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EMA/144164/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

IMDYLLTRA

International non-proprietary name: tarlatamab

Procedure No. EMEA/H/C/006451/0000

Note

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

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Table of contents

1. Administrative/regulatory information and recommendations on the procedure 8
1.1. Information on the product 8
1.2. Scientific Advice 8
1.3. Eligibility to the centralised procedure 9
1.4. Legal basis and dossier content 9
1.5. Information on paediatrics 9
1.6. Information on orphan market exclusivity 9
1.6.1. Similarity with authorised orphan medicinal products 10
1.7. Applicant's request(s) for consideration 10
1.7.1. New active substance status 10
1.8. Patient experience data 10
1.9. Steps taken for the assessment of the product 10
1.10. CHMP outcome 11
1.10.1. Considerations related to paediatrics 11
1.10.2. Considerations related to orphan market exclusivity 11
1.10.3. CHMP Opinion 12
1.10.4. Conditions or restrictions regarding supply and use 12
1.10.5. Other conditions and requirements of the marketing authorisation 12
1.10.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product 12

2. Introduction 13
2.1. Therapeutic context 13
2.2. Aspects of development 15
2.2.1. Scientific advice/Protocol assistance 15
2.3. Description of the product 17
2.4. Inspection issues 18
2.4.1. Good manufacturing practice (GMP) inspection(s) 18
2.4.2. Good laboratory practice (GLP) inspection(s) 18
2.4.3. Good clinical practice (GCP) inspection(s) 18

3. Quality aspects 18
3.1. Introduction 18
3.2. Active substance 18
3.2.1. General information 18
3.2.2. Manufacture, characterisation, and process controls 19
3.2.2. Specification 20
3.3. Finished medicinal product 21
3.3.1. Description of the product and pharmaceutical development 21
3.3.2. Manufacture of the product and process controls 25
3.3.3. Product specification 26
3.3.4. Stability of the product 27
3.3.5. Post approval change management protocol(s) 29
3.3.6. Adventitious agents 29

3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects 30
3.5. Recommendation(s) for future quality development 31

4. Non-clinical aspects 31
4.1. Introduction 31
4.2. Pharmacology 32
4.2.1. Pharmacodynamics 32
4.2.2. Pharmacokinetics 34
4.3. Toxicology 35
4.3.1. Overview of the non-clinical toxicology program 35
4.3.2. Single-dose toxicity 35
4.3.3. Repeat-dose toxicity 35
4.3.4. Genotoxicity 36
4.3.5. Carcinogenicity 36
4.3.6. Developmental and reproductive toxicity 36
4.3.7. Toxicokinetics and exposure margins 36
4.3.8. Local tolerance 36
4.3.9. Other toxicity studies 36
4.3.10. Ecotoxicity/environmental risk assessment 37
4.4. Overall discussion and conclusions on non-clinical aspects 37
4.4.1. Discussion 37
4.4.2. Conclusions 39

5. Clinical aspects 39
5.1. Introduction 39
5.1.1. Good Clinical Practice (GCP) aspects 39
5.1.2. Tabular overview of clinical trials 39
5.2. Clinical pharmacology 41
5.2.1. Methods 41
5.2.2. Pharmacokinetics 41
5.2.3. Pharmacodynamics 50
5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD) 52
5.2.5. Dose selection and therapeutic window 53
5.2.6. Overall discussion and conclusions on clinical pharmacology 54
5.3. Clinical efficacy 59
5.3.1. Dose response studies 59
5.3.2. Main study 59
5.3.3. Clinical studies in special populations 88
5.3.4. In vitro biomarker test for patient selection for efficacy 89
5.3.5. Supportive studies 89
5.3.6. Patient experience data (PED) 92
5.3.7. Overall discussion and conclusions on clinical efficacy 93
5.4. Clinical safety 96
5.4.1. Safety data collection 97
5.4.2. Patient exposure 98
5.4.3. Adverse events 101

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events 108
5.4.5. Discontinuation due to adverse events 124
5.4.6. Safety in special populations 125
5.4.7. Immunological events 125
5.4.8. Safety related to drug-drug interactions and other interactions 126
5.4.9. Vital signs and laboratory findings 126
5.4.10. Post-marketing experience 127
5.4.11. Overall discussion and conclusions on clinical safety 127

6. Risk management plan 131
6.1. Safety specification 131
6.1.1. Proposed safety specification 131
6.1.2. Discussion on proposed safety specification 131
6.2. Pharmacovigilance plan 132
6.2.1. Proposed pharmacovigilance plan. 132
6.2.2. Discussion on the pharmacovigilance plan 133
6.3. Risk minimisation measures 134
6.3.1. Proposed risk minimisation measures 134
6.3.2. Discussion on the risk minimisation measures 136
6.4. Overall conclusion on the Risk Management Plan 137

7. Pharmacovigilance 137
7.1. Pharmacovigilance system 137
7.2. Periodic safety update reports (PSURs) submission requirements 137

8. Product information 137
8.1. Summary of product characteristics (SmPC) 137
8.1.1. SmPC section 4.1 justification 137
8.2. Labelling 137
8.2.1. User consultation 137
8.3. Additional monitoring 137

9. Benefit-risk assessment 138
9.1. Therapeutic context 138
9.1.1. Disease or condition 138
9.1.2. Available therapies and unmet medical need 138
9.2. Main clinical studies 139
9.3. Favourable effects 139
9.3.1. Uncertainties and limitations about favourable effects 139
9.4. Unfavourable effects 140
9.4.1. Uncertainties and limitations about unfavourable effects 141
9.5. Effects table 141
9.6. Benefit-risk assessment and discussion 142
9.6.1. Importance of favourable and unfavourable effects 142
9.6.2. Balance of benefits and risks 143
9.7. Benefit-risk conclusions 143
9.7.1. CHMP conclusions 143

