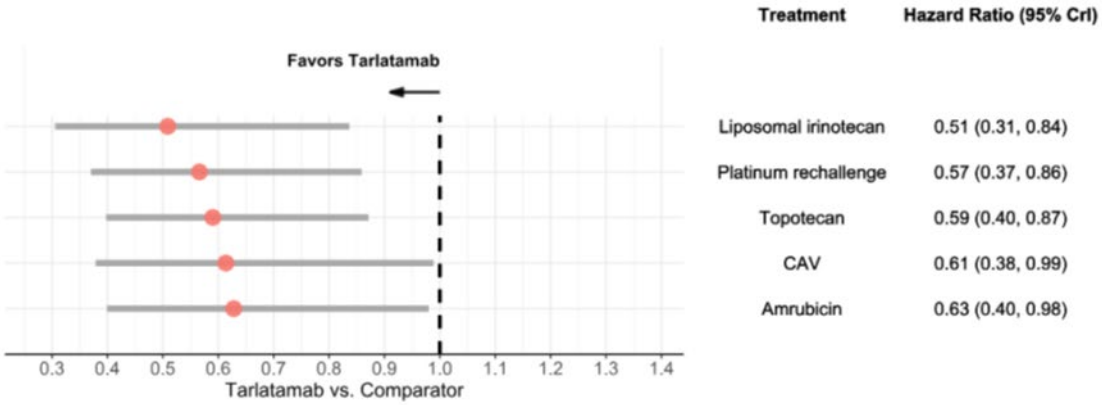
Figure 5. Forest Plot for OS: Overall 2L ES-SCLC Population



2L, second line; CAV, cyclophosphamide, doxorubicin, and vincristine; CrI, credible interval; ES-SCLC, extensive-stage small cell lung cancer; OS, overall survival

In the platinum-sensitive subgroup (CFI ≥ 90 days), the sponsor conducted a sensitivity NMA including CAV based on the study by von Pawel et al. (1999). However, the sponsor acknowledged that this study applied a different platinum-sensitivity threshold (CFI ≥ 60 days) and did not report the exact distribution of patients with CFI ≥ 90 days. In this sensitivity analysis, tarlatamab was reported to be associated with improved OS compared with CAV, with a HR of 0.61 (95% CrI: 0.38, 0.99) (Figure 6). The sponsor also reported favourable ORs for ORR and DCR in this subgroup. These findings were presented by the sponsor as supportive of a survival advantage for tarlatamab over CAV also in patients with platinum-sensitive disease. However, the analysis was based on sensitivity modelling and included a study with differences in subgroup definition.

Figure 6. Forest Plot for OS: Platinum Sensitive Population (CFI ≥ 90 days)



CFI, chemotherapy-free interval; CrI, credible interval; OS, overall survival

The sponsor highlighted several strengths of the NMA, including the use of a high-quality systematic literature review, restriction to randomised controlled trials, broader inclusion of comparators than reported in earlier published analyses, rigorous identification of treatment effect modifiers, assessment of proportional hazards assumptions for survival outcomes, and consistent results from pre-specified sensitivity analyses. At the same time, several limitations were acknowledged. Cross-trial heterogeneity was observed in baseline prognostic factors, such as ECOG PS, disease stage, and CFI thresholds. Baseline characteristics were incompletely reported in some subgroup analyses. The only available CAV evidence came from a single, relatively old trial (von Pawel et al., 1999), which applied a CFI cutoff of ≥ 60 days instead of ≥ 90 days and did not report the CFI distribution, introducing heterogeneity into the platinum-sensitive sensitivity analysis. Variability in the proportion of patients with liver or brain metastases across trials may also contribute to uncertainty, although this bias is expected to be limited as patients were typically under active management. Additional limitations included differences in response assessment methods, variability in tumour assessment frequency and assessor type (investigator vs. blinded independent central review), reliance on published aggregate data, and assumptions regarding equivalence between some treatment regimens, including intravenous versus oral topotecan and different platinum rechallenge strategies. For OS (and PFS), treatment effects were measured using hazard ratios, which assume proportional hazards. While this assumption was validated for most studies, it was not feasible to evaluate for trials lacking KM data, introducing potential uncertainty. The sponsor also noted that publication bias, evolving treatment standards (particularly the introduction of PD-1/PD-L1 inhibitors in first-line therapy), and residual bias from inconsistency, heterogeneity, or transitivity violations, could not be excluded. As with all indirect treatment comparisons, potential bias from unmeasured confounding cannot be fully excluded. Only direct head-to-head randomised trials can minimize this risk. Results may not fully generalize to certain patient populations, such as those with ECOG ≥2, or to real-world treatment sequences. These limitations should be carefully considered when interpreting the findings.

For the platinum-refractory or platinum-resistant setting, where the sponsor considered NMA infeasible due to the lack of a common comparator arm, unanchored MAICs were conducted to compare tarlatamab with CAV. The sponsor identified the GFPC 0501 study as the relevant source for the CAV comparator and restricted the individual patient data from the tarlatamab arm of DeLLphi-304 to patients with CFI < 90 days (n = 108) and aggregate-level data from the CAV arm of the GFPC 0501 trial (Gervais 2015, n = 66). The sponsor described the covariates selected for matching, which included age, sex, ECOG PS, and stage at diagnosis in the base case, with additional sensitivity

analyses using alternative variable sets. After reweighting, the effective sample size (ESS) was 72.6% in the base case, well above the arbitrary prespecified futility threshold of 25.

The base case MAIC is reported at a 52.5% relative reduction in the risk of death with tarlatamab compared to CAV (HR 0.475, 95% CI: 0.324, 0.697; p < 0.001), with consistent findings across two sensitivity analyses (HRs of 0.500 and 0.450) (Table 6, Figure 7). Results for PFS (HR 0.888, 95% CI: 0.627, 1.257), ORR (OR 0.932, 95% CI: 0.451, 1.924), and DCR (OR 1.547, 95% CI 0.794, 3.014) were numerically favourable for tarlatamab in most analyses but did not reach statistical significance (Figure 8). Thus, within the MAIC framework, the observed comparative advantage versus CAV was primarily driven by OS. E-values for the OS comparison exceeded 2.00, suggesting that the observed OS benefit is unlikely to be fully explained by unmeasured confounding.

Table 6. MAIC Results for Unweighted, Base Case, and Sensitivity Analyses: Tarlatamab vs CAV

Population	**Analysis[a]**		**HR or OR (95% CI)[b]**	**p value**
OS				
Tarlatamab	Unweighted	-	0.473 (0.330, 0.677)	<0.001
	MAIC	Base case	0.475 (0.324, 0.697)	<0.001
	MAIC	Sensitivity 1	0.500 (0.349, 0.716)	<0.001
	MAIC	Sensitivity 2	0.450 (0.305, 0.665)	<0.001
CAV	Reference	-	Reference	-
PFS				
Tarlatamab	Unweighted	-	0.873 (0.632, 1.206)	0.410
	MAIC	Base case	0.888 (0.627, 1.257)	0.502
	MAIC	Sensitivity 1	0.900 (0.655, 1.235)	0.514
	MAIC	Sensitivity 2	0.896 (0.632, 1.271)	0.539
CAV	Reference	-	Reference	-
ORR				
Tarlatamab	Unweighted	-	1.279 (0.651, 2.511)	0.476
	MAIC	Base case	0.932 (0.451, 1.924)	0.849
	MAIC	Sensitivity 1	1.180 (0.589, 2.364)	0.641
	MAIC	Sensitivity 2	0.970 (0.468, 2.011)	0.934
CAV	Reference	-	Reference	-
DCR				
Tarlatamab	Unweighted	-	1.487 (0.803, 2.754)	0.206
	MAIC	Base case	1.547 (0.794, 3.014)	0.200
	MAIC	Sensitivity 1	1.397 (0.741, 2.636)	0.302
	MAIC	Sensitivity 2	1.553 (0.793, 3.042)	0.199
CAV	Reference	-	Reference	-

[a] Sensitivity analysis 1: imbalanced variables only (SMD>0.1) and excluding disease stage at initial diagnosis. Sensitivity analysis 2: same as base case except time since diagnosis controlled for as a continuous variable
[b] For OS and PFS, HR with 95% CI was reported; for ORR and DCR, OR with 95% CI was reported
CAV, cyclophosphamide, doxorubicin, and vincristine; DCR, disease control rate; HR, hazard ratio; MAIC, matching

adjusted indirect comparison; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SMD, standardized mean difference

Figure 7. OS: Tarlatamab (Unweighted and Weighted) versus CAV

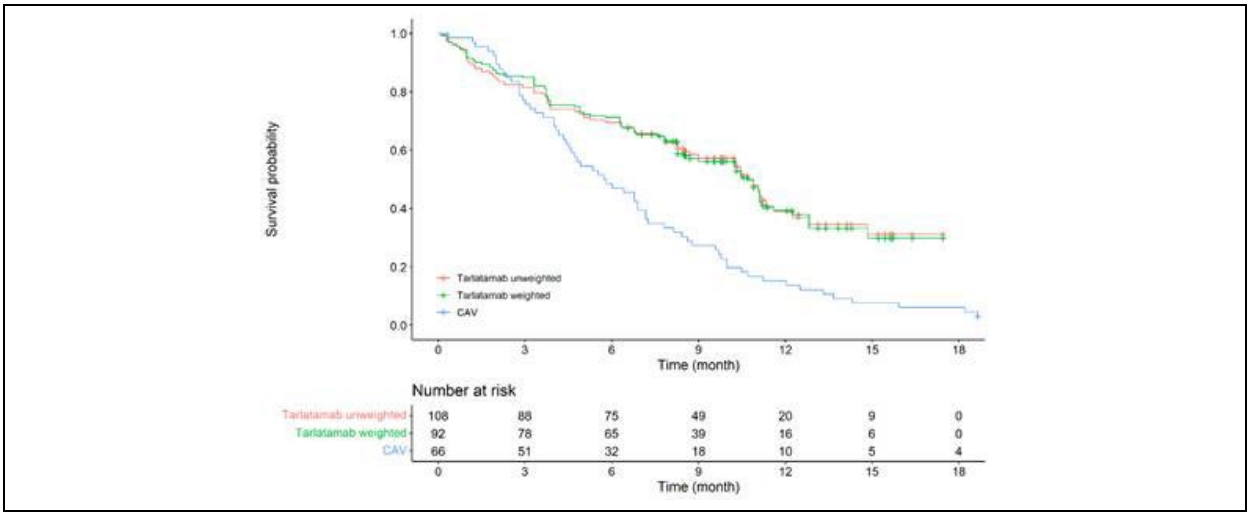
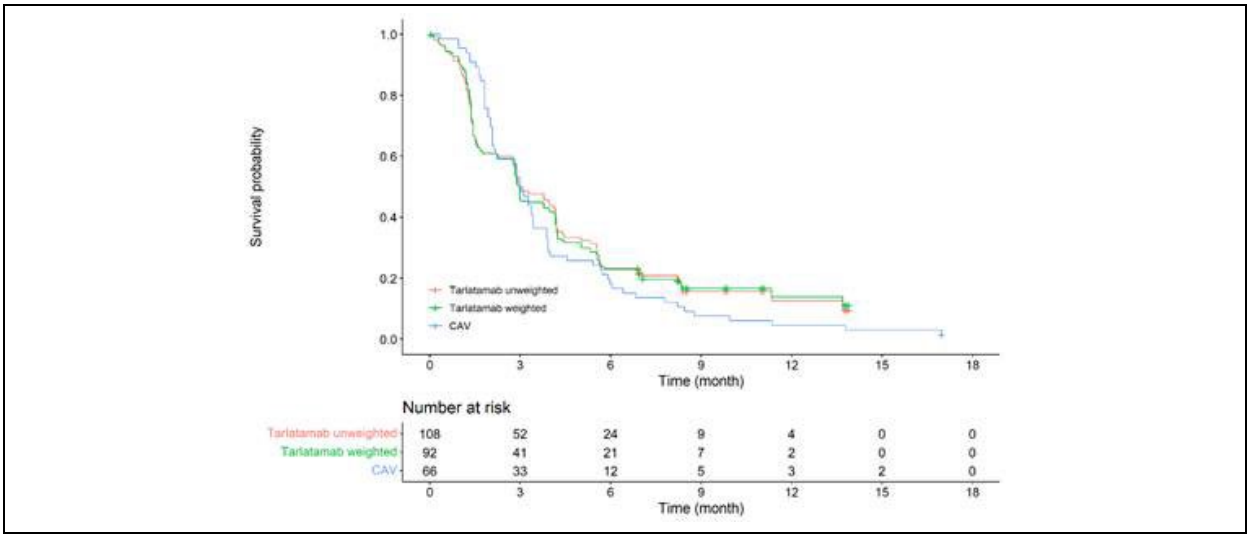


Figure 8. PFS: Tarlatamab (Unweighted and Weighted) versus CAV



The sponsor also acknowledged several limitations of the MAIC analyses. The GFPC 0501 trial included a proportion of patients with ECOG PS 2 (15.2%) and was conducted prior to the widespread use of immuno-oncology therapies. While differences in prior immuno-oncology exposure are unlikely to have had a major impact on the MAIC results, the inclusion of ECOG PS 2 patients introduces a risk of bias in favour of tarlatamab. Another potential source of bias relates to measurement error in the digitised Kaplan-Meier curve data from the comparator trials. Although digitisation of KM survival curves has been shown to provide a reasonable approximation (Guyot et al., 2012), it may not perfectly replicate the true patient-level data. The sponsor considered this risk to be low, given that patient follow-up in both trials appeared relatively complete with minimal censoring, and that the median survival times and shapes of the KM curves derived from pseudo-IPD were close to the reported values. Small between-trial differences in tumour response assessment frequency could also have introduced bias: DeLLphi-304 applied a scan interval at every cycle, whereas GFPC 0501 assessed response rates every two months, which may have biased the results in favour of CAV. In addition, the results of the MAIC analyses may not be generalisable to populations with baseline characteristics that meaningfully differ

from those of the comparator trials, as the unanchored MAICs provide estimates of treatment effect confined to the study population of those trials. Finally, residual confounding due to unmeasured effect modifiers cannot be fully excluded in any of the analyses. These limitations should be carefully considered when interpreting the findings of the MAICs.

The sponsor also provided additional post hoc subgroup analyses from the DeLLphi-304 study comparing tarlatamab with topotecan. As shown in table 2, treatment with tarlatamab was associated with improved OS in the intention-to-treat population, with a median OS of 12.0 months compared to 7.5 months for topotecan (HR 0.564; 95% CI: 0.425, 0.749). PFS was also improved, with a median PFS of 4.2 months (95% CI: 3.0, 4.3) for tarlatamab versus 3.1 months (95% CI: 2.9, 4.1) for topotecan (HR 0.773; 95% CI: 0.614, 0.974).

Table 2. Analysis of Overall Survival (Tarlatamab vs. Topotecan) (ITT Analysis Set).

	Tarlatamab (N = 196)	**Topotecan (N = 185)**
Subject status		
Events - n (%)		
Death	85 (43.4)	113 (61.1)
Censored - n (%)	111 (56.6)	72 (38.9)
Alive at last follow-up	111 (56.6)	71 (38.4)
Withdrawal of consent from study	0 (0.0)	1 (0.5)
Decision by sponsor	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)
Completed study without death	0 (0.0)	0 (0.0)
Kaplan-Meier analysis		
Median OS (95% CI)[a]	12.0 (11.1, 17.1)	7.5 (6.3, 9.1)
p-value (2-sided)[b]	-	< 0.001
Cox proportional hazard regression[c]		
Hazard ratio (95% CI)	-	0.564 (0.425, 0.749)
p-value (2-sided)	-	< 0.001

N = Number of subjects in the analysis set; n = Number of subjects with observed data; CI = confidence interval; OS = overall survival;

[a] Median overall survival was estimated using the Kaplan-Meier (KM) method; 95% CI of the median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method

[b] P-values were estimated using unstratified log-rank test

[c] Hazard ratios were estimated using an unstratified Cox proportional hazards model; the associated 95% CIs and p-values were estimated using a model-based variance estimator for hazard ratio; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm

Treatment arms include subjects who are randomised to the amrubicin or topotecan strata, and whose country is not Japan

COMP discussion and final conclusion

The sponsor submitted two complementary analytical approaches to substantiate the claim of significant benefit over CAV: (i) Bayesian NMAs in the overall second-line population and in the platinum-sensitive subgroup (CFI ≥ 90 days), and (ii) unanchored MAICs in the platinum-resistant/refractory population (CFI < 90 days). The supporting documentation included a feasibility assessment, study protocol, statistical analysis plan, and detailed results reports, reflecting a methodologically structured approach.

A key limitation of the indirect evidence is the paucity and age of the source data for CAV. Within the NMA framework, only a single study — von Pawel et al. (1999) — included CAV as a treatment arm. This trial, conducted over two decades ago, presents several limitations that constrain the robustness of the comparison. No PFS data were reported, precluding any indirect comparison of tarlatamab versus CAV for this endpoint. In addition, its eligibility criteria differed from contemporary standards, most notably with respect to the definition of platinum sensitivity (CFI ≥ 60 days instead of the current ≥ 90 days). As the distribution of patients according to the ≥ 90-day cutoff could not be retrieved from the publication, the inclusion of this study in the sensitivity NMA for the platinum-sensitive subgroup — while understandable given the absence of alternative evidence — introduces uncertainty about the comparability of the study populations.

For the platinum-resistant/refractory population, the sponsor relied on the GFPC 0501 study (recruitment period 2009–2011) within an unanchored MAIC framework. Although PFS data were reported, the absence of a clearly defined endpoint adds uncertainty to the interpretation of this outcome. Furthermore, the inclusion of patients with ECOG PS 2 (15.2%) and the lack of prior first-line immuno-oncology therapy in GFPC 0501 create residual differences in patient populations that could not be fully addressed through reweighting.

The efforts undertaken by the sponsor to generate comparative evidence from limited data are acknowledged. Nevertheless, several methodological and reporting aspects warrant consideration. For example, the absence of comprehensive tabulated summaries of eligibility criteria and baseline characteristics across the included trials limits the ability to fully assess the extent of heterogeneity. The qualitative descriptions provided by the sponsor, while informative, remain relatively general and do not always allow a clear appraisal of differences across studies. This is particularly pertinent for CAV, where the evidence base used in the NMAs relies on a single historical trial which is over 25 years old. Regarding the statistical methodology of the Bayesian NMA, limited information is provided on the specification and justification of prior distributions. Although the use of non-informative priors is stated and the submitted code allows reconstruction of the analyses, the limited reporting reduces transparency. Similarly, while a structured, multi-step approach was applied to identify prognostic factors and potential treatment effect modifiers — drawing on targeted literature review, physician interviews, regression analyses of DeLLphi-301 data, and clinical expert input — it remains uncertain whether all clinically relevant variables have been fully captured, particularly given the heterogeneity across the trials. For example, key effect modifiers classified as high (i.e., number of previous lines of therapy) or medium importance (e.g., brain metastases and time from SCLC diagnosis) were not included in the matching. Additionally, certain lower-importance factors (e.g., previous use of PD-1/PD-L1 inhibitors, liver metastases, race, and smoking status), while less critical, are still relevant. The omission of these factors, particularly those ranked as high and medium importance, likely contributes to residual confounding and may limit the robustness of the matching process.

For the MAIC analyses, the reporting of the weighting procedure is limited. While ranges of weights and the ESS are presented and exceed the prespecified futility threshold, the absence of detailed

information on the weight distribution constrains the ability to fully appraise the robustness of the reweighting and its impact on the ESS.

Notwithstanding these limitations, the results across analytical approaches and patient populations consistently indicate a favourable effect of tarlatamab on OS compared with CAV. In the overall second-line population, the NMA estimated an OS HR of 0.57 (95% CrI: 0.38, 0.84), and in the platinum-sensitive subgroup an HR of 0.61 (95% CrI: 0.3, –0.99). For the platinum-resistant/refractory population, the MAIC produced a consistent estimate (HR 0.475, 95% CI: 0.324, 0.697), supported by E-values above 2.00, suggesting that unmeasured confounding is unlikely to fully account for the observed OS benefit.

The MAIC analyses did not demonstrate statistically significant differences for PFS, ORR, or DCR, which introduces some uncertainty in the interpretation of the overall treatment effect in the platinum-resistant/refractory subgroup. However, point estimates for these endpoints were numerically favourable for tarlatamab, and no analysis across any population or endpoint suggested inferiority of tarlatamab versus CAV.

Overall, the sponsor has made substantial efforts to derive comparative evidence for tarlatamab versus CAV despite the limited data available. The methodological uncertainties identified are largely inherent to the evidence base — specifically, the scarcity, age, and heterogeneity of trials evaluating CAV in this setting — and the nature of the indirect comparison methods. These uncertainties are unlikely to be resolved through additional analyses but are not expected to materially impact the overall interpretation of the data. The available evidence is therefore considered sufficient to support the claim of significant benefit of tarlatamab over both CAV and topotecan.

In conclusion, the clinical data provided demonstrated significant improvements in OS, PFS, and ORR for tarlatamab compared to topotecan in adult patients with ES-SCLC, who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. Furthermore, indirect comparisons showed prolonged OS compared to the CAV regimen in the target patient population.

5. COMP position adopted on 16 April 2026

The Committee for Orphan Medicinal Product (COMP) considered that the designated orphan condition "treatment of small cell lung cancer" should be renamed as "treatment of pulmonary neuroendocrine carcinoma" (hereinafter referred to as "the condition").

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of pulmonary neuroendocrine carcinoma was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a poor 5-year overall survival;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Imdylltra is of significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication is established. The sponsor has provided clinical data from the comparative, pivotal phase 3 study demonstrating improved efficacy of tarlatamab compared to topotecan, with improvements in overall survival, progression-free survival, and overall response rate in adult patients with extensive-stage small cell lung cancer, who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy. Additionally, indirect comparisons were conducted, which showed prolonged overall survival compared to the CAV regimen (cyclophosphamide, doxorubicin, vincristine) in the target patient population. The COMP considered that this constituted a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Imdylltra, tarlatamab for treatment of pulmonary neuroendocrine carcinoma (EU/3/23/2876) is not removed from the Community Register of Orphan Medicinal Products.