31 March 2026
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EMADOC-360526170-3033533
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Zepzelca (lurbinectedin)
Treatment of pulmonary neuroendocrine carcinoma
EU/3/19/2143

Sponsor: Pharma Mar S.A.

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Designated active substance(s)	Lurbinectedin
Other name(s)	Zepzelca, Lurbinectedin,
International Non-Proprietary Name	Lurbinectedin
Tradename	Zepzelca
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:	Pharma Mar S.A. Avenida De Los Reyes 1 Poligono Industrial La Mina 28770 Colmenar Viejo Spain
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pharma Mar S.A.
COMP opinion	24 January 2019
EC decision	26 February 2019
EC registration number	EU/3/19/2143
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Selma Arapovic Dzakula / Elita Poplavska
Applicant	Pharma Mar S.A.
Application submission	20 May 2025
Procedure start	19 June 2025
Procedure number	EMA/H/C/006673/0000
Invented name	Zepzelca
Therapeutic indication	ZEPZELCA, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Zepzelca
CHMP opinion	26 March 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Bozenna Dembowska-Baginska
Sponsor's report submission	9 October 2025
COMP discussion	17-18 March 2026

COMP opinion (adoption via written procedure)	31 March 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2019 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing lurbinectedin was considered justified based on preliminary clinical data demonstrating that patients respond to treatment;
- the condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a 5-year overall survival of 5-10%;
- the condition was estimated to be affecting approximately 1.4 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 lurbinectedin will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients respond to treatment. Indirect comparisons suggest that patients that were treated with the proposed products had better outcomes compared to published historical data of patients that have been treated with the best standard of care including authorised products. 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 fulfilled. The COMP therefore recommends the designation of this medicinal product, containing lurbinectedin 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).

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."

The approved therapeutic indication "ZEPZELCA, in combination with atezolizumab, is indicated for the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide" falls within the scope of the designated orphan condition "treatment of pulmonary neuroendocrine carcinoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the 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

The sponsor's strategy to estimate the prevalence of Small Cell Lung Carcinoma (SCLC) in the European Economic Area (EEA) is based on a stepwise approach combining population-based cancer registry data, subtype distribution assumptions, survival-derived disease duration, and the application of the standard prevalence formula ($P = I \times D$), in accordance with the Committee for Orphan Medicinal Products (COMP) guidance (COMP/436/01).

Epidemiological data were derived primarily from population-based cancer registries, which systematically collect incidence and survival data at national level. For pan-European estimates, the sponsor relied on the European Cancer Information System (ECIS), which aggregates data from European cancer registries and provides national and EU-level estimates of total lung cancer incidence. As ECIS reports lung cancer according to ICD-10 codes C33–C34 without histological stratification, the sponsor estimated the proportion attributable to SCLC using subtype-specific data from the Netherlands Cancer Registry (NCR, 2024). The NCR is one of the few European registries that consistently reports lung cancer by histological subtype (NSCLC, SCLC, and unspecified lung cancer) over a long-time horizon.

According to NCR data covering the period 1990–2023, the absolute annual number of SCLC cases has remained relatively stable, while the incidence of non-small cell lung cancer (NSCLC) and unspecified lung cancer has increased substantially. Consequently, the relative proportion of SCLC among all lung cancer cases has declined from approximately 20% in 1990 to 11–12% in recent years (Table 1). Based on these most recent data, the sponsor assumed that SCLC accounts for 12% of all lung cancer cases for the purposes of the prevalence calculation. This proportion was applied uniformly across EEA Member States.

Table 1. Frequency of lung cancer subtypes.

Year of diagnosis	Cases of NSCLC	Cases of SCLC	Cases of unspecified lung cancer	Total lung cancer cases	Percentage SCLC cases
2023	10,297	1,731	2,776	14,804	12
2022	9,860	1,608	2,725	14,193	11
2021	9,818	1,633	2,875	14,326	11
2020	9,503	1,612	2,682	13,797	12
2019	9,951	1,648	2,777	14,376	11
2018	9,995	1,636	2,535	14,166	12
2017	9,390	1,700	2,291	13,381	13
2016	9,356	1,690	2,319	13,365	13
2015	9,495	1,751	2,087	13,333	13
2014	9,109	1,761	1,560	12,430	14
2013	9,110	1,689	1,628	12,427	14
2010	8,865	1,764	1,272	11,901	15
2005	7,457	1,599	960	10,016	16
2000	6,663	1,505	800	8,968	17
1995	6,685	1,533	733	8,951	17
1990	6,273	1,732	626	8,631	20

Source: Netherlands Cancer Registry, 2024.

Using ECIS 2022 data, the total number of lung cancer cases in the EEA-29 (EU-27 plus Norway and Iceland; Liechtenstein assumed comparable) was 323,036, corresponding to a crude incidence rate of approximately 70.97 per 100,000 persons. Applying the 12% proportion, the estimated number of new SCLC cases was 38,764, corresponding to a crude SCLC incidence of 7.15 per 100,000 persons. Country-specific crude rates ranged from 5.1 per 100,000 (e.g., Sweden) to 12.3 per 100,000 (e.g., Hungary), reflecting underlying differences in lung cancer epidemiology.

To convert incidence into point prevalence, the sponsor estimated the mean disease duration of SCLC. Because survival in SCLC is poor and declines rapidly after diagnosis, duration was derived from relative survival data provided by the Netherlands Cancer Registry. Reported survival rates for SCLC were 34% at 1 year, 11% at 3 years, 8% at 5 years, and 5% at 10 years after diagnosis. Using yearly survival increments up to 10 years and attributing deaths to intervals between survival points, the sponsor calculated a weighted average duration by multiplying the proportion of patients dying in each interval by the mean time spent in that interval. For patients surviving beyond 10 years, a residual duration estimate of 15 years was assumed, reflecting the possibility of cure in early-stage cases and considering the median age at diagnosis (>70 years; Robert Koch Institute, 2024). This approach yielded an estimated mean disease duration (D) of 1.8 years.

Under the assumption of stable incidence and disease duration, point prevalence (P) was calculated using the formula $P = I \times D$. Applying the crude incidence rate of 7.15 per 100,000 persons and a mean duration of 1.8 years resulted in an estimated point prevalence of 12.9 per 100,000 persons, corresponding to 1.29 per 10,000 persons in the EEA.

COMP discussion

The Committee agrees with the methodology applied by the sponsor, including the use of ECIS 2022 incidence data and the derivation of SCLC prevalence through an incidence–duration approach in the absence of directly reported prevalence figures. The use of survival data from the Netherlands Cancer Registry to estimate mean disease duration is considered appropriate, given the aggressive clinical course and limited survival associated with small cell lung cancer (SCLC).

Despite some limitations that could introduce uncertainty surrounding the incidence and disease duration estimation, the Committee considers that the approach adequately reflects the natural history of SCLC, particularly its short survival and rapid decline after diagnosis, which are not captured in prevalence estimates based on long-duration cancer pools. The resulting mean disease duration of 1.8 years is consistent with the known epidemiology of SCLC and supports the use of an incidence-based method for prevalence estimation.

Taking into account the robustness of the ECIS dataset, the consistency of the assumptions with clinical knowledge, and the alignment of the resulting estimate with previously reported SCLC-specific data, the COMP considers the calculated point prevalence of approximately 1.29 per 10,000 persons in the EEA to be plausible.

On this basis, the Committee concludes that the available data support a prevalence of approximately 1.3 per 10,000 persons for pulmonary neuroendocrine carcinoma in the EU/EEA population, which is consistent with earlier assessments and remains below the threshold for orphan designation.

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 presented a list of medicinal products authorised for the treatment in SCLC, and therapeutic indications have been added to assess whether these are satisfactory methods for the target population of lurbinectedin.

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 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).

Zepzelca (lurbinectedin) is positioned in combination with atezolizumab as a maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide. An overview of medicinal products authorised for the first-line treatment of 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 lurbinectedin in SCLC, is presented in Table 2 below.

The treatment algorithm for patients with ES-SCLC proposed in the ESMO guideline (Dingemans et al. 2021) is shown in Figure 1. According to clinical guidelines (Dómine et al., 2020; Früh et al., 2013), the preferred first-line chemotherapy regimen is cisplatin or carboplatin plus etoposide (with options for atezolizumab, durvalumab, irinotecan, gemcitabine, or topotecan).

Among the available treatments, Atezolizumab is considered the only satisfactory method of treatment relevant for the discussion of significant benefit of lurbinectedin in the target SCLC patient population, as the proposed treatment is authorised only in combination with atezolizumab used as continuation therapy following induction including atezolizumab.

In contrast, other immune checkpoint inhibitors authorised in the same therapeutic setting, such as Durvalumab, Serplulimab, and Tislelizumab, are not considered satisfactory methods of treatment in the present context. As the clinical development programme for the proposed treatment involves Atezolizumab-based induction and continuation therapy, there is no overlap with treatment regimens based on other immune checkpoint inhibitors. Furthermore, given that results with other switch IO-based maintenance regimens have been mixed (Owonikoko et al., 2021) and the therapeutic indication is restricted to the combination with atezolizumab without reference to other IO, these therapies are not considered satisfactory methods of treatment relevant for the discussion of significant benefit in the present context.

Topotecan monotherapy is indicated for the treatment of patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. Therefore, it is not considered a satisfactory method of treatment in the present context and the demonstration of significant benefit versus topotecan is not required.

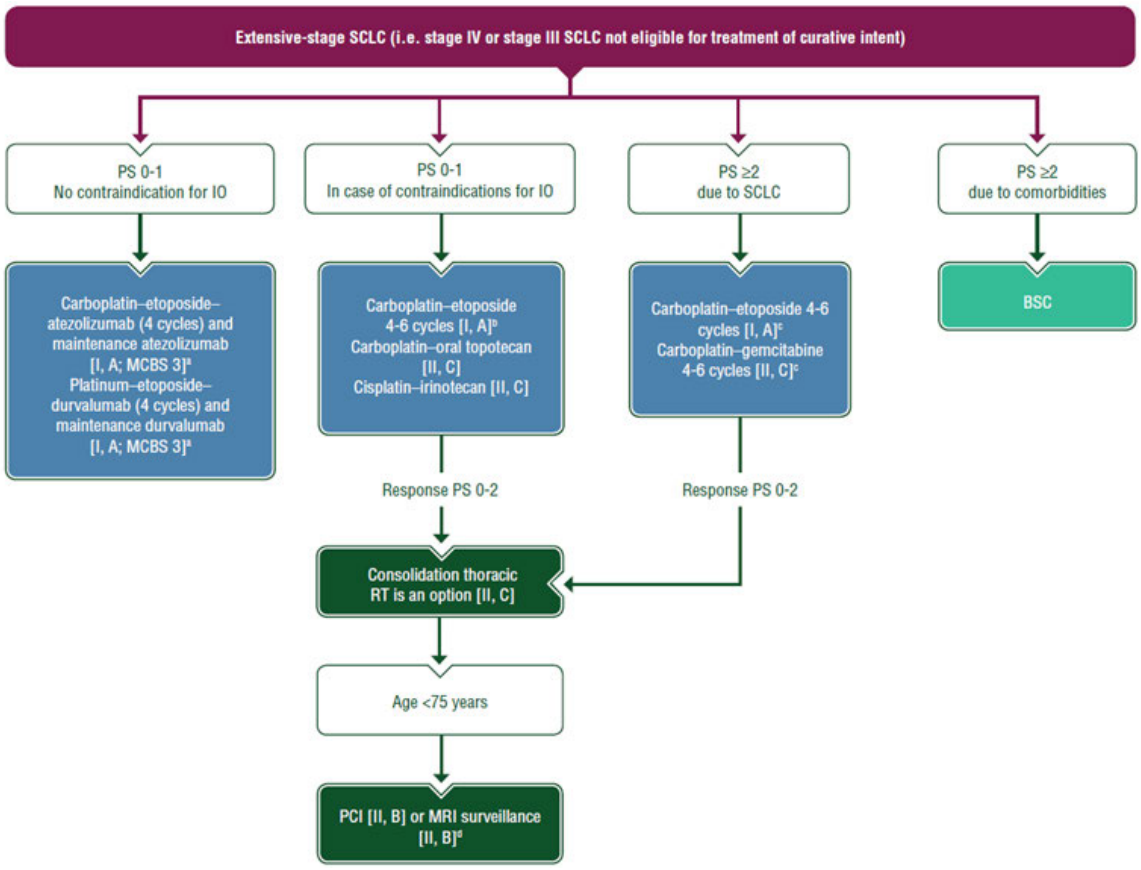
Similarly, the combination of Cyclophosphamide, Doxorubicin, and Vincristine is also not considered a satisfactory method of treatment at present, as its use according to international clinical treatment guidelines is limited to the second-line treatment setting and does not correspond to the maintenance treatment setting relevant to lurbinectidin.

Table 2. Authorised treatments for the proposed condition.

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. The comparator products are primarily used in the induction phase of treatment, whereas the new product is intended for use in the continuation phase. Therefore, a direct comparison in terms of improvement over earlier-line (induction) therapies is not considered applicable
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 small cell lung cancer (SCLC) for whom re-treatment with the first-	No. Later line product; therefore, no need to show improvement over an earlier-line product.

	line regimen is not considered appropriate	
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	No. Product established/used for later line; therefore, no need to show improvement over an earlier-line product
Doxorubicin	Doxorubicin hydrochloride is indicated for the treatment of small-cell lung cancer (SCLC)	No. Later line product; therefore, no need to show improvement over an earlier-line product
Epirubicin	Epirubicin is used in the treatment of a range of neoplastic conditions including small cell lung cancer	No. Later line product; therefore, no need to show improvement over an earlier-line product
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.	No. Later line product; therefore, no need to show improvement over an earlier-line product
Immunotherapeutic agents		
Atezolizumab (Tecentriq)	Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)	Yes. In view of the authorised indication as continuation treatment following first-line therapy with atezolizumab in combination with carboplatin and etoposide, resulting in full overlap in the patient population and the active comparator in the clinical development programme.
Durvalumab (Imfinzi)	Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC)	No. The proposed treatment is authorised only in combination with atezolizumab and as continuation therapy following induction including atezolizumab, there is no overlap with maintenance regimens based on other immune checkpoint inhibitors.
Serplulimab (Hetronifly)	Hetronifly in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)	No. The proposed treatment is authorised only in combination with atezolizumab and as continuation therapy following induction including atezolizumab, there is no overlap with maintenance regimens based on other immune checkpoint inhibitors. Given that results with other IO-based maintenance treatments have been mixed, extrapolation between IOs is not considered appropriate.
Tislelizumab (Tevimbra)	Tevimbra in combination with etoposide and platinum chemotherapy is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC)	No. The proposed treatment is authorised only in combination with atezolizumab and as continuation therapy following induction including atezolizumab, there is no overlap with maintenance regimens based on other immune checkpoint inhibitors. Given that results with other IO-based maintenance treatments have been mixed, extrapolation between IOs is not considered appropriate.

Figure 1. Treatment algorithm for SCLC in patients with extensive-stage disease (i.e., stage IV or stage III SCLC not eligible for treatment of curative intent).



Purple: general categories or stratification; dark green: radiotherapy; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management. a ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA or FDA. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. b Carboplatin may be replaced by cisplatin in patients <70 years of age or based on the toxicity profile [II, C]. c In patients with a PS of ≥2, consider ChT. BSC, best supportive care; ChT, chemotherapy; G-CSF, granulocyte colony-stimulating factor; IO, immunotherapy; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MRI, magnetic resonance imaging; PCI, prophylactic cranial irradiation; PS, performance status; RT, radiotherapy; SCLC, small-cell lung cancer. Source: (Dingemans et al. 2021).

Significant benefit

Scientific advice was sought regarding key aspects of the clinical development programme, including study design, the adequacy of the pivotal study to support a marketing authorisation application, and the proposed wording of the indication. Scientific advice was not specifically sought with respect to the demonstration of significant benefit at the time of the marketing authorisation application.

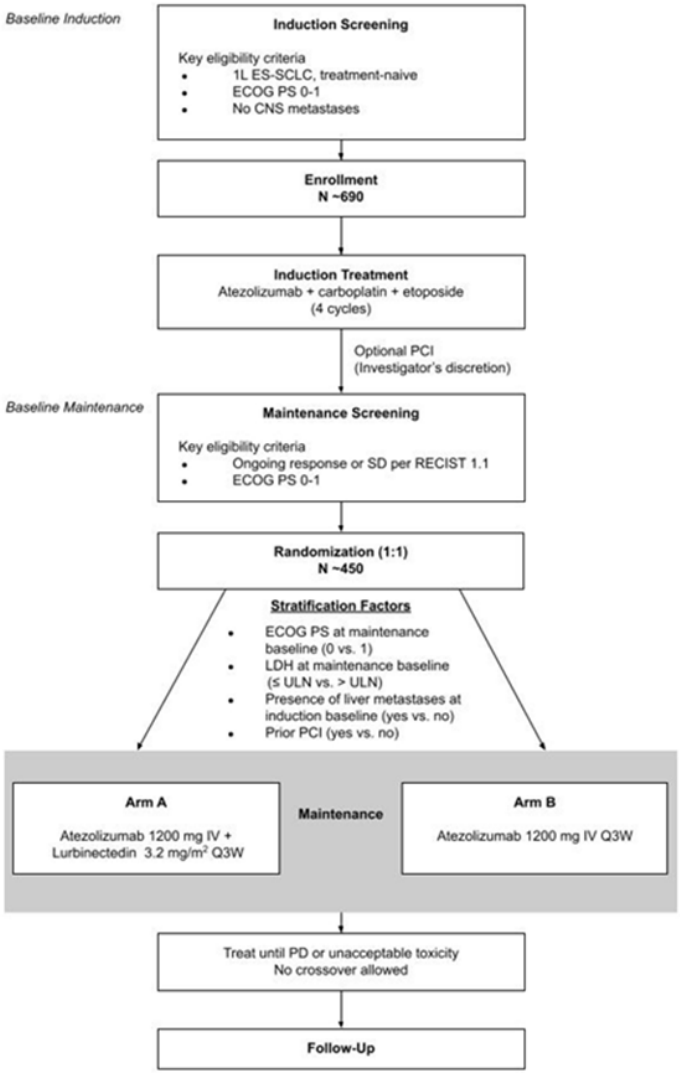
The sponsor seeks to demonstrate significant benefit for lurbinectedin in combination with atezolizumab in the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease has not progressed after first-line induction therapy with atezolizumab, carboplatin and etoposide.

The claim of significant benefit is based on the potential for improved efficacy compared with the relevant satisfactory method, namely atezolizumab maintenance monotherapy. In particular, the sponsor seeks to demonstrate a clinically meaningful advantage across key efficacy endpoints, including progression-free survival (PFS) and overall survival (OS), thereby supporting an incremental therapeutic benefit in this setting.

This claim is primarily supported by the phase III IMforte trial, a randomised study conducted in the maintenance setting of ES-SCLC after first-line induction treatment, which directly compared lurbinectedin plus atezolizumab versus atezolizumab monotherapy in patients without disease progression following induction therapy (Figure 2). The study is reported to show statistically significant and clinically relevant improvements in both PFS and OS for the combination compared with atezolizumab alone and is presented by the sponsor as the main evidence supporting significant benefit.

The trial was conducted across 96 centres in 13 countries. Enrolment was planned for 690 participants in total, with 450 participants randomized in a 1:1 ratio (225 per arm) to the maintenance phase following induction therapy.

Figure 2. IMforte study design.



The study consists of two sequential phases: induction and maintenance. During the induction phase, eligible participants receive four 21-day cycles of standard-of-care treatment consisting of carboplatin, etoposide, and a fixed dose of atezolizumab 1200 mg administered intravenously on Day 1 of each cycle. Induction treatment may be discontinued earlier in the event of disease progression, unacceptable toxicity, or withdrawal of consent.

Participants who complete exactly four induction cycles and demonstrate CR, PR, or SD per RECIST v1.1 within 28 days prior to randomization are eligible for the maintenance phase, provided they maintain ECOG performance status 0–1 and meet protocol-defined laboratory and clinical criteria. Randomization must occur within protocol-specified time windows following the last induction dose, with allowances for patients receiving prophylactic cranial irradiation (PCI).

In the maintenance phase, participants are randomized to one of two arms:

- Arm A receives atezolizumab 1200 mg IV plus lurbinectedin 3.2 mg/m² IV on Day 1 of each 21-day cycle. Lurbinectedin dosing is body surface area–based and permits up to two dose reductions (to 2.6 mg/m² and 2.0 mg/m²), without re-escalation. Permanent discontinuation is required if toxicity occurs at the lowest dose level. Atezolizumab dosing is fixed and does not permit dose reductions, though temporary interruption for toxicity management is allowed. The two agents may be interrupted or discontinued independently based on toxicity attribution.
- Arm B receives atezolizumab 1200 mg IV monotherapy every 21 days. In both arms, treatment continues until disease progression, unacceptable toxicity, or fulfillment of other discontinuation criteria.

The primary efficacy endpoints were PFS (IRF-assessed) and overall survival. At the prespecified cut-off (29 July 2024; median follow-up of around 15 months), the addition of lurbinectedin to atezolizumab in maintenance was associated with:

- Improved IRF-assessed PFS: median 5.36 vs 2.14 months; HR 0.54 (95% CI 0.43–0.67), p<0.0001, corresponding to an approximate 3-month prolongation in median PFS (Table 3 and Figure 3).
- Improved OS: median 13.24 vs 10.64 months; HR 0.73 (95% CI 0.57–0.95), p=0.0174, corresponding to an approximate 2.5-month prolongation in median OS (Table 4 and Figure 4).

Table 3. Time to Event Summary for IRF-Assessed Progression-Free Survival (FAS)

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
Patients with event (%)	202 (83.8%)	174 (71.9%)
Earliest contributing event		
Death	19	31
Disease progression	183	143
Patients without event (%)	39 (16.2%)	68 (28.1%)
Time to event (months)		
Median (95% CI)	2.14 (1.64-2.73)	5.36 (4.24-5.75)
25% and 75%-percentiles	1.41-4.96	2.60-10.81
Range	0.13 to 23.36 [a]	0.03 [a] to 21.26 [a]
Unstratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.56 (0.46-0.69)	
Stratified analysis p-value (log-rank)	<.0001	
Hazard ratio (95% CI)	0.54 (0.43-0.67)	
Time point analysis - 6 months		
Patients remaining at risk	34	76
Event-free rate (%) (95% CI)	18.66 (13.45-23.87)	41.22 (34.58-47.86)
Difference in event-free rate (95% CI)	22.56 (14.12-31.00)	
Time point analysis - 12 months		
Patients remaining at risk	13	24
Event-free rate (%) (95% CI)	12.03 (7.27-16.80)	20.54 (14.37-26.72)

Difference in event-free rate (95% CI)	8.51 (0.72-16.31)

[a] Censored observation.
Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The stratification factors are ECOG PS at randomisation (0 *vs.* 1), LDH at randomisation (≤ULN *vs.* >ULN) via local laboratory test, presence of liver metastases at enrolment (yes *vs.* no), and prior receipt of PCI (yes *vs.* no).
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.

Figure 3. Kaplan-Meier Plot for IRF-assessed progression-free survival (FAS)

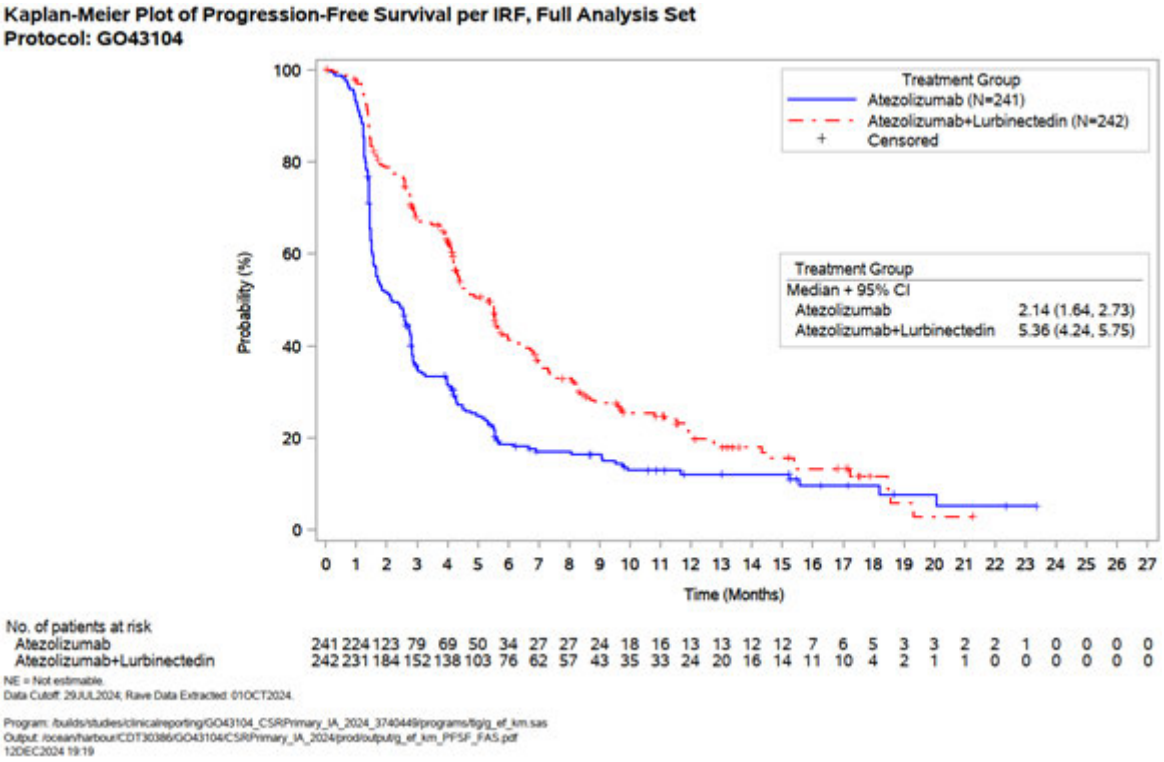


Table 4. Time to Event Summary for Overall Survival (FAS)

	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
Patients with event (%)	136 (56.4%)	113 (46.7%)
Earliest contributing event		
Death	136	113
Patients without event (%)	105 (43.6%)	129 (53.3%)
Time to event (months)		
Median (95% CI)	10.64 (9.49-12.16)	13.24 (11.89-16.36)
25% and 75%-percentiles	5.98-18.20	7.66-NE
Range	0.62 to 23.69 [a]	0.23 to 26.09 [a]
Unstratified analysis p-value (log-rank)	0.0203	
Hazard ratio (95% CI)	0.74 (0.58-0.96)	
Stratified analysis p-value (log-rank)	0.0174	
Hazard ratio (95% CI)	0.73 (0.57-0.95)	
Time point analysis - 12 months		
Patients remaining at risk	69	81
Event-free rate (%) (95% CI)	44.10 (37.00-51.21)	56.25 (48.97-63.53)

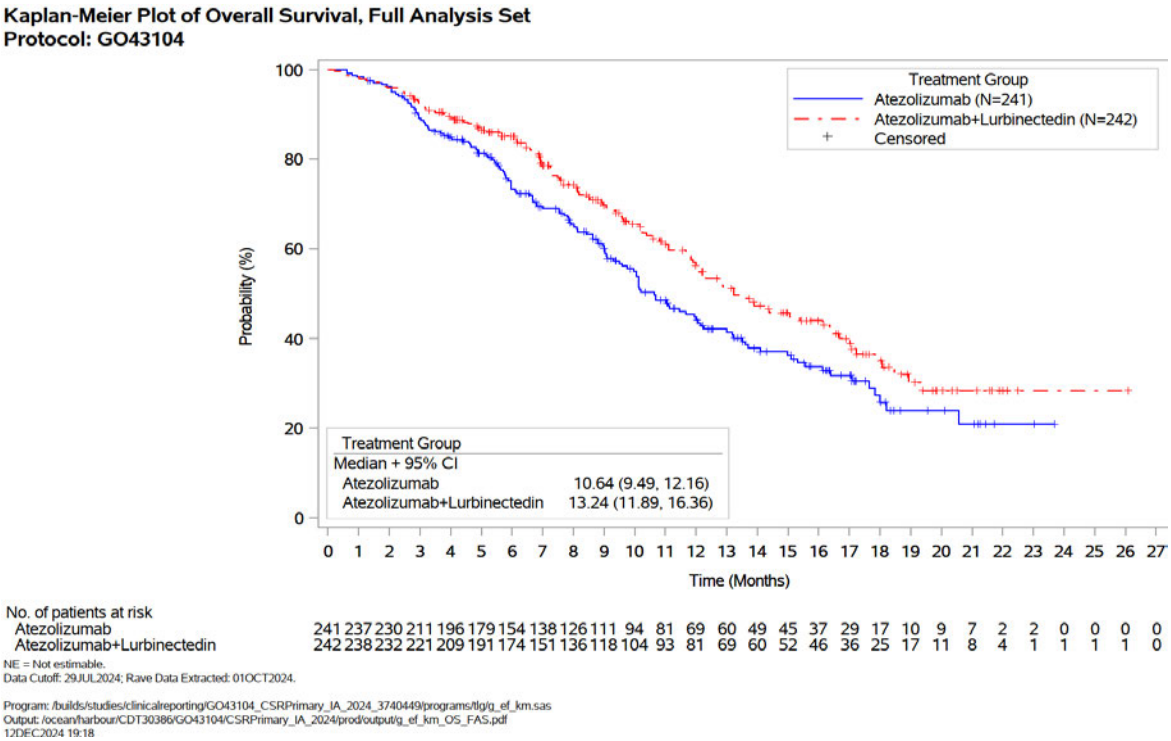
	Atezolizumab (n=241)	**Atezolizumab + Lurbinectedin** (n=242)
Difference in event-free rate (95% CI)	12.14 (1.97-22.31)	
Time point analysis - 24 months		
Patients remaining at risk	0	1
Event-free rate (%) (95% CI)	NE (NE)	28.32 (19.28-37.36)
Difference in event-free rate (95% CI)	NE (NE)	

[a] Censored observation.

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The stratification factors are ECOG PS at randomisation (0 *vs.* 1), LDH at randomisation (≤ULN *vs.* >ULN) via local laboratory test, presence of liver metastases at enrolment (yes *vs.* no), and prior receipt of PCI (yes *vs.* no).

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not estimable; PCI, prophylactic cranial irradiation; PS, performance status; ULN, upper limit of normal.

Figure4: Kaplan-Meier Plot for Overall Survival (FAS)



On this basis, the sponsor concludes that IMforte demonstrates a clinically relevant efficacy advantage when lurbinectedin is added to atezolizumab in the maintenance phase of first-line ES-SCLC.

COMP discussion and conclusion

The Committee concluded that the results of the pivotal Phase III IMforte study indicate that the addition of lurbinectedin to atezolizumab in the maintenance setting is associated with improved clinical outcomes compared with atezolizumab maintenance monotherapy. The observed prolongation in progression-free survival, supported by consistent hazard ratios and separation of Kaplan–Meier curves, together with favourable overall survival outcome, suggest a clinically relevant advantage on efficacy grounds in this setting.

These findings are of particular relevance in ES-SCLC, where patients typically experience rapid disease progression following an initial response to induction therapy and where therapeutic options remain limited. The magnitude of benefit observed in PFS, alongside the positive trend in OS, indicates that the combination may contribute to more sustained disease control during the maintenance phase.

Furthermore, the study design - restricting randomisation to patients with non-progressive disease following standard induction - supports the interpretation that the observed benefit is attributable to the maintenance strategy rather than differences in induction response. In this context, the addition of lurbinectedin represents an intensification of maintenance therapy, introducing a complementary mechanism of action aimed at delaying relapse.

This distinction is clinically relevant in ES-SCLC because:

- Induction aims to achieve rapid tumour shrinkage with an intensive regimen; platinum-etoposide is typically limited to four cycles due to cumulative toxicity.
- Maintenance aims to delay relapse and extend survival in a disease characterised by high initial response rates but rapid progression for most patients after induction.

Overall, the IMforte thereby results support the sponsor's claim of a clinically relevant efficacy advantage of lurbinectedin in combination with atezolizumab compared with atezolizumab alone in the maintenance treatment of ES-SCLC.

4. COMP position adopted on 31 March 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 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 Zepzelca is of significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication is established. In a head-to-head comparison with atezolizumab, treatment with Zepzelca as add-on to continued atezolizumab showed improvements in overall survival, progression-free survival, and overall response rate. These results suggest that Zepzelca may offer a significant benefit in terms of efficacy.

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 of Article 3(1)(a) 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 Zepzelca, lurbinectedin for treatment of pulmonary neuroendocrine carcinoma (EU/3/19/2143) is not removed from the Community Register of Orphan Medicinal Products.