List of abbreviations

ADA	anti-drug antibodies
AE	adverse events
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMQ	Amgen MedDRA query
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
BICR	blinded independent central review
BiTE	bispecific T-cell engager
BLQ	below limit of quantification
BTSR	best tumour-size response
BW	bodyweight
CAV	cyclophosphamide, doxorubicin, and vincristine
Cavg	average concentration over a dosing interval
CD3	cluster of differentiation 3
CEX	Cation exchange chromatography
CHMP	Committee for Medicinal Products for Human Use
CHO cells	Chinese hamster ovary cells
CKD	chronic kidney disease
CL	clearance
Cmax	maximum concentration
COPD	chronic obstructive pulmonary disease
CQA	Critical quality attribute
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	concentration at trough
CYP450	cytochrome P450
DAP	data analysis plan
DCR	disease control rate
DDI	drug drug interaction
DLL3	delta-like ligand 3
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEG	electroencephalogram
EMA	European Medicines Agency
EOI	events of interest
ER	exposure-response
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive-stage small cell lung cancer
EU	European Union
Fc	Fragment crystallizable
FcRn	The neonatal Fc receptor
FDA	Food and Drug Administration
FIH	first-in-human
FOCEi	first-order conditional estimation with interaction
GLMM	generalized linear mixed model
GMP	Good manufacturing practice
GoF	goodness-of-fit
HCP	host cell protein
HLE	half-life extended
HMW	High molecular weight

HR	hazard ratio
ICANS	immune effector cell-associated neurotoxicity syndrome
IIV	interindividual variability
IPC	In process control
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IV	intravenous(ly)
IVSS	intravenous solution stabilizer
LMW	Low molecular weight
LS	least squares
LS-SCLC	limited-stage small cell lung cancer
MAA	marketing authorisation application
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified RECIST
MMA	Mixed mode anion exchange chromatography
MMRM	mixed model for repeated measurement
MoA	Mode of action
MTD	maximum tolerated dose
Nab	neutralizing antibody
NCA	non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National cancer institute
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NE	not estimable
NEPC	neuroendocrine prostate cancer
NPACT	non-protocol anti-cancer therapy
OFV	objective function value
ORR	objective response rate
OS	overall survival
PA	primary analysis
PBRER	Periodic Benefit-Risk Evaluation Report
pcVPC	Prediction-corrected visual predictive check
PD	pharmacodynamics
PD-1	programmed cell death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
Ph.Eur	European pharmacopoeia
PIP	Paediatric investigation plan
PK	pharmacokinetic(s)
PopPK	Population pharmacokinetics
PR	partial response
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	patient-reported outcomes
PSC	potential safety concern
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ-C30	Quality of Life Questionnaire 30
QLQ-LC13	Quality of Life Questionnaire Lung Cancer 13
QTcB	corrected QT interval by Bazett
QTcF	Fridericia's heart-rate corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumours
REML	restricted maximum likelihood-based
RMP	risk management plan
RP2D	recommended phase 2 dose
RSE	residual standard error
SCE	summary of clinical efficacy
SCLC	small cell lung cancer
SCP	summary of clinical pharmacology
SCS	summary of clinical safety
SD	stable disease

SmPC	summary of product characteristics
SMQ	standardized MedDRA query
SOC	standard of care; or system organ class
t1/2	terminal elimination half-life
TA	Tumour assessment
TE-ADA	treatment-emergent anti-drug antibodies
TEAE	treatment-emergent adverse events
Tmax	time to first occurrence of Cmax
TRAE	treatment-related adverse events
TSBS	Sum of target tumour lesion diameters at baseline
TSE	Transmissible spongiform encephalopathy
TTR	time to response
UF/DF	Ultrafiltration/diafiltration
V1	central volume of distribution
V2	peripheral volume of distribution
VF	Viral filtration
VI	Viral inactivation
VPC	visual predictive check
US	United States

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	IMDYLLTRA
Active substance	Tarlatamab
INN or common name	Tarlatamab
Applicant	Amgen Europe B.V. Minervum 7061 4817 ZK Breda NETHERLANDS
EMA product number	EMEA/H/C/006451
ATC code and pharmacotherapeutic group	L01FX33
Pharmaceutical form(s) and strength (s)	Powder for concentrate and solution for solution for infusion 1 mg and 10 mg
Packaging	powder: vial (glass); solution: vial (glass)
Package size(s)	1 powder vial + 2 solution vials
Route of administration	Intravenous use
Device or diagnostic	Not applicable
Orphan designation	Yes (EU/3/23/2876; EMA/OD/0000146101)
Orphan indication status confirmed	Pending
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	IMDYLLTRA is indicated as monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy.
New active substance status	Qualified as new active substance

1.2. Scientific Advice

Table 1. Scientific advice and protocol assistance

Date	***Topic (quality/ non-clinical/ clinical)***	***Reference number / Coordinator(s)***	***Brief summary of the advice***
23 June 2022	Non-clinical	EMA/SA/0000086836	The Scientific Advice pertained to the following non-clinical aspects:

		Dina Apele-Freimane, Livia Puljak	• Plan to assess the embryofoetal toxicology of tarlatamab to support a Marketing Authorisation Application
26 January 2023	Clinical	EMA/SA/0000115184 Livia Puljak, Olli Tenhunen	The Scientific Advice pertained to the following clinical aspects: • The proposed clinical development plan for tarlatamab monotherapy and the adequacy of the study design for the phase 3 study 20210004 in second-line SCLC (clinical endpoints, PRO endpoints, interim analyses, and SOC arm), to support a marketing authorisation for the treatment of patients with SCLC who have experienced disease progression on or after platinum-based chemotherapy

1.3. Eligibility to the centralised procedure

The applicant Amgen Europe B.V. submitted on 27 June 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for IMDYLLTRA (Tarlatamab), through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2023.

The applicant applied for the following indication:

IMDYLLTRA is indicated as monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies).

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision(s) P/0090/2022 on the granting of a product-specific waiver.

1.6. Information on orphan market exclusivity

IMDYLLTRA was designated as an orphan medicinal product (EU/3/23/2876) on 12 January 2024 in the following condition: treatment of small cell lung cancer.

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure Hetronifly.

1.7. Applicant's request(s) for consideration

1.7.1. New active substance status

The applicant requested the active substance Tarlatamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.7.1.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that tarlatamab is to be qualified as a new active substance in itself, as it is not a constituent of a medicinal product previously authorised within the European Union.

1.8. Patient experience data

Table 2. Patient experience data relevant to the application

Patient experience data submitted with this application				***Section where discussed (if applicable)***
x	Patient experience data submitted by the applicant:			
	☐	Clinical outcome assessments (COAs) such as		
		x	Patient-reported outcomes (PRO)	5.3.7; 5.3.9
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		

1.9. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

rapporteur:	Eva Skovlund
Co-rapporteur:	Robert Porszasz

The rapporteur and Co-rapporteur appointed by the PRAC were:

PRAC rapporteur:	Sonja Radowan
PRAC Co-rapporteur:	Pernille Harg

The application was received by the EMA on	27 June 2025
The procedure started on	17 July 2025
The CHMP rapporteur's first assessment report was received on	6 October 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	8 October 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	20 October 2025
The Quality working party agreed on the Assessment Overview during their meeting	6 November 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	13 November 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	9 December 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	23 December 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 February 2026
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	26 February 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	3 March 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	11 March 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to IMDYLLTRA on	26 March 2026
The CHMP adopted a report on similarity of Imdylltra with Hetronifly on (see appendix on similarity)	26 March 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see appendix on NAS)	26 March 2026

1.10. CHMP outcome

1.10.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

1.10.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in

section 1.6 of this report.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Imdylltra as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/imdylltra.

1.10.2.1. Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that imdylltra is not similar to Hetronifly within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See the appendix on similarity.

1.10.3. CHMP Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of IMDYLLTRA is favourable in the following indication):

IMDYLLTRA is indicated as monotherapy for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), who require systemic therapy following disease progression on or after first-line treatment with platinum-based chemotherapy.

The CHMP, therefore recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.10.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.10.5. Other conditions and requirements of the marketing authorisation

1.10.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.10.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.10.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.10.6.2. Additional risk minimisation measures

Prior to the launch of IMDYLLTRA in each Member State, the Marketing Authorisation 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 programme 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

2. Introduction

2.1. Therapeutic context

Globally, lung cancer is the most commonly diagnosed cancer and leading cause of cancer death, representing approximately 1 in 8 (12.4%) cancers diagnosed and 1 in 5 (18.7%) cancer deaths (Bray et al., 2024). Small cell lung cancer (SCLC) accounts for ~10-15% of lung cancer cases, with an estimated 248 000 to 372 000 new cases globally in 2022, based on lung cancer incidence estimates (American Cancer Society, 2024; Rudin et al., 2021). SCLC represents approximately 200,000 new cases globally each year. Extensive stage SCLC (ES-SCLC) accounts for about two-thirds of all diagnosed SCLC cases. In Europe there were an estimated 48 000 to 72 000 new SCLC cases in 2020, based on lung cancer incidence estimates (American Cancer Society 2024; Dyba et al., 2021; Rudin et al., 2021; Dingemans et al., 2021).

SCLC is an aggressive, poorly differentiated, high-grade neuroendocrine carcinoma of the lungs. SCLC is associated with a poor prognosis due to its aggressive nature. If left untreated, the disease progresses rapidly, leading to significant morbidity and mortality. ES-SCLC refers to disease that has spread beyond one hemithorax, including distant metastases. While ES-SCLC is rarely curable, the

initial response to chemotherapy is often robust, but relapse is common. Mortality remains high, with a 5-year survival rate of less than 5% for extensive stage disease.

SCLC predominantly affects older adults, with peak incidence between ages 60 and 70. It is strongly associated with tobacco smoking, with over 95% of cases linked to smoking history. Men are slightly more affected than women, though the gender gap is narrowing. Geographic and cultural factors influence prevalence, with higher rates observed in regions with elevated smoking rates.

Common symptoms include cough, dyspnea, chest pain, weight loss, and fatigue. Symptoms vary depending on disease stage and severity, with advanced stages often causing systemic manifestations such as bone pain, neurological deficits, or liver dysfunction. Patients frequently report anxiety and depression related to the poor prognosis and treatment side effects. ES-SCLC significantly impairs health-related quality of life (HRQoL), with patients often experiencing physical limitations, psychological distress, and social challenges due to the disease and its treatment.

Therapies for relapsed ES-SCLC patients in the EU

Current first-line treatment of SCLC generally consists of etoposide in combination with either cisplatin or carboplatin. For ES-SCLC, the etoposide-platinum regimen is frequently combined with a programmed death ligand 1 (PD-L1) immune checkpoint inhibitor, either atezolizumab or durvalumab, as part of first-line treatment. However, the benefits of immunotherapy in first-line treatment of ES-SCLC are relatively modest, i.e., approximately two months gain in OS when compared to chemotherapy alone. Recently, the PD-1 inhibitor serplulimab obtained a marketing authorization (MA) in the EU for the treatment of first-line treatment of ES-SCLC. This was based on data from an RCT where serplulimab, in combination with carboplatin and etoposide, showed an improvement in overall survival (OS) compared to carboplatin and etoposide alone, with a difference of 4.5 months (15.4 months vs. 10.9 months) (Hetronifly EU SmPC).

Treatment options for patients with relapsed SCLC are limited, and prognosis remains poor with currently available therapies. For patients with platinum-sensitive relapse (<90 days after completing first-line therapy), platinum rechallenge or clinical trial participation may be considered. Other recommended regimens in the relapsed or refractory setting include topotecan, CAV (cyclophosphamide/doxorubicin/vincristine), or single agent chemotherapy (e.g., docetaxel, etoposide, gemcitabine, temozolomide) (ESMO Clinical Practice Guideline: Small Cell Lung Cancer). Topotecan is the only chemotherapeutic agent specifically approved in the EU for second-line treatment of relapsed SCLC. It is available in both intravenous and oral formulations. Topotecan has shown modest efficacy, with response rates of approximately 20% in platinum-sensitive patients and lower in platinum-resistant cases. Median OS typically ranges from 6 to 7 months. OS was not improved compared to CAV in a RCT (Hycamtin EU SmPC). Treatment with topotecan is associated with significant toxicity, including myelosuppression (e.g., neutropenia and thrombocytopenia), fatigue, and gastrointestinal side effects such as diarrhea and nausea. Immunotherapy (nivolumab, pembrolizumab) has not shown improved outcomes compared to topotecan in the second-line or later setting.

The ESMO guideline also mentions lurbinectedin as a treatment option for patients with platinum-resistant SCLC in second- and subsequent lines. However, lurbinectedin does not have a MA in the EU. Lurbinectedin received accelerated approval by FDA in August 2020 based on an ORR as assessed by investigator of 35% (95% CI: 26, 45) and median DOR of 5.1 (95% CI: 4.9, 6.4) months (Zepzelca US Prescribing Information, 2025). Of the 105 patients in the study, 60 had platinum-sensitive SCLC while the remaining 45 had platinum-resistant SCLC. There were more responders to lurbinectedin among the patients with platinum-sensitive SCLC, i.e. 45% (95% CI: 32, 58), versus 22% (95% CI: 11, 37) among the platinum-resistant patients. All patients in this study had progressed on or after platinum-based chemotherapy (which included immunotherapy in only 8%). OS for lurbinectedin as

monotherapy in the second-line treatment of ES-SCLC remains to be reported from the Phase 3 trial named Lagoon. Top-line results are anticipated in Q1 2026.

In summary, SCLC is a serious, life-threatening condition with poor prognosis and limited survival. Treatment options are scarce following initial systemic therapies, including platinum-based chemotherapy. Outcomes with currently available therapies remain poor, highlighting an unmet medical need for new, effective therapies in this patient population.

2.2. Aspects of development

Tarlatamab was developed to address the unmet medical need of patients with previously treated SCLC.

This marketing authorisation application (MAA) provides a clinical data package to support the approval of tarlatamab as monotherapy for the treatment of adult patients with ES-SCLC requiring systemic therapy following disease progression on or after first-line platinum-based chemotherapy.

The primary support for the proposed indication is based on efficacy results from subjects with relapsed SCLC following platinum-based first-line chemotherapy, enrolled in the pivotal phase 3 study 20210004 (DeLLphi-304). Further efficacy support is based on the results from the phase 2 study 20200491 (DeLLphi-301), an ongoing study evaluating tarlatamab monotherapy in subjects who had progressed or recurred following one platinum-based regimen (with or without a checkpoint inhibitor) and at least one other line of therapy, and the FIH phase 1 study 20160323 (DeLLphi-300), which assessed multiple doses of tarlatamab in subjects with SCLC who progressed or recurred after at least one platinum-based regimen.

All 3 studies were conducted in North America, Europe, and Asia, with additional study centres in Australia for the phase 1 and phase 3 studies and in South America for the phase 3 study.

The primary support for the analysis of tarlatamab safety for the proposed indication is based on both: (1) data from tarlatamab versus standard of care (SOC) chemotherapy in study 20210004 and (2) pooled data from subjects who received tarlatamab 10 mg Q2W, the selected dose, and from subjects who received all doses of tarlatamab across studies 20210004, 20200491, and 20160323 (N = 730). In addition, assessment of safety and cytokine release syndrome (CRS) in additional studies with different monitoring requirements is used to support the appropriate monitoring period after tarlatamab administration. This includes supportive aggregate safety data (not identifying treatment) from ongoing blinded studies 20230016 and 20200041 (with 1- to 2-hour monitoring), as well as CRS data from phase 2 China study 20230273 (with 6- to 8-hour monitoring) as additional evidence supporting the safety profile of tarlatamab.

Support for the overall characterization of the clinical pharmacology of tarlatamab is based on cross-study population pharmacokinetic (PK) analyses, exposure-response analyses for efficacy and safety, and analyses of the impact of immunogenicity on PK, safety, and efficacy, using combined data from studies 20210004, 20200491, and 20160323.

2.2.1. Scientific advice/Protocol assistance

For an overview of CHMP scientific advice received, please see section 2.2 of this report. Additionally, a summary of topics discussed in the scientific advice is provided below.

Phase 3 study 20210004

Endpoints

Advice was given that while OS as a primary endpoint was supported, the key secondary endpoints should preferably include PFS, ORR, disease control rate, DOR, PFS rate at 1 year from randomization, and OS at 1 year, 2 years, and 3 years from randomization. It was recommended that PRO data should be downgraded, considering that the pivotal phase 3 study has an open-label design. Furthermore, the plan for gathering PRO data was limited to the first 18 weeks from randomisation. The applicant was warned that inclusion of PROs from a non-blinded study in the SmPC would be highly challenging. Additionally, advice was given to include BICR to assess the responses. However, this advice was not adhered to.

Comparator arm

The choice of leaving out CAV (cyclophosphamide-doxorubicin-vincristine) from the composite SOC comparator arm was criticized. To provide the best option for all patients in the study, it was suggested that multiple trials could be conducted in different geographical areas. The applicant has adhered to their original plan regarding SOC options.

Eligibility criteria

The possibility of including patients recurring on or after adjuvant platinum-etoposide was questioned since these patients were not included in the tentative indication. The study was executed allowing these patients without further explanation.

Stratification

Randomization was planned to be stratified by prior anti PD (L)1 exposure (yes *versus* no), chemotherapy-free interval (≥ 180 days; < 180 to ≥ 90 days; < 90 days), and presence of brain metastases (yes versus no).

The CHMP did not support the presence of brain metastases as a stratification factor as the prognostic relevance of this factor regarding second-line therapy probably was minor. However, the presence of brain metastases was kept as a stratification factor.

While the CHMP considered that region could be a relevant stratification factor, the applicant rather included SOC category (topotecan/amrubicin vs. lurbinectedin) as a stratification factor.

Concerns were expressed by the CHMP regarding whether the trial would enrol a sufficient number of patients across all strata, particularly those with a very long chemotherapy-free interval, where the typical preferred treatment is rechallenge with platinum-based therapy. These concerns have been alleviated by the fact that the study has successfully recruited sufficient numbers of patients within these categories.

Across studies

Predictive biomarker

The Applicant was encouraged to utilize all available data on DLL3 expression to fully characterize its role. Thus, the exploratory endpoint aimed to further characterise the role of DLL3 was supported. However, this exploratory endpoint was later removed. DLL3 tumour expression remains a concern.

Dose

The target recommended dose for the phase 3 study has been determined using data from the FIH study 20160323 and an interim analysis of part 1 of study 20200491. At the time of the SA, the CHMP considered that it was not convincingly demonstrated that those data would be sufficient to determine the adequate dose for a phase 3 study. The basis for the choice of dose for the phase 3 study was later expanded with part 2 and 3 of study20200491.

Embryofoetal Toxicity Study for Tarlatamab Development

In June 2022, scientific advice relevant to non-clinical development was provided. The advice focused on the plan to conduct an embryofoetal toxicity study in mice using the murine surrogate version of tarlatamab, muS757, along with available literature, to appropriately assess the embryofoetal toxicology of tarlatamab in support of its future Marketing Authorization Application, as required by ICH S9. The DLL3 binding domain of tarlatamab binds to human, cynomolgus monkey, and murine DLL3, while the CD3 arm binds to human and cynomolgus monkey CD3 but does not cross-react with murine CD3. Due to its cross-reactivity with murine DLL3, the target-binding scFv of tarlatamab was used to create muS757, which was combined with the murine CD3ε specific scFv genetically fused to the N terminus of a murine scFc region. In the scientific advice, the CHMP responded that the Applicant's stance on conducting an embryofoetal toxicity study in mice using the murine surrogate version of tarlatamab, along with the available literature, to assess the embryofoetal toxicology of tarlatamab was generally supported. However, using a surrogate antibody in embryofoetal toxicology studies in mice as a single species involves certain limitations, and therefore, should be backed by strong justification and thorough analysis of available literature data. In the nonclinical overview, the Applicant has provided a detailed review of relevant literature and a suitable justification for the choice of species.

2.3. Description of the product

Mechanism of action

Tarlatamab is a bispecific DLL3-directed CD3 T-cell engager that binds to DLL3 expressed on the surface of tumour cells and CD3 expressed on the surface of T-cells. The bispecific binding of tarlatamab to T-cells and DLL3-positive tumour cells triggers T-cell activation, production of inflammatory cytokines, and release of cytotoxic proteins, which results in redirected lysis of tumour cells.

Proposed posology:

Dose of IMDYLLTRA	
Day 1	1 mg
Day 8	10 mg
Day 15 and every 2 weeks thereafter	10 mg

Regulatory approval outside the EU

At the time of application, tarlatamab was approved in 10 countries/regions for the treatment of adult patients with ES-SCLC who have experienced disease progression on or after at least one or two prior lines of therapy, including platinum-based chemotherapy. The wording of the approved therapeutic indication varies by country/region. Initial approvals for tarlatamab were primarily based on results demonstrating a positive benefit-risk profile from the pivotal, phase 2, open-label study 20200491. This study included subjects with SCLC who had progressed or recurred following one platinum-based regimen (with or without immune checkpoint inhibitor) and at least one other line of therapy (retreatment with a platinum-based regimen was considered a second line of therapy). Marketing authorizations were granted under accelerated or conditional approval in countries such as the US, Canada, and the UK.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

There are no concerns regarding GMP compliance, and no inspection is required.

2.4.2. Good laboratory practice (GLP) inspection(s)

There are no concerns regarding the GLP compliance of the toxicology studies, and no inspection is required.

2.4.3. Good clinical practice (GCP) inspection(s)

There are no concerns regarding the GCP compliance of the clinical studies included in the dossier, and no inspection is required.

3. Quality aspects

3.1. Introduction

The finished product, Imdylltra is presented as a powder for concentrate and solution for solution for infusion, containing 1 mg or 10 mg of the active substance (tarlatamab). Other ingredients are: powder (glutamic acid, sucrose, polysorbate 80, sodium hydroxide (for pH-adjustment)); intravenous (IV) solution stabiliser (IVSS) (citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide (for pH-adjustment), water for injections).

Imdylltra is supplied as two packaging configurations. Each Imdylltra pack contains 1 vial of powder for concentrate for solution for infusion and 2 vials of 7 mL of solution (stabiliser).

The reconstitution of the 1 mg tarlatamab powder with water for injections results in a final tarlatamab concentration of 0.9 mg/mL; reconstitution of the 10 mg tarlatamab powder with water for injections results in a final tarlatamab concentration of 2.4 mg/mL.

3.2. Active substance

3.2.1. General information

Tarlatamab is a novel single-chain antibody derivative of the bispecific T-cell engager (BiTE) class, expressed in a Chinese hamster ovary (CHO) cell line.

Tarlatamab consists of two single-chain variable fragment (scFv) binding domains, specific for antigen delta-like ligand 3 (DLL3) and for the T-cell receptor associated complex cluster of differentiation 3 (CD3). The immunoglobulin domains of heavy (VH) and light chain variable regions (VL) are shown in Figure 1 with the disulfide bonds indicated (in red). The scFv binding domains are fused to a single-chain fragment crystallizable (Fc) half-life extension (scFc HLE) moiety.

Tarlatamab is aglycosylated through engineering by eliminating the glycosylation site in the CH2 domain of the Fc.

The HLE moiety is capable of binding to the neonatal Fc receptor (FcRn) thereby prolonging the serum half-life of tarlatamab. The bispecific design of tarlatamab allows for redirected lysis of DLL3-expressing target cells by the T cell via the simultaneous engagement of T cells through CD3 binding, and target cells, through DLL3 binding. The ability to bind to both cell types brings the T cells into proximity of the target cells and induces T cell mediated cytotoxicity (TDCC) of the DLL3-expressing cancer cells.

3.2.2. Manufacture, characterisation, and process controls

Manufacturers

The active substance is manufactured at Immunex Rhode Island, US. All the active substance manufacturing and testing sites are GMP compliant.

Description of manufacturing process and process controls

The manufacture of the active substance follows a standard process consisting of culture expansion, harvest and purification of the expressed antibody (tarlatamab).

A clear narrative has been provided for the manufacturing process with sufficient details including process parameters, acceptable ranges and in-process controls. In brief, a working cell bank vial, containing stably transfected CHO cells, is thawed and selectively expanded in shake flasks, further expanded before inoculation to a production bioreactor.

Tarlatamab is purified and prepared from the harvest by chromatography steps, viral inactivation (VI), ultrafiltration/diafiltration (UF/DF), polysorbate 80 addition, and active substance final filtration. The filled active substance containers are stored. Pool hold times are validated and no reprocessing is proposed.

The Applicant sufficiently describes the creation of the production cell line, including its origin, cloning and establishment of the master cell bank (MCB) and working cell bank (WCB). Characterisation of the cell banks includes identity testing, conformation of the tarlatamab coding sequence, viability over time, and appropriate genetic stability studies establishing the limit of *in vitro* cell age (LIVCA). Should a new WCB be created, it will meet the same criteria as the current WCB. This is acceptable.

No raw materials of human or animal origin are used. Raw materials used in cell culture and purification are adequately described. Certificates of analysis (CoA) are provided and specifications for non-compendial materials are provided. All vendor sourced raw materials are tested. The quantitative compositions of the cell culture media are provided.

The in-process controls (IPCs) approach presented is considered acceptable.

Process performance qualification (PPQ) was performed with three successful and consecutive active substance lots. Notably, some IPC limits were tightened after the completion of PPQ. All in all, there is good consistency between process validation batch data demonstrating robustness and good control of the manufacturing process. The process validation is considered acceptable.

Manufacturing process development

The development of the active substance manufacturing process was sufficiently described.

During manufacturing development different processes were used. Process changes and rationale of these changes are adequately detailed. The process changes included several modifications. The manufacturing process changes are sufficiently described and justified. Comparability was assessed for active substance batches manufactured with the different processes. Comparability exercises were presented and results demonstrate that AS manufactured by different processes are considered

comparable.

The manufacturing process design is based on prior knowledge, risk assessments and product specific development studies (including small-scale) as well as manufacturing experience. The process development addresses appropriate parameters, critical quality attributes, and the use of small-scale models where appropriate is adequately justified. Acceptable ranges were established based on viral clearance studies, process characterisation studies, development studies and prior knowledge.

Overall, the process development is thorough and appropriate, and the control strategy is thoroughly presented and appropriately justified.

Characterisation

A thorough biochemical characterisation of tarlatamab primary and higher order structure has been performed, using an appropriate set of analytical methods. The biological function of tarlatamab is characterised. The tarlatamab mechanism of action is well reflected by this assay. The information provided is sufficient and adequate.

Impurities

The process and product related impurities have been adequately characterised for tarlatamab, and routine monitoring is in place to control the levels of impurities.

The formation of product related impurities is well understood and all are present at low levels in the active substance. Reduction of the process related impurities has been demonstrated in challenge studies performed at small-scale during process characterisation and confirmed during process validation. The levels of process reagents in the active substance are low and considered well-controlled. These are classified as generally regarded as safe or as potential safety concern (PSC). For the reagents identified as PSC, toxicology-based acceptable exposure limits were derived following the principles and methods outlined in the ICH Q3C guideline. Maximum theoretical amount of reagent present in active substance was estimated and measured clearance results were presented for the ones above a certain level of estimated safety margin. PSC reagents were concluded to be efficiently cleared through the purification process.

The information provided is sufficient and adequate.

3.2.2. Specification

The active substance specifications cover tests for appearance, identity, potency, purity and impurities, endotoxins, bioburden.

Reduction of the process related impurities is demonstrated in challenge studies performed at small-scale during process characterisation and confirmed during process validation.

The proposed specification and justifications are acceptable.

Analytical procedures

The analytical methods are described. Method validation reports are included.

The methods are adequately validated including specificity, linearity, precision, accuracy and range in accordance with the ICH Q2 Guideline.

Batch analysis

Relevant batch data has been presented. All Commercial Process 2 lots meet the commercial specification. The batch analyses data demonstrate that the active substance can be manufactured

reproducibly to a high level of purity, with very low levels of impurities, consistent levels of product variants and consistent high quality.

Reference standards

Appropriate reference material characterisation has been performed.

Release data from interim, primary and working reference standard has been provided and demonstrates that these are consistent. Stability data for the tarlatamab primary reference standard data remain within acceptance criteria, no out of trend results were observed. A broad set of release tests are performed at qualification of future reference standards, and the acceptance criteria are considered appropriate. An expiry extension schedule including annual testing of tarlatamab has been presented. The information provided is sufficient and adequate.

Container closure

The active substance container closure system is a single-use bag with associated lines (tubing and fittings). The container closure system is supplied as ready-to-use by the supplier, and irradiation is used for sterilization.

The specifications are listed and conformance to relevant Ph. Eur. texts is stated. Extraction studies were conducted. None of the organic compounds or inorganic extracted elements were assessed to be of toxicological concern.

Based on the extractables results, no significant amount of leachables in active substance at the recommended storage condition is expected and therefore no leachable testing was performed which is endorsed. Leachable testing is performed at the finished product level. Container closure integrity testing evaluated minimum and maximum fill volumes. A microbial aerosol challenge test was used to evaluate the integrity of the container closure system.

The container closure system is considered appropriate.

3.2.4 Stability

Stability studies were performed in line with relevant ICH guidance. The stability of active substance lots was also evaluated at an accelerated storage condition and a stressed storage condition. The stability containers are identical to the container closure system used in manufacturing.

Stability data from primary and production batches stored at the intended storage temperature is presented. Long term data from primary batches is presented and supports the proposed shelf life.

Based on the available stability data the claimed shelf life for tarlatamab active substance is acceptable.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product, Imdylltra, is presented as a powder for concentrate and solution for solution for infusion, containing 1 mg or 10 mg of the active substance tarlatamab.

Other ingredients are: powder (glutamic acid, sucrose, polysorbate 80, sodium hydroxide (for pH-adjustment)); intravenous (IV) solution stabiliser (IVSS) (citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide (for pH-adjustment), water for injections). All

excipients in the finished product formulation are specified in the Ph. Eur.

Finished product [1 mg/vial] Tarlatamab

The finished product is supplied in a vial as a sterile, white to slightly yellow lyophilized powder for reconstitution. Reconstitution with water for injections results in a final tarlatamab concentration of 0.9 mg/mL.

Tarlatamab is reconstituted with 1.3 mL of sterile water for injection. The reconstituted product is clear to opalescent and colorless to slightly yellow. Upon reconstitution, the product is intended for dilution in normal saline (0.9% (w/v) sodium chloride) and an intravenous solution stabilizer (IVSS) for intravenous (IV) administration. A delivered volume of 1.1 mL reconstituted finished product will allow delivery of 1 mg. The container closure system consists of an ISO 2R Type I glass vial, elastomeric stopper, and aluminum seal with flip-off cap.

The finished product description pre- and post-reconstitution have been provided.

The IVSS is supplied with tarlatamab for administration via IV infusion. The IVSS is supplied as a sterile solution in ISO 10R Type I glass vials containing 7 mL of deliverable product. The IVSS is a buffered, preservative-free, colorless to slightly yellow, and clear to slightly opalescent solution. The container closure system for the IVSS is 10R Type I glass vial, elastomeric stopper, and aluminum seal with flip-off cap.

The tarlatamab IV infusion is prepared by first aseptically adding the appropriate amount of the IVSS to an infusion bag containing normal saline. Following reconstitution, an appropriate amount of tarlatamab is added aseptically to the infusion bag containing the IVSS and saline.

Finished product [10 mg/vial] Tarlatamab

The finished product is supplied in a vial as a sterile, white to slightly yellow lyophilized powder for reconstitution. Reconstitution with water for injections results in a final tarlatamab concentration of 2.4 mg/mL.

Tarlatamab is reconstituted with 4.4 mL of sterile water for injection. The reconstituted product is clear to opalescent and colorless to slightly yellow. Upon reconstitution, the product is intended for dilution in normal saline (0.9% (w/v) sodium chloride) and an intravenous solution stabilizer (IVSS) for intravenous (IV) administration. A delivered volume of 4.2 mL reconstituted finished product will allow delivery of 10 mg. The container closure system consists of an ISO 6R Type I glass vial, elastomeric stopper, and aluminum seal with flip-off cap.

The finished product description pre- and post-reconstitution is provided.

The IVSS is supplied with tarlatamab for administration via IV infusion. The IVSS is supplied as a sterile solution in ISO 10R Type I glass vials containing 7 mL of deliverable product. The IVSS is a buffered, preservative-free, colorless to slightly yellow, and clear to slightly opalescent solution and is further discussed below.

The finished product and its composition are sufficiently described.

Pharmaceutical development

Formulation development studies were performed to determine the stability of tarlatamab as a function of pH, protein concentration, buffer concentration, and excipient concentration. The formulation

development data for active substance and finished product are discussed in detail in 3.2.P.2.2 (Formulation Development).

Tarlatamab active substance contains 5 mg/mL protein, is formulated with sucrose, L-glutamic acid, polysorbate 80 and is stored at a recommended storage condition of -30°C. Development was conducted to confirm that the formulation is stable during the finished product process.

The compatibility of 5 mg/mL tarlatamab active substance and 1 mg/vial finished product, and 10 mg/vial finished product, with the excipients has been demonstrated through stability studies.

The tarlatamab infusion is prepared for administration by first aseptically adding an appropriate volume of IVSS to an infusion bag containing an appropriate volume of normal saline (0.9% (w/v) sodium chloride solution). The tarlatamab finished product is reconstituted with 1.3 mL for or 4.4 mL for 10 mg/vial product sterile water for injection for 1 mg/ml vial product or 10 mg/vial product respectively. Following reconstitution, 1.1 mL of 1 mg/vial or 4.2 mL of 10 mg/vial tarlatamab is added aseptically to the infusion bag containing the IVSS and the saline.

The excipients selected for the formulation include sucrose, L-glutamic acid, polysorbate 80, sodium hydroxide, and water for injection. The excipients, concentrations, and functions are provided.

The excipients are commonly used in parenteral products and comply with applicable compendia. Due to the low concentration of tarlatamab administered to patients, an intravenous solution stabilizer (IVSS) is included in the tarlatamab intravenous infusion preparation to prevent loss through adsorption of tarlatamab to the surfaces of the infusion bag and tubing. The composition of the IVSS is citric acid monohydrate, lysine hydrochloride, and polysorbate 80. The IVSS is supplied as a sterile solution in a clear glass ISO 10R vial and is stored at 2°C to 8°C.

Tarlatamab finished product is formulated at concentrations of 3 mg/mL and 5 mg/mL for two lyophilized presentations (1 mg/vial and 10 mg/vial, respectively). The formulation includes sucrose, L-glutamic acid, and polysorbate 80. This formulation is designed to provide a sterile, single-use, preservative-free product for intravenous administration. The finished product is stored at 2–8°C, reconstituted with sterile water for injection, and diluted in saline with an intravenous solution stabilizer prior to infusion.

The formulation evolved from clinical studies into a single commercial formulation with two presentations (1 mg/vial and 10 mg/vial). Robustness studies assessed the stability of tarlatamab under variations in protein concentration, pH, and excipient concentrations. Two design-of-experiment studies were conducted. Both studies demonstrated that tarlatamab is physically and chemically stable under manufacturing and storage conditions. Statistical analysis confirmed robustness under recommended storage conditions (2–8°C).

Visible and subvisible particle characterization further confirmed formulation robustness. No visible particles were detected during visual inspection. Subvisible particle counts across all size ranges showed variability but no trends. All samples met regulatory limits specified by USP, Ph. Eur., and JP.

A study evaluated the stability of tarlatamab under elevated residual moisture levels. Tarlatamab remained stable at elevated moisture levels. Results showed no significant impact on physical or chemical stability, including aggregation, charge variants, fragmentation, subvisible particles, cake appearance, or reconstitution time.

Formulation development studies confirm the ability of the commercial formulation to maintain product stability under variations in pH, protein concentration, and excipient concentrations. No formula overages are included.

The finished product development studies for tarlatamab, confirm the formulation's robustness and stability under recommended and accelerated storage conditions. Key attributes such as pH, protein concentration, buffer composition, and excipient concentration were optimized to ensure stability. Forced degradation studies demonstrate the formulation’s resilience under stressed conditions, with consistent excipient concentrations and pH between the active substance and finished product. The oxidation tendency was effectively monitored and showed no significant impact on product quality under worst-case manufacturing conditions. Stability evaluations, including light exposure and temperature cycling, confirm that the finished product remains stable within acceptance criteria at the recommended storage condition of 2°C to 8°C.

The development of the 1 mg/vial finished product manufacturing process progressed through nonclinical, clinical, and commercial phases, with each phase adapting processes to meet evolving requirements. Early nonclinical manufacturing (Process 1 Nonclinical) supported toxicology studies, while early-phase clinical manufacturing (Process 1 Clinical) introduced lyophilized 5 mg/vial finished products, demonstrating comparability between the two processes. Late-phase clinical manufacturing transitioned to Process 2, introducing lyophilized 1 mg/vial and 10 mg/vial presentations in new primary containers, with stability studies and analytical comparability assessments confirming product consistency. Commercial manufacturing scaled up Process 2 to Process 2 (Commercial), incorporating minor adjustments while maintaining comparability. Comparability exercises throughout development demