EUROPEAN UNION RISK MANAGEMENT PLAN

IMDYLLTRA® (Tarlatamab)

Marketing Authorization Applicant:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	0.3
Date:	27 February 2026
Supersedes:	Version 0.2, dated 12 December 2025

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	0.3
Data lock point of this RMP:	29 January 2025
Date of final sign-off:	27 February 2026
Rationale for submitting an updated RMP:	Not Applicable

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part I: Product(s) Overview	Added details about pharmaceutical form(s) and strength(s)	Version 0.3; 27 February 2026
Part II: Safety Specification		
SVII: Identified and Potential Risks	Added Long-term Safety Data as missing information.	Version 0.2; 12 December 2025
	Updated severity information about Important Identified Risk, Cytokine Release Syndrome (CRS) and Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)	Version 0.3; 27 February 2026
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	Added routine pharmacovigilance activities for Central Nervous System (CNS) Including ICANS	Version 0.2; 12 December 2025
	Updated milestone for Additional Pharmacovigilance Activities 'Integrated Safety Analysis'	Version 0.3; 27 February 2026
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Added missing information 'Long-term safety data'	Version 0.2; 12 December 2025
	Added new Additional Risk Minimization Measure: Patient Card for CRS and ICANS.	
	Updated routine risk minimization measures by safety concern	Version 0.3; 27 February 2026
Part VI: Summary of the Risk Management Plan	Updated to include new missing information: Long-term Safety Data.	Version 0.2; 12 December 2025
Part VII: Annexes		
Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	Added planned and ongoing studies addressing long-term safety data.	Version 0.2; 12 December 2025
	Updated milestone for Integrated Safety Analysis to evaluate long-term safety of tarlatamab over 3 years.	Version 0.3; 27 February 2026
Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	Added clinical trials that will contribute to the Integrated Safety Analysis.	Version 0.2; 12 December 2025
Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)	Added key messages of the additional risk minimization measures for CRS and ICANS	Version 0.2; 12 December 2025

Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	Not applicable
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization applicant's QPPV. The electronic signature is available on file.

Table of Contents

List of Tables

List of Annexes

List of Abbreviations

Term/Abbreviation	Explanation
CD3	cluster of differentiation 3
COPD	chronic obstructive pulmonary disease
CRS	cytokine release syndrome
DLL3	delta-like-ligand 3
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EPAR	European Public Assessment Report
ES-SCLC	extensive stage small cell lung cancer
EU	European Union
ICANS	immune effector cell-associated neurotoxicity syndrome
ICU	intensive care unit
ILD	interstitial lung disease
IV	intravenous
LS	limited-stage
MedDRA	Medical Dictionary for Regulatory Activities
OS	overall survival
PCI	prophylactic cranial irradiation
PI	Product Information
PL	Package Leaflet
RMP	Risk Management Plan
SCLC	small cell lung cancer
SES	socioeconomic status
SmPC	Summary of Product Characteristics

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Tarlatamab
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Antineoplastic agents, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX33
Marketing authorization applicant	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	IMDYLLTRA®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Tarlatamab is a bispecific delta-like-ligand 3 (DLL3)-directed cluster of differentiation 3 (CD3) T-cell engager.
Summary of mode of action	Tarlatamab binds to DLL3 expressed on the surface of tumor cells and CD3 expressed on the surface of T cells. The bispecific binding of tarlatamab to T cells and DLL3-positive tumor cells triggers T cell activation, production of inflammatory cytokines, and release of cytotoxic proteins, which results in redirected lysis of tumor cells.
Important information about its composition	Tarlatamab is produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.
Indication(s) in the EEA	
Current	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.

Table 1. Product(s) Overview

<table>
<tr><td>Dosage in the EEA</td><td></td></tr>
<tr><td>Current</td><td>The recommended dosing schedule of IMDYLLTRA is an initial dose of 1 mg on day 1 followed by 10 mg on days 8, 15, and every 2 weeks thereafter as shown below. Patients should be treated until disease progression or unacceptable toxicity.
<table>
<tr><th colspan="2">Dose of IMDYLLTRA</th></tr>
<tr><td>Day 1</td><td>1 mg</td></tr>
<tr><td>Day 8</td><td>10 mg</td></tr>
<tr><td>Day 15 and every 2 weeks thereafter</td><td>10 mg</td></tr>
</table>
IMDYLLTRA treatment should be initiated under the direction of and supervised by physicians experienced in the use of cancer therapy. IMDYLLTRA should be administered as a 1-hour intravenous (IV) infusion in an appropriate healthcare facility.</td></tr>
<tr><td>Pharmaceutical form(s) and strength(s)</td><td></td></tr>
<tr><td>Current</td><td>IMDYLLTRA is supplied as:
Tarlatamab powder (powder for concentrate): White to slightly yellow powder.
Solution (stabiliser): Colourless to slightly yellow, clear solution with a pH of 7.0.
<u>IMDYLLTRA 1 mg powder for concentrate and solution for infusion</u>
One mg tarlatamab powder in a Type 1 glass vial with an elastomeric stopper, aluminium seal and a grey flip-off cap.
Reconstitution with water for injections results in a final tarlatamab concentration of 0.9 mg/mL.
<u>IMDYLLTRA 10 mg powder for concentrate and solution for infusion</u>
Ten mg tarlatamab powder in a Type 1 glass vial with an elastomeric stopper, aluminium seal and an orange flip-off cap.
Reconstitution with water for injections results in a final tarlatamab concentration of 2.4 mg/mL.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the European Union (EU)?</td><td>Yes</td></tr>
</table>

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Small Cell Lung Cancer

Incidence	Globally, lung cancer is the most commonly diagnosed form of cancer and the leading cause of cancer death, representing 1 in 8 (12.4%) cancers diagnosed and 1 in 5 (18.7%) cancer deaths in 2022 (Bray et al, 2024). Within the EU, lung cancer was the fourth most commonly diagnosed cancer in 2022, with approximately 320 000 new cases reported (Ferlay et al, 2024). Small cell lung cancer represents approximately 10% to 15% of all lung cancers, representing an estimated 32 000 to 48 000 patients newly diagnosed in the EU in 2022 based on lung cancer incidence estimates (American Cancer Society, 2024; Ferlay et al, 2024; Rudin et al, 2021).
Prevalence	The estimated restaged 5-year prevalence of small cell lung cancer (SCLC) in 2024 was reported for four European countries: Germany (approximately 15 500), Spain (approximately 7000), France (approximately 9700), and Italy (approximately 6100). (CancerMPact, 2024).
Demographics of population in the proposed indication and risk factors for the disease	Small cell lung cancer is most prevalent in men, but the proportion of cases in women compared to men has risen worldwide over the past 50 years, reflecting tobacco consumption trends (Huang et al, 2015). Most people diagnosed with SCLC are 65 or older (Blackhall et al, 2023; Dumoulin et al, 2023; Lee et al, 2022). The median age at diagnosis has also risen over the past 40 years, from 63 years in 1975 to 69 years in 2019 (Cittolin-Santos et al, 2024). The rate of SCLC in individuals of European ancestry, is higher relative to those of African ancestry (6.4 versus 5.2 per 100 000 in 2019) (Wang et al, 2023). In addition, the incidence of SCLC is higher among people with low socioeconomic status (SES), which parallels the patterns of tobacco consumption (Hovanec et al, 2018). A pooled analysis of case-control studies revealed that lower SES is associated with statistically significant increased risk of lung cancer including SCLC when compared to higher SES (odds ratio [OR] = 2.13, 95% confidence interval [CI]: 1.63 to 2.77 in males; OR = 2.85, 95% CI: 1.57 to 5.18 in females; p for trend < 0.001 for both sexes), after controlling for smoking behaviors (Hovanec et al, 2018). Risk factors for SCLC include: • Cigarette smoking (Wang et al, 2023; Rudin et al, 2021) • Chronic obstructive pulmonary disease (COPD) (Rudin et al, 2021; Huang et al, 2015) • Radon exposure (Rudin et al, 2021; Rodríguez-Martínez et al, 2018) Cigarette smoking is the major risk factor accounting for more than 95% of SCLC cases (Govindan et al, 2006). As the prevalence of cigarette smoking has decreased over time so has the incidence of SCLC with a lag time of approximately 30 years (Huang et al, 2015).

Table 2. Summary of Epidemiology of Small Cell Lung Cancer

Demographics of population in the proposed indication and risk factors for the disease (continued)	Chronic obstructive pulmonary disease is a common comorbidity in SCLC and was shown to be an independent risk factor in a large epidemiologic study (Huang et al, 2015). Radon exposure has also been reported to increase the risk of SCLC among non-smokers (Rodríguez-Martínez et al, 2018). Unlike non-small cell lung cancer, genome-wide association studies explain only a small proportion of the overall genetic variance for SCLC (Wang et al, 2023). The one exception is the smoking-related 15q25 locus, which has a significant association with SCLC risk, reflecting the strong association with tobacco smoking (Wang et al, 2023). Expression of the Notch-family ligand DLL3 has been explored as a potential therapeutic target in SCLC. Transcription of DLL3 is regulated by the SCLC oncogenic driver achaete-scute homolog-1, and as such, DLL3 has been implicated in neuroendocrine tumorigenesis (Borromeo et al, 2016, Jiang et al, 2009). DLL3 is highly expressed in SCLC, with a systematic review finding a range of between 80% to 94% positivity using a threshold of ≥ 1% of tumor cells (Bylsma et al, 2023) and no associations were demonstrated between level of DLL3 expression and a number of prognostic factors, including SCLC stage or Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis (Bylsma et al, 2023; Rojo et al, 2020).
Main existing treatment options	Treatment for SCLC varies by stage and ECOG performance status. Patients with limited-stage (LS) SCLC often present with disease that involves the mediastinal and hilar nodes with LS-SCLC being defined as a tumor confined to 1 hemi-thorax and 1 radiation port; no malignant pleural or pericardial effusion and having a disease extent that can be safely treated with definitive radiation doses (Rudin et al, 2021). Surgery is generally not a treatment option in these patients, and is reserved for patients with very limited disease (N0). The standard of care for patients with LS-SCLC with a performance status of 0 to 1 is twice-daily thoracic radiotherapy (45 Gy in 3 weeks) with concurrent cisplatin-etoposide (Rudin et al, 2021). If twice-daily radiotherapy cannot be delivered for patient-specific or practical reasons, once-daily radiotherapy is a reasonable alternative. In LS-SCLC with partial response or complete response to primary treatment, prophylactic cranial irradiation (PCI) is part of the standard management, as it significantly reduces the risk of brain metastases and improves survival (Rudin et al, 2021). However, given the neurotoxicity induced by PCI, recently brain MRI monitoring has been proposed as an alternative. Consolidation therapy with durvalumab in patients who do not experience disease progression after systemic therapy with concurrent radiation has been recently recommended (NCCN SCLC Guidelines, 2025; Guidelines for Diagnosis and Treatment of Lung cancer in Japan, 2024; Ganti et al, 2021, Rudin et al, 2021). In LS, cure can be obtained in 20% to 30% of cases (Toh and Lok, 2021).

Table 2. Summary of Epidemiology of Small Cell Lung Cancer

Main existing treatment options (continued)	First-line regimens in ES-SCLC (disease not meeting criteria for LS), including chemotherapy plus immune checkpoint inhibitor (carboplatin/etoposide/atezolizumab or platinum-based chemotherapy/etoposide/durvalumab), have a relatively high response rate of 60% to 70%; however, resistance and relapse almost always occur, usually within the first year after treatment for nearly all patients with ES-SCLC (Rudin et al, 2021; Yoon et al, 2019; Chan and Coward, 2013) and median overall survival (OS) is approximately 12 to 13 months (Dingemans et al, 2021; Tariq et al, 2021; Paz-Ares et al, 2019; Horn et al, 2018). Treatment options for patients with relapsed SCLC are limited. In addition, patients who had a response of at least 3 to 6-month duration to first-line chemotherapy, may benefit from the same treatment (NCCN, 2025). In addition to consideration of platinum rechallenge or clinical trial participation, other recommended regimens in the relapsed or refractory setting include topotecan (US and EU) (Eckardt et al, 2007; O'Brien et al, 2006; von Pawel et al, 1999), lurbinectedin (Trigo et al, 2020), amrubicin in Japan, other chemotherapy agents (eg, cyclophosphamide/doxorubicin/vincristine; docetaxel, etoposide; gemcitabine; temozolomide), or immunotherapy agents (eg, nivolumab, pembrolizumab). Best supportive care is recommended for patients with ES-SCLC with a ECOG PS ≥ 2 (Dingemans et al, 2021). In the EU, topotecan is the only drug specifically licensed for use as second-line therapy in SCLC.
Natural history of the indicated condition in the untreated/treated population, including mortality and morbidity	Small cell lung cancer has the most aggressive clinical course of any type of pulmonary tumor. The most important prognostic factor is the extent of disease (stage) at presentation. Without treatment the median survival from SCLC diagnosis is only 2 to 4 months (PDQ, 2025). Patients with LS-SCLC account for approximately 30% of SCLC (Rudin et al, 2021). Among patients with LS-SCLC treated with contemporary radio-chemotherapy and PCI, the overall response rates range from 80% to 90%%, including 50% to 60% complete remission rates. Though the initial response to first-line therapies is high and up to 30% of patients with LS-SCLC may be cured, most patients (approximately 70%) and nearly all with ES-SCLC relapse after initial therapy (Blackhall et al, 2023; Bogart et al, 2023; Rudin et al, 2021; Faivre-Finn et al, 2017; Chan and Coward, 2013; Jänne et al, 2002).

Table 2. Summary of Epidemiology of Small Cell Lung Cancer

Natural history of the indicated condition in the untreated/treated population, including mortality and morbidity	Patients with ES-SCLC treated with first-line systemic therapy have relatively high response rates, however, most patients relapse, usually within the first year after treatment (Bogart et al, 2023; Rudin et al, 2021; Yoon et al, 2019; Chan and Coward, 2013). Recent clinical trials have shown median OS of approximately 12 to 13 months in the first-line setting (Tariq et al, 2021; Paz-Ares et al, 2019; Horn et al, 2018). In patients diagnosed with ES-SCLC in the real-world setting, the median survival for patients is about 8 to 13 months from the time of first-line therapy initiation (Blackhall et al, 2023; Zugazagoitia et al, 2022). In the second-line real-world setting, patients receiving systemic therapy have an overall median OS of 4.2 to 7.0 months (Shaw et al, 2024; Blackhall et al, 2023; O'Sullivan et al, 2021; Rojo et al, 2020; Schwartzberg et al, 2018; Imai et al, 2017; Garassino et al, 2011). The 5 year survival rate of SCLC (all stages combined) is less than 10% (American Cancer Society, 2024; Cittolin Santos et al, 2024). In addition to poor survival outcome associated with relapsed SCLC, patients also face significant challenges in managing cancer-related symptoms, including cough, dyspnea, chest pain, and hemoptysis (Bebb et al, 2023). The symptoms, which are frequently debilitating, substantially impair patients' physical functioning and ability to perform basic activities of daily living (Bennett et al, 2017).
Important comorbidities	Small cell lung cancer is closely linked with cigarette smoking and thus these patients often have tobacco-related conditions. The most common comorbidities in the SCLC population are (Tas et al, 2024; Dingemans et al, 2021; Dima et al, 2018; Aarts et al, 2015; Janssen-Heijnen et al, 1998). • COPD • hypertension • cardiovascular disease • diabetes mellitus • other malignancies

Page 4 of 4

Part II: Module SII - Nonclinical Part of the Safety Specification

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity • Key issues identified from acute or repeat-dose toxicity studies	In a 28-day IV infusion repeat-dose toxicology study in the cynomolgus monkey, there was a minimal to mild tarlatamab-related mixed cell infiltrate in the pituitary gland at both 50 and 500 µg/kg tarlatamab doses. The infiltrate was characterized as predominantly lymphocytes with a variable degree of eosinophils; this cellular pattern was restricted to the interface between the pars intermedia and pars nervosa, which is consistent with the expression pattern of DLL3 in the pituitary gland. No evidence of tissue injury was associated with the cellular infiltrate in the pituitary gland. At the higher exposure level of 4500 µg/kg group, there was an absence of the pituitary change (infiltrate) and this absence correlated with the presence of antidrug antibodies (ADAs) in all animals at this dose level. After the 500 µg/kg recovery phase, there was a minimal focal to multifocal mononuclear cell infiltrate in the pituitary gland. Similar to that observed in the dosing phase, the infiltrate was located at the interface between the pars intermedia and pars nervosa. Based on the reduced distribution and change from a mixed cell infiltrate to a mononuclear cell infiltrate, the change in the pituitary gland was considered to have partially reversed after the recovery phase and full reversibility would be expected with additional time (Perry et al, 2013). The tarlatamab-related mixed cell infiltrate in the cynomolgus monkey pituitary is morphologically distinct and much less severe than the hypophysitis that has been reported and clinically managed in some patients treated with immune checkpoint inhibitors. Checkpoint inhibitor-related hypophysitis has been reported to be an autoimmune-related condition associated with diffuse, tissue damaging inflammation with pituitary enlargement detectable by magnetic resonance imaging, clinical symptoms (eg, headache, fatigue), and secondary endocrine dysfunction involving the adrenal glands, thyroid, and gonads (Rossi et al, 2016; Torino et al, 2016). In contrast, the tarlatamab-related mixed cell infiltrate in the cynomolgus monkey was restricted in distribution and not associated with pituitary weight change, cellular injury, overt evidence of endocrine gland dysfunction, or clinical signs. Based on these significant differences and the reversible nature of the change, the tarlatamab-related mixed cell infiltrate in the pituitary was considered not adverse.	Based on the significant differences to hypophysitis that have been reported and clinically managed in some patients treated with immune checkpoint inhibitors, as well as the reversible nature of the change, the tarlatamab-related mixed cell infiltrate in the pituitary was not considered adverse and is not considered relevant as a safety concern. Based on the available data from clinical studies, no effect of tarlatamab on pituitary function has been observed.

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
• Key issues identified from acute or repeat-dose toxicity studies (continued)	The development of ADAs in animals does not predict whether a protein therapeutic will be immunogenic in humans (Ponce, 2009).	
• Reproductive/ developmental toxicity	An embryofetal development toxicity study was performed using the murine surrogate molecule of tarlatamab designated muS757 in mice. The study objectives were to detect potential adverse effects of muS757 on pregnant female mice and development of the embryo and fetus consequent to exposure of the female from implantation to closure of the hard palate. Timed-mated female mice received the vehicle control, 500 or 4500 µg/kg muS757 via IV bolus injection on gestation days (GD) 6 and 13. MuS757 exposure increased in pregnant female mice approximately in proportion to dose. Fetal serum concentrations were 22.6- to 29.5-fold higher than maternal serum concentrations at the single sampling time point included (GD 18). The fetal muS757 serum concentrations were considered pharmacologically relevant since they were well above the half maximal effective concentration (EC_{50}) values from in vitro assays evaluating redirected lysis of a murine DLL3-expressing cell line by murine effector cells.	In line with the highly restricted expression pattern of DLL3 during embryofetal development, the intracellular localization of DLL3 and the results of the embryofetal development toxicity study in mice, tarlatamab-mediated embryofetal toxicity in pregnant patients is of low likelihood. There are no data from the use of tarlatamab in pregnant women. An embryofetal developmental toxicity study conducted in mice does not indicate direct or indirect harmful effects with respect to reproductive toxicity. The pharmacological mechanism of action of tarlatamab involves its binding to DLL3-expressing tumor cells and CD3-positive T cells, which is expected to result in potent T-cell activation and proliferation, and the release of pro-inflammatory cytokines, such as IL-6, IFN-γ, and TNF-α. This immune activation could potentially have harmful effects on pregnancy and on the developing embryo-fetus, even in the absence of direct DLL3-mediated toxicity in embryofetal tissues.

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
• Reproductive/ developmental toxicity (continued)	There were no muS757-related effects on any maternal parameters, including mean maternal body weights or body weight gains. In addition, there were no muS757-related macroscopic findings or effects on any ovarian, uterine, or litter parameters at any dose level. Administration of muS757 did not produce any fetal external, visceral, or skeletal malformations or variations.	IMDYLTTRA is not recommended during pregnancy and in women of childbearing potential not using contraception. Women of childbearing potential have to use effective contraception during and for 2 months after treatment with IMDYLTTRA. Pregnancy status for females of childbearing potential should be verified prior to starting treatment with tarlatamab. It is unknown whether tarlatamab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with tarlatamab and for at least 2 months after the last dose.
Safety pharmacology		
• Cardiovascular system (including potential effect on the QT interval)	In a 28-day IV infusion repeat-dose toxicology study in the cynomolgus monkey, there was a tarlatamab-related slight increase in heart rate on day 2 associated with decreased PR, RR, and QT intervals at doses ≥ 500 µg/kg. Throughout the 24 hour collection period, the mean change in heart rate was < 10.0% higher than the control group (individual changes up to 23% were recorded).	Given the low magnitude of the heart rate increase and the absence of an effect at the end of study despite continued dosing, this finding was not considered adverse and is not considered relevant as a safety concern. Based on the available data from clinical studies, no effect of tarlatamab on cardiac function has been observed.

ADA = antidrug antibodies, DLL3 = delta-like-ligand 3; GD = gestation days; IV = intravenous; PR interval = the period that extends from the beginning of the P-wave until the beginning of the QRS complex; QT interval = the time from the start of the Q wave to the end of the T wave; RR interval = the time between successive R waves in the QRS complex

Part II: Module SIII - Clinical Trial Exposure

Table 4. Total Subject Exposure to Tarlatamab in Clinical Trials by Indication and Duration
Safety Analysis Set

	Exposure to Tarlatamab by Duration						
Indication Therapy	< 1 Month n (subj-yrs)	1 - < 3 Months n (subj-yrs)	3 - < 6 Months n (subj-yrs)	6 - < 9 Months n (subj-yrs)	9 - < 12 Months n (subj-yrs)	≥ 12 Months n (subj-yrs)	Total n (subj-yrs)
SCLC							
Monotherapy tarlatamab (all doses)	181 (6.971)	153 (25.221)	130 (47.521)	97 (60.326)	59 (50.426)	110 (188.181)	730 (378.645)

n = number of subjects exposed to tarlatamab; SCLC = small cell lung cancer; subj-yrs = total subject-years of exposure
The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.
Monotherapy cohorts of Study 20160323, Study 20200491, and tarlatamab group of Study 20210004 are included.
Total subject-years of exposure to tarlatamab is calculated as subj-yrs = (last non-missing tarlatamab dose date - first non-missing tarlatamab dose date + 1)/365.25.
Data cutoff date: 18Oct2024 for studies 20160323 and 20200491; 29Jan2025 for study 20210004.
Program: /userdata/stat/amg757/meta/rmp/analysis/rmp_2025/tables/t-rmp-core-exp-ind-dur.sas
Output: t14-05-001-rmp-core-exp-ind-dur.rtf (Date Generated: 09JUN25:03:04:22) Source: adam.adexsum

Table 5. Total Subject Exposure to Tarlatamab in Clinical Trials by Age Group and Gender
Safety Analysis Set

Indication / Age Group	Number of Subjects			Subject-years of Exposure		
	Male	Female	Total	Male	Female	Total
SCLC						
18 - < 65 years	256	137	393	125.062	84.810	209.873
≥ 65 - < 75 years	173	99	272	91.874	52.049	143.923
≥ 75 - < 85 years	51	12	63	18.070	5.958	24.027
≥ 85 years	1	1	2	0.003	0.819	0.821
Total	481	249	730	235.009	143.636	378.645

SCLC = small cell lung cancer
The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.
Monotherapy cohorts of study 20160323, study 20200491, and tarlatamab group of study 20210004 are included.
Total subject-years of exposure to tarlatamab is calculated as (last non-missing tarlatamab dose date - first non-missing tarlatamab dose date + 1)/365.25.
Data cutoff date: 18Oct2024 for studies 20160323 and 20200491; 29Jan2025 for study 20210004.
Program: /userdata/stat/amg757/meta/rmp/analysis/rmp_2025/tables/output/t-rmp-core-exp-age-sex.sas
Output: t14-05-002-rmp-core-exp-age-sex.rtf (Date Generated: 09JUN25:03:04:22) Source: adam.adsl

Table 6. Exposure to Tarlatamab in Clinical Trials by Indication and Dose Level
Safety Analysis Set

Indication Therapy	Study 20160323 Tarlatamab < 10 mg n (mean exposure in days) (subj-yrs)	Studies 20210004, 20200491, and 20160323 Tarlatamab 10 mg n (mean exposure in days) (subj-yrs)	Studies 20200491 and 20160323 Tarlatamab > 10 mg n (mean exposure in days) (subj-yrs)	Studies 20210004, 20200491, and 20160323 Tarlatamab All Doses n (mean exposure in days) (subj-yrs)
SCLC				
Monotherapy tarlatamab	35 (150.3) (14.404)	473 (185.9) (240.701)	222 (203.3) (123.540)	730 (189.5) (378.645)

D = day; eIV = extended intravenous; hr = hour; n = number of subjects exposed to tarlatamab; Q3W = every 3 weeks; SCLC = small cell lung cancer; subj-yrs = total subject-years of exposure

The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.

Tarlatamab < 10 mg includes study 20160323 cohorts 1-7. Tarlatamab 10 mg includes study 20210004 1->10 mg; study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); study 20160323 cohorts 8, 32, and 35. Tarlatamab > 10 mg includes study 20200491 1->100 mg (part 1 randomized arm); study 20160323 cohort 9 (1->30 mg), cohorts 10, 30 (1->100 mg), cohort 11 (tarlatamab + dexamethasone), cohort 34 (1->100 mg 24-hr outpatient), cohort 26 (30 mg eIV-100mg), cohorts 27 and 31 (100 mg eIV-100 mg), 2-step-dosing cohort 23 (1->25->100 mg), cohort 37 (1->100->200 mg Q3W 21 day/cycle), and cohort 38 (1->100 mg D1/D8 21 day/cycle). Tarlatamab All Doses includes all subjects who receive any dose of tarlatamab monotherapy from studies 20210004, 20200491, and 20160323.

Total subject-years of exposure to tarlatamab is calculated as subj-yrs = (last non-missing tarlatamab dose date - first non-missing tarlatamab dose date + 1)/365.25.

Data cutoff date: 18Oct2024 for studies 20160323 and 20200491; 29Jan2025 for study 20210004.

Program: /userdata/stat/amg757/meta/rmp/analysis/rmp_2025/tables/output/t-rmp-core-exp-dose-ind.sas

Output: t14-05-003-rmp-core-exp-dose-ind.rtf (Date Generated: 09JUN25:03:04:24) Source: adam.adsl

Table 7. Total Subject Exposure to Tarlatamab in Clinical Trials by Indication and Race Group
Safety Analysis Set

	Race								
Indication Therapy	White n (subj-yrs)	American Indian or Alaska Native n (subj-yrs)	Black or African American n (subj-yrs)	Native Hawaiian or Other Pacific Islander n (subj-yrs)	Asian n (subj-yrs)	Multiple n (subj-yrs)	Other n (subj-yrs)	Missing n (subj-yrs)	Total n (subj-yrs)
SCLC									
Monotherapy tarlatamab (all doses)	492 (248.991)	1 (0.085)	12 (3.896)	0 (-)	201 (111.266)	0 (-)	23 (13.599)	1 (0.808)	730 (378.645)

n = number of subjects exposed to tarlatamab; SCLC = small cell lung cancer; subj-yrs = total subject-years of exposure
The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.
Monotherapy cohorts of study 20160323, study 20200491, and tarlatamab group of study 20210004 are included.
Total subject-years of exposure to tarlatamab is calculated as subj-yrs = (last non-missing tarlatamab dose date - first non-missing tarlatamab dose date + 1)/365.25.
Data cutoff date: 18Oct2024 for studies 20160323 and 20200491; 29Jan2025 for study 20210004.
Program: /userdata/stat/amg757/meta/rmp/analysis/rmp_2025/tables/t-rmp-core-exp-ind-race.sas
Output: t14-05-004-rmp-core-exp-ind-race.rtf (Date Generated: 09JUN25:03:04:23) Source: adam.adsl

Table 8. Total Subject Exposure to Tarlatamab in Clinical Trials by Indication and Ethnicity Group White Subgroup of Safety Analysis Set

Indication Therapy	Ethnicity[a] Hispanic or Latino n (subj-yrs)	 Non-Hispanic or Latino n (subj-yrs)	 Total n (subj-yrs)
SCLC			
Monotherapy tarlatamab (all doses)	21 (7.677)	471 (241.314)	492 (248.991)

n = number of subjects exposed to tarlatamab; SCLC = small cell lung cancer; subj-yrs = total subject-years of exposure
The safety analysis set is defined as all subjects who receive at least 1 dose of tarlatamab.
Monotherapy cohorts of study 20160323, study 20200491, and tarlatamab group of study 20210004 are included.
Total subject-years of exposure to tarlatamab is calculated as subj-yrs = (last non-missing tarlatamab dose date - first non-missing tarlatamab dose date + 1)/365.25.
[a] Summarized for race = white only.
Data cutoff date: 18Oct2024 for studies 20160323 and 20200491; 29Jan2025 for study 20210004.
Program: /userdata/stat/amg757/meta/rmp/analysis/rmp_2025/tables/t-rmp-core-exp-ind-eth.sas
Output: t14-05-005-rmp-core-exp-ind-eth.rtf (Date Generated: 09JUN25:03:04:23) Source: adam.adsl

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subjects pregnant or breastfeeding, or planning to become pregnant	Adequate and well-controlled studies with tarlatamab have not been conducted in pregnant women due to the potential risk to the fetus. It is not known whether tarlatamab is transferred into human milk.	No	There are no data from the use of tarlatamab in pregnant and breastfeeding women to draw conclusions about the safety in this population. Despite the results from nonclinical studies showing that tarlatamab-mediated embryofetal toxicity in pregnant patients is of low likelihood, tarlatamab is not recommended for use in these populations. The Summary of Product Characteristics (SmPC) states that IMDYLTTRA is not recommended during pregnancy and in women of childbearing potential not using contraception. Women of child-bearing potential have to use effective contraception during and for 2 months after treatment with IMDYLTTRA. Pregnancy status for females of child-bearing potential should be verified prior to starting treatment with tarlatamab. It is unknown whether tarlatamab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with tarlatamab and for at least 2 months after the last dose.

Page 1 of 6

Abbreviations and footnotes are defined on the last page of this table.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Hypersensitivity to the active substance or to any of the excipients	To ensure the safety of subjects and that the evaluation of the safety profile in clinical studies was not affected by pre-existing hypersensitivity to the product.	No	Hypersensitivity is a non-important potential risk with tarlatamab treatment. Hypersensitivity to the active substance or to any of its excipients is a contraindication in the SmPC. Patients are monitored from the start of tarlatamab infusion for 6 to 8 hours on day 1 and day 8. Additional monitoring and monitoring on subsequent infusions is at the discretion of the healthcare provider; therefore, hypersensitivity events would be identified in the clinical setting. Details on monitoring and management of hypersensitivity reactions are provided in the SmPC in the special warnings and precautions for use section.
Subjects with symptomatic brain metastases and leptomeningeal disease	Due to the poor outcome and short survival of subjects with symptomatic brain metastases, the efficacy and safety of tarlatamab has not been evaluated in this patient population in tarlatamab clinical studies.	No	No effect of tarlatamab on brain tissue is known or suspected. The safety profile is not expected to differ in this patient population.

Page 2 of 6

Abbreviations and footnotes are defined on the last page of this table.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subject has evidence of interstitial lung disease (ILD) or active, non-infectious pneumonitis	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing ILD, or active, non-infectious pneumonitis.	No	Exclusion was based on hypothetical assumption of potential risk of ILD; however, there are no preclinical data suggesting any correlation. In addition, the currently available clinical data do not support ILD as a risk for tarlatamab, and the safety profile is not expected to differ in this population.
Subjects who experienced severe, life-threatening, or recurrent (grade 2 or higher) immune-mediated adverse events or infusion-related reactions, including those that lead to permanent discontinuation while on treatment with immune oncology agents	Subjects with a history of severe, life-threatening, or recurrent immune-mediated adverse events were excluded due to potential risk to the subject and to ensure accurate evaluation of the safety profile of tarlatamab in clinical studies.	No	Based on the available data from clinical studies, cytokine release syndrome (CRS) is an important identified risk of tarlatamab in the RMP (Table 13), but no high-grade infusion-related reactions or other immune-mediated adverse reactions have been observed. The SmPC provides recommendations, including step-dosing, premedication with dexamethasone or equivalent, monitoring, dosage interruption, and treatment for patients who experience signs or symptoms of CRS.
Subjects with unresolved toxicity from prior anti-tumor therapy	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing toxicity to prior therapy.	No	Unresolved toxicity from prior anti-tumor therapy is unlikely to predict adverse outcome with tarlatamab. The safety profile is not expected to differ in this population.

Page 3 of 6

Abbreviations and footnotes are defined on the last page of this table.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
History of other malignancy within the past 2 years[a]	Due to competing risks of death due to other active cancer, the treatment effect of tarlatamab in this setting would be confounded. This patient population was excluded from clinical studies to enable clearer interpretation of data.	No	The coexistence of another active malignancy is unlikely to predict adverse outcome with tarlatamab. The safety profile is not expected to differ in this population.
Myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months of first dose of tarlatamab	To ensure that the evaluation of the safety profile of tarlatamab in clinical studies was not affected by pre-existing cardiac conditions.	No	Based on the available data from clinical studies, no effect of tarlatamab on cardiac function is known or suspected. The safety of tarlatamab is not expected to differ between subjects with or without cardiac disease.
History of arterial thrombosis (eg, stroke or transient ischemic attack) within 12 months of first dose of tarlatamab	To ensure that the evaluation for the safety profile in clinical studies was not affected by underlying history of arterial thrombosis.	No	No effect of tarlatamab on coagulation is known or suspected. The safety of tarlatamab is not expected to differ between subjects with or without arterial thrombosis.
Subject with symptoms and/or clinical signs and/or radiographic signs that indicate an acute and/or uncontrolled active systemic infection within 7 days prior to the first dose of tarlatamab	To ensure that the evaluation for the safety profile in clinical studies was not affected by underlying infection.	No	Neutropenia is an identified risk for tarlatamab. Details on monitoring and management are provided in the SmPC in both the warnings and precautions and dosage and administrations sections; therefore, it is not anticipated that tarlatamab will be utilized in patients with acute and/or active systemic infections.

Page 4 of 6

Abbreviations and footnotes are defined on the last page of this table.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subjects with a history of hypophysitis or pituitary dysfunction	Based on the expression of DLL3 in the pituitary and observations in the cynomolgus monkey toxicology study, there was a hypothetical safety concern for pituitary dysfunction. Given this, subject with a history of hypophysitis or pituitary dysfunction were excluded to enable clearer interpretation of data.	No	Nonclinical tarlatamab studies did not show adverse tarlatamab-related pituitary changes. Based on the available data from clinical studies, no effect of tarlatamab on the pituitary gland is known or suspected. The safety of tarlatamab is not expected to differ between subjects with or without hypophysitis or pituitary dysfunction.
Subject received prior anticancer therapy within 30 days prior to first dose of tarlatamab	A wash-out/recovery period after other anticancer therapies was required before initiating treatment with tarlatamab to ensure clinical trial efficacy and safety results were not confounded.	No	Tarlatamab is indicated for the treatment of adult patients with SCLC with disease progression on or after platinum therapy. Based on the available safety data from clinical studies, the safety profile is not expected to differ in this population.
Subjects with active human immunodeficiency virus (HIV) infection	To ensure that the evaluation for the safety profile in clinical studies was not affected by pre-existing immunodeficiency.	No	The currently available data do not suggest that tarlatamab causes immunosuppression and therefore it is not expected to affect immunologic functions in subjects with HIV infection on antiviral therapy and undetectable viral load. Therefore, the safety profile is not anticipated to be different in this patient population.

Page 5 of 6

Abbreviations and footnotes are defined on the last page of this table.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subjects receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of tarlatamab	To ensure that the evaluation for the safety profile in clinical studies was not affected by ongoing receipt of systemic steroids or any other form of immunosuppressive therapy.	No	Based on the available safety data from clinical studies, no effect of systemic steroid therapy on the safety profile of tarlatamab is anticipated.
Subjects with active hepatitis infection	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing disease.	No	The currently available data do not suggest that tarlatamab causes immunosuppression and therefore, reactivation of hepatitis is not expected. Therefore, the safety profile is not anticipated to be different in this patient population.
Subjects with renal impairment	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing disease.	No	Tarlatamab is not expected to undergo renal elimination and thus the safety profile is not expected to differ in this population.
Subjects with hepatic impairment	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing disease.	No	Tarlatamab is not expected to undergo metabolism by hepatic metabolic enzymes and thus the safety profile is not expected to differ in this population.

Page 6 of 6

CRS = cytokine release syndrome; DLL3 = delta-like-ligand 3; HIV = Human immunodeficiency virus; ILD = interstitial lung disease; RMP = Risk management plan; SCLC = small cell lung cancer; SmPC = Summary of Product Characteristics.

[a] Except for malignancy (other than in situ) treated with curative intent and with no known active disease present for ≥ 2 years before first dose of tarlatamab and felt to be at low risk for recurrence by the treating physician; adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease; adequately treated in situ cancer without evidence of disease; prostatic intraepithelial neoplasia without evidence of prostate cancer; or adequately treated urothelial papillary noninvasive carcinoma.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 10. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the clinical development program
Patients with renal impairment	Not included in the clinical development program
Patients with cardiovascular impairment	Not included in the clinical development program
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	The race and ethnicity of subjects included in the clinical trial program are included in Table 7 and Table 8, respectively.
Subpopulations carrying relevant genetic polymorphisms	The exposure of tarlatamab in subpopulations carrying relevant genetic polymorphisms is not known.

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials), and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country and are converted to estimates of patient time and patient count (when feasible), using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

Estimates of postmarketing exposure by age and sex are not yet available for tarlatamab.

SV.1.2 Exposure

Cumulatively, since the International Birth Date (16 May 2024; the approval date in the US) through 15 November 2024, there has been an estimated 289 patient-years of postmarketing exposure to tarlatamab. As of that date, tarlatamab was commercially available in 2 countries (US and Canada).

Postauthorization Use From Business Partners

There has been no postauthorization use of tarlatamab from business partners.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 11. Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated): • Based on the available data, the adverse event of neutropenia was not classified as a safety concern and was included in Sections 4.2, 4.4, and 4.8 of the SmPC as an adverse drug reaction. The data in the tarlatamab monotherapy studies indicated that the events were mostly nonserious, and most of the events resolved with no treatment utilization. Generally, the neutropenia events did not lead to febrile neutropenia or infections and there was a good response in the few cases for which granulocyte colony stimulating factor (G-CSF) was required. Furthermore, patients did not need treatment discontinuation, withholding, or interruption of tarlatamab. However, given the incidence rate, it is crucial for patients to be aware of the event.	Neutropenia

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 12. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Identified Risks	
Cytokine Release Syndrome (CRS)	Based on the totality of the available data, there is evidence to suggest a causal relationship between tarlatamab and CRS. CRS was classified as an identified risk (adverse drug reaction). This risk is considered important because in tarlatamab clinical trials, CRS events were reported in 58.4% of the subjects in the tarlatamab monotherapy studies for all doses and 56.7% of subjects at the proposed 10 mg dose, using the CRS Amgen MedDRA Query (AMQ) narrow search strategy. Across tarlatamab monotherapy studies, most of the CRS events were mild or moderate. Specific clinical recommendations to mitigate and manage the risk of CRS are included in the labelling (including step-dosing, premedication, close monitoring, appropriate treatment, and recommendation to interrupt or discontinue tarlatamab treatment depending on the severity of the event).
Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)	Based on the data from tarlatamab clinical trials, ICANS was classified as important identified risk (adverse drug reaction). Across all monotherapy studies, most ICANS events were mild to moderate. Two fatal events using the ICANS AMQ broad search strategy have been reported (Preferred Terms of Immune effector cell-associated neurotoxicity syndrome and seizure); however, the event of seizure was considered confounded and was not reported to be associated with ICANS or its symptoms. Amgen's medical review also assessed the event of ICANS as confounded. Most of the events were manageable and reversible and rarely required treatment discontinuation or dose interruption. Specific clinical recommendations to mitigate the risk of ICANS are included in the labelling (including close monitoring, appropriate treatment, and recommendation to interrupt or discontinue tarlatamab treatment depending on the severity of the event).
Important Potential Risks	
None	
Missing Information	
Long-term Safety Data	The long-term safety of tarlatamab has not been studied as the duration of exposure to tarlatamab monotherapy for most patients in the clinical trials was less than 12 months and the median exposure for tarlatamab monotherapy at 10 mg across Studies 20200491, 20210004 and 20160323 was 14.14 weeks. Therefore, there is limited long-term safety data available for tarlatamab and further information is required postauthorization to determine whether there are additional risks with the use of tarlatamab for a prolonged time.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable, as this is an initial marketing authorization application.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 13. Important Identified Risk: Cytokine Release Syndrome (CRS)

Potential mechanisms	Cytokine release syndrome (CRS) is a frequently observed adverse event occurring with the use of T-cell activators, such as tarlatamab, and results from the release of cytokines from T cells targeted by the molecule as well as immune effector cells recruited to the area.
Evidence source(s) and strength of evidence	This risk was identified based on the data from tarlatamab clinical studies.
Characterization of the risk	
Frequency	In the tarlatamab monotherapy Studies 20210004 (data cutoff date 29 January 2025), 20200491 (data cutoff date 18 October 2024), and monotherapy cohort of Study 20160323 (data snapshot date 18 October 2024), N = 730, CRS events using the Cytokine Release Syndrome AMQ narrow search strategy were observed in 426 subjects (58.4%) (all doses). At the proposed 10 mg tarlatamab dose, N = 473, CRS events based on the narrow search strategy were observed in 268 subjects (56.7%).
Severity	Administration of tarlatamab has been associated with CRS, including life-threatening or fatal events. Across the tarlatamab monotherapy studies (all doses), most CRS events were low grade (mild [grade 1] or moderate [grade 2]).
Reversibility	In general, CRS is clinically reversible with or without medical intervention. The SmPC includes guidelines for CRS management including symptomatic treatment (antipyretic treatment, dexamethasone or equivalent), hospitalization with monitoring, oxygen supplementation, IV fluids, tocilizumab, or equivalent, intensive monitoring, and vasopressor and oxygen support, depending on the severity of the event. In some cases, tarlatamab treatment interruption or discontinuation may be required for reversibility.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	CRS may lead to hospitalization or prolongation of hospitalization and in some cases may require permanent discontinuation of tarlatamab treatment.
Risk factors and risk groups	In the tarlatamab monotherapy studies, the greatest risk of developing CRS was predominantly following the first two doses of tarlatamab treatment, with a greater number of events following the first dose.

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of the table.

Table 13. Important Identified Risk: Cytokine Release Syndrome (CRS)

Preventability	The SmPC includes the following clinical recommendations for the preventability of CRS in the dosage and administration and special warnings and precautions for use sections. • Step-dosing with the recommended dosage and schedule of IMDYLLTRA (initial dose of 1 mg on day 1 followed by 10 mg on days 8, 15, and every 2 weeks thereafter. • Premedication with IV dexamethasone 8 mg (or equivalent) within 1 hour prior to the first 2 doses of tarlatamab on day 1 and day 8 • Administration of IV sodium chloride 9 mg/mL (0.9%) solution for injection immediately after completion of tarlatamab infusion on day 1 and day 8, • Close monitoring for signs or symptoms of CRS following tarlatamab infusion
Impact on the risk-benefit balance of the product	Cytokine release syndrome has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive. The impact of CRS events can be minimized through information provided in the product labelling and the use of a Patient Card.
Public health impact	This patient population is carefully monitored and due to the relatively small number of patients exposed to the drug, the number of patients per year that would be expected to experience the events would not represent a substantial public health issue.

Page 2 of 2

AMQ = Amgen MedDRA Query; CRS = cytokine release syndrome; ICU = intensive care unit; IL = interleukin; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; SmPC = Summary of Product Characteristics.

Table 14. Important Identified Risk: Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Potential mechanisms	Potential factors involved include systemic cytokine release, alterations in adhesion molecule expression on endothelial cells, presence of tumor cells in the brain and effects of disease or prior therapy on the integrity/function of the blood brain barrier.
Evidence source(s) and strength of evidence	This risk was identified based on the data from tarlatamab clinical studies.
Characterization of the risk	
Frequency	In the tarlatamab monotherapy Studies 20210004 (data cutoff date 29 January 2025), 20200491 (data cutoff date 18 October 2024), and monotherapy cohort of Study 20160323 (data cutoff date 18 October 2024), N = 730, ICANS events using the ICANS AMQ broad search strategy, were observed in 113 subjects (15.5%). At the proposed 10 mg tarlatamab dose, N = 473, ICANS events based on the broad search strategy were observed in 53 subjects (11.2%).
Severity	Administration of tarlatamab has been associated with ICANS, including life-threatening or fatal events. Across the tarlatamab monotherapy studies (all doses), most ICANS events were low grade (mild [grade 1] to moderate [grade 2]). Two fatal events using the ICANS AMQ broad search strategy have been reported (Preferred Terms of Immune effector cell-associated neurotoxicity syndrome and Seizure); however, the event of seizure was considered confounded and was not reported to be associated with ICANS or its symptoms. Amgen's medical review also assessed the event of ICANS as confounded.
Reversibility	Most ICANS events were manageable and rarely required treatment discontinuation or dose interruption and in general, neurological adverse events associated with ICANS observed with tarlatamab treatment are clinically reversible. The SmPC includes guidelines for the management of ICANS, including supportive care, steroid treatment (dexamethasone, methylprednisolone, or equivalent), intensive monitoring (ICU care), mechanical ventilation, and convulsive status epilepticus treatment, depending on the severity of the event. In some cases, tarlatamab treatment interruption or discontinuation may be required for reversibility.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	Neurological adverse events associated with ICANS may lead to hospitalization or prolongation of hospitalization and in some cases may require permanent discontinuation of treatment. In event of any neurological symptoms, the SmPC advises patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until they resolve.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 14. Important Identified Risk: Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Risk groups or risk factors	Patients with pre-existing neurologic and medical comorbidities, high disease burden, increased intensity of lymphodepleting therapy and cytopenias, and severe CRS with high levels of inflammatory cytokines may be at higher risk of developing neurologic events.
Preventability	The SmPC includes clinical recommendations for the preventability of ICANS in the dosage and administration and special warnings and precautions for use sections. Mitigation strategies for ICANS includes monitoring for signs and symptoms of ICANS during IMDYLLTRA treatment.
Impact on the risk-benefit balance of the product	ICANS has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive. The impact of neurological adverse events associated with ICANS can be minimized through information in the product labelling and the use of a Patient Card.
Public health impact	This patient population is carefully monitored and due to the relatively small number of patients exposed to the drug, the number of patients per year that would be expected to experience the events would not represent a substantial public health issue.

Page 2 of 2

AMQ = Amgen MedDRA Query; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; ICU = intensive care unit; MedDRA = medical dictionary for regulatory activities; SmPC = summary of product characteristics.

SVII.3.2 Presentation of the Missing Information

Table 15. Missing Information: Long-term Safety Data

Evidence source(s) and strength of evidence	The long-term safety of tarlatamab has not been studied. Most subjects in the clinical studies were exposed to tarlatamab monotherapy for less than 1 year.
Population in need of further characterization	The long-term safety profile of subjects receiving tarlatamab has not been characterized.

Part II: Module SVIII - Summary of the Safety Concerns

Table 16. Summary of Safety Concerns

Important identified risks	• Cytokine Release Syndrome (CRS) • Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)
Important potential risks	• None
Missing information	• Long-term safety data

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

There are no further routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

III.2 Additional Pharmacovigilance Activities

Table 17. Summary of Additional Pharmacovigilance Activities

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Integrated Safety Analysis[a] Category 3	To evaluate the long-term safety of tarlatamab for 3 years	Integrated safety analysis	Subjects with small cell lung cancer	Interim analysis report: Q3 2026 Annual interim summaries will be provided with corresponding PSUR/ PBRER. Final analysis: Q3 2030

PBRER = periodic benefit-risk evaluation report; PSUR = periodic safety update report; Q3 = third quarter
[a] List of clinical studies from which available safety data will be drawn for the integrated safety analysis is included in Annex 3.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned tarlatamab category 1 or 2 studies.

Ongoing and planned category 3 studies are presented below in Table 18.

Table 18. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Integrated Safety Analysis[a]	To evaluate the long-term safety of tarlatamab for 3 years, including incidence of related adverse events	Long-term safety data	Interim analysis report Final analysis	Q3 2026 Annual interim summaries will be provided with corresponding PSUR/ PBRER. Q3 2030

PBRER = periodic benefit-risk evaluation report; PSUR = periodic safety update report; Q3 = third quarter
[a] List of clinical studies from which available safety data will be drawn for the integrated safety analysis is included in Annex 3.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 19. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Cytokine Release Syndrome (CRS)	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • Package leaflet (PL) Section 2, Section 3, and Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • The following recommendations are included in Section 4.2 of the SmPC: – IMDYLLTRA treatment should be initiated under the direction of and supervised by physicians experienced in the use of cancer therapy. – Patients should be premedicated with IV dexamethasone 8 mg (or equivalent) within 1 hour prior to the first 2 doses (day 1 and day 8) and 1 liter of IV sodium chloride 9 mg/mL (0.9%) solution for injection should be administered immediately after completion of IMDYLLTRA infusion (day 1 and day 8). – Step-dosing with the recommended dosing schedule of IMDYLLTRA (initial dose of 1 mg on day 1, followed by 10 mg on days 8 and 15, and every 2 weeks thereafter). – Patients should be monitored from the start of the infusion for 6 to 8 hours on day 1 and day 8. Additional monitoring and monitoring on subsequent infusions is at the discretion of the physician. On day 1 and day 8, patients should be instructed to remain within proximity of an appropriate healthcare facility for 24 hours starting from each IMDYLLTRA infusion, accompanied by a caregiver. – Patients and caregivers should be informed on the signs and symptoms of CRS prior to discharge. – Guidelines for grading, dosage modifications, and management of CRS. • The following recommendations are included in Section 4.4: – IMDYLLTRA should be administered in a healthcare facility equipped to monitor and manage CRS. It should be ensured that patients are euvolemic prior to initiating the infusions. – Patients should be closely monitored for signs and symptoms of CRS during the initiation of IMDYLLTRA treatment and should be managed according to the recommendations in the SmPC Section 4.2. – Patients and caregivers should be advised of the potential for CRS onset after discharge and instructed to seek immediate medical attention if any signs or symptoms occur.

Table 19. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Cytokine Release Syndrome (CRS) (continued)	– To mitigate the risk of CRS, it is important to initiate IMDYLLTRA at the recommended starting dose. Other risk minimization measures beyond the PI: • Legal status: Restricted medical prescription
Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)	Routine risk communication: • SmPC Sections 4.2, 4.4, 4.7, and 4.8 • PL Section 2, Section 3, and Section 4 Routine risk minimization activities recommending specific clinical measures to address the risks: • The following recommendations are included in Section 4.2: – Patients should be monitored from the start of the infusion for 6 to 8 hours on day 1 and day 8. Additional monitoring and monitoring on subsequent infusions is at the discretion of the physician. On day 1 and day 8, patients should be instructed to remain within proximity of an appropriate healthcare facility for 24 hours starting from each IMDYLLTRA infusion, accompanied by a caregiver. – Patients and caregivers should be informed on the signs and symptoms of ICANS prior to discharge. – Guidelines for grading, dosage modifications, and management of ICANS. • The following recommendation is included in Section 4.4: – Patients should be closely monitored for signs and symptoms of ICANS during IMDYLLTRA treatment. – Patients and caregivers should be advised of the potential for ICANS onset after discharge and instructed to seek immediate medical attention if any signs or symptoms occur. • The following recommendation is included in Section 4.7: – In the event of any neurological symptoms, patients should be advised to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until they resolve. Other routine risk minimization measures beyond the PI: • Legal status: Restricted medical prescription
Important Potential Risks	
None	Not applicable

Table 19. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Missing Information	
Long-term safety data	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risks: • None Other routine risk minimization measures beyond the PI: • Legal status: Restricted medical prescription

Page 3 of 3

V.2 Additional Risk Minimization Measures

Table 20. Additional Risk Minimization Measure: Patient Card

Objectives	To increase patients' and caregivers' awareness of the key signs and symptoms of CRS and ICANS and when to seek urgent attention and to provide a reminder of the importance of appropriate monitoring following IMDYLLTRA infusion. The Patient Card contains information for patients and caregivers on the following key risks of IMDYLLTRA: • CRS • ICANS
Rationale for the additional risk minimization activity	This additional risk minimization activity is proposed to ensure patients and caregivers have a good understanding of the risks of CRS and ICANS associated with IMDYLLTRA treatment, of the importance of appropriate monitoring after treatment, and seeking immediate medical attention if they experience any of the key signs and symptoms.
Target audience and planned distribution path	Patients and/or caregivers will receive the Patient Card from their healthcare professional (HCP) who prescribes IMDYLLTRA. Copies of the Patient Card will be provided to the prescribers.
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness of the Patient Card will be assessed over time through routine pharmacovigilance, including ongoing monitoring and evaluation of postmarketing safety data, with findings reported in successive PBRERs/PSURs. The proposed risk minimization measure will describe the proportion of CRS and ICANS cases over time in successive annual reports. This measure will be considered successful if no emerging patterns attributable to delayed recognition are identified, including trends suggesting increased severity or higher rates of fatal or life-threatening outcomes beyond expected variability, consistent with effective risk communication and appropriate ongoing management of CRS and ICANS, and if the safety assessment based on the totality of postmarketing evidence indicates no change in the benefit-risk profile attributable to the patient card use.
Evaluation of the effectiveness of risk minimization activities	Not yet assessed.

CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; PBRER =periodic benefit-risk evaluation report; PSUR = periodic safety update report

V.3 Summary of Risk Minimization Measures

Table 21. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Cytokine Release Syndrome (CRS)	Routine risk minimization measures: • SmPC Section 4.2 where the following recommendations are provided: – IMDYLLTRA treatment should be initiated under the direction of and supervised by physicians experienced in the use of cancer therapy. – Patients should be premedicated with IV dexamethasone 8 mg (or equivalent) within 1 hour prior to the first 2 doses (day 1 and day 8) and 1 liter of IV sodium chloride 9 mg/mL (0.9%) solution for injection should be administered immediately after completion of IMDYLLTRA infusion (day 1 and day 8). – Step-dosing with the recommended dosing schedule of IMDYLLTRA (initial dose of 1 mg on day 1, followed by 10 mg on days 8 and 15, and every 2 weeks thereafter). – Patients should be monitored from the start of the infusion for 6 to 8 hours on day 1 and day 8. Additional monitoring and monitoring on subsequent infusions is at the discretion of the physician. On day 1 and day 8, patients should be instructed to remain within proximity of an appropriate healthcare facility for 24 hours starting from each IMDYLLTRA infusion, accompanied by a caregiver. – Patients and caregivers should be informed on the signs and symptoms of CRS prior to discharge. – Guidelines for grading, dosage modifications, and management of CRS. • SmPC Section 4.4 where the following recommendations are provided: – IMDYLLTRA should be administered in a healthcare facility equipped to monitor and manage CRS. It should be ensured that patients are euvolemic prior to initiating the infusions. – Patients should be closely monitored for signs and symptoms of CRS during the initiation of IMDYLLTRA treatment and should be managed according to the recommendations in the SmPC Section 4.2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Table 21. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Cytokine Release Syndrome (CRS) (continued)	Routine risk minimization measures (continued): • SmPC Section 4.4 where the following recommendations are provided (continued): • Patients and caregivers should be advised of the potential for CRS onset after discharge and instructed to seek immediate medical attention if any signs or symptoms occur. • To mitigate the risk of CRS, it is important to initiate IMDYLLTRA at the recommended starting dose. • SmPC Section 4.8 • PL Section 2 • PL Section 3 • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • Patient Card	
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Routine risk minimization measures: • SmPC Sections 4.2 where the following recommendations are provided: – Patients should be monitored from the start of the infusion for 6 to 8 hours on day 1 and day 8. Additional monitoring and monitoring on subsequent infusions is at the discretion of the physician. On day 1 and day 8, patients should be instructed to remain within proximity of an appropriate healthcare facility for 24 hours starting from each IMDYLLTRA infusion, accompanied by a caregiver. – Patients and caregivers should be informed on the signs and symptoms of ICANS prior to discharge. – Guidelines for grading, dosage modifications, and management of ICANS. • SmPC Section 4.4 where the following recommendation is provided: – Patients should be closely monitored for signs and symptoms of ICANS during IMDYLLTRA treatment. – Patients and caregivers should be advised of the potential for ICANS onset after discharge and instructed to seek immediate medical attention if any signs or symptoms occur.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Table 21. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (continued)	• SmPC Section 4.7 where the following recommendation is provided: • In the event of any neurological symptoms, patients should be advised to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until they resolve. • SmPC Section 4.8 • PL Section 2 • PL Section 3 • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • Patient Card	
Important Potential Risks		
None		
Missing Information		
Long-term safety data	Routine risk minimization measures: • Restricted medical prescription Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Integrated Safety Analysis (Final report due date: Q3 2030)

Page 3 of 3

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for tarlatamab is presented below.

Summary of Risk Management Plan for IMDYLLTRA® (tarlatamab)

This is a summary of the risk management plan (RMP) for tarlatamab. The RMP details important risks of IMDYLLTRA, how these risks can be minimized, and how more information will be obtained about IMDYLLTRA's risks and uncertainties (missing information).

IMDYLLTRA's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how IMDYLLTRA should be used.

This summary of the RMP for IMDYLLTRA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of IMDYLLTRA's RMP.

I. The Medicine and What it is Used for

IMDYLLTRA is authorized 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 (see SmPC for the full indication). It contains tarlatamab as the active substance and it is given intravenously.

Further information about the evaluation of IMDYLLTRA's benefits can be found in IMDYLLTRA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: <link to the EPAR summary landing page>>.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of IMDYLLTRA, together with measures to minimize such risks and the proposed studies for learning more about IMDYLLTRA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of IMDYLLTRA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of IMDYLLTRA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Cytokine Release Syndrome (CRS) • Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)
Important potential risks	• None
Missing information	• Long-term Safety Data

II.B. Summary of Important Risks

Important identified risk: Cytokine Release Syndrome (CRS)	
Evidence for linking the risk to the medicine	This risk was identified based on the data from tarlatamab clinical studies.
Risk factors and risk groups	In the tarlatamab monotherapy studies, the greatest risk of developing cytokine release syndrome was predominantly in cycle 1 (day 1 and day 8) of tarlatamab treatment.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 where the following recommendations are provided: – IMDYLLTRA treatment should be initiated under the direction of and supervised by physicians experienced in the use of cancer therapy. – Patients should be premedicated with IV dexamethasone 8 mg (or equivalent) within 1 hour prior to the first 2 doses (day 1 and day 8) and 1 liter of IV sodium chloride 9 mg/mL (0.9%) solution for injection should be administered immediately after completion of IMDYLLTRA infusion (day 1 and day 8). – Step-dosing with the recommended dosing schedule of IMDYLLTRA (initial dose of 1 mg on day 1, followed by 10 mg on days 8 and 15, and every 2 weeks thereafter). – Patients should be monitored from the start of the infusion for 6 to 8 hours on day 1 and day 8. Additional monitoring and monitoring on subsequent infusions is at the discretion of the physician. On day 1 and day 8, patients should be instructed to remain within proximity of an appropriate healthcare facility for 24 hours starting from each IMDYLLTRA infusion, accompanied by a caregiver. – Patients and caregivers should be informed on the signs and symptoms of CRS prior to discharge. – Guidelines for grading, dosage modifications, and management of CRS.

Important identified risk: Cytokine Release Syndrome (CRS) (continued)	
Risk minimization measures (continued)	Routine risk minimization measures (continued) • SmPC Section 4.4 where the following recommendations are provided: – IMDYLLTRA should be administered in a healthcare facility equipped to monitor and manage CRS. It should be ensured that patients are euvolemic prior to initiating the infusions – Patients should be closely monitored for signs and symptoms of CRS during the initiation of IMDYLLTRA treatment and should be managed according to the recommendations in the SmPC Section 4.2. – Patients and caregivers should be advised of the potential for CRS onset after discharge and instructed to seek immediate medical attention if any signs or symptoms occur. – To mitigate the risk of CRS, it is important to initiate IMDYLLTRA at the recommended starting dose. • SmPC Section 4.8 • PL Section 2 • PL Section 3 • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • Patient Card

Important identified risk: Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)	
Evidence for linking the risk to the medicine	This risk was identified based on the data from tarlatamab clinical studies.
Risk factors and risk groups	Patients with pre-existing neurologic and medical comorbidities, high disease burden, increased intensity of lymphodepleting therapy and cytopenias, and severe cytokine release syndrome with high levels of inflammatory cytokines may be at higher risk of developing neurologic events.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 where the following recommendations are provided: – Patients should be monitored from the start of the infusion and for 6 to 8 hours on day 1 and day 8. Additional monitoring and monitoring on subsequent infusions is at the discretion of the healthcare provider. On day 1 and day 8, patients should be instructed to remain within proximity of an appropriate healthcare facility for 24 hours starting from each IMDYLLTRA infusion, accompanied by a caregiver. – Patients and caregivers should be informed on the signs and symptoms of ICANS prior to discharge. – Guidelines for grading, dosage modifications, and management of ICANS. • SmPC Section 4.4 where the following recommendation is provided: – Patients should be closely monitored for signs and symptoms of ICANS during IMDYLLTRA treatment. • SmPC Section 4.7 where the following recommendation is provided: – In the event of any neurological symptoms, patients should be advised to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until they resolve. • SmPC Section 4.8 • PL Section 2 • PL Section 3 • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • Patient Card

Missing information: Long-term Safety Data	
Risk minimization measures	Routine risk minimization measures: • Restricted medical prescription Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Integrated Safety Analysis

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of IMDYLLTRA.

II.C.2. Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Integrated Safety Analysis[a] Category 3	To evaluate the long-term safety of tarlatamab for 3 years, Safety concerns addressed: • Long-term safety data

[a] List of clinical studies from which available safety data will be drawn for the integrated safety analysis is included in Annex 3.

PART VII: ANNEXES

Table of Contents

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Prior to the launch of IMDYLLTRA in each Member State, the Marketing Authorization Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational program is aimed at instructing patients/carers about the important identified risks of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) associated with IMDYLLTRA.

The MAH shall ensure that in each Member State where IMDYLLTRA is marketed, all patients/carers who are expected to use IMDYLLTRA have access to/are provided with a Patient Card:

The Patient Card will include the following key messages:

- A description of the key signs and symptoms of CRS and ICANS
- A description of when to seek urgent medical care from the healthcare provider, or seek emergency help, should signs and symptoms of CRS or ICANS occur
- A reminder that patients should stay within proximity of a healthcare facility for 24 hours from the start of each IMDYLLTRA infusion, on day 1 and day 8, accompanied by a caregiver.
- The prescribing physician’s contact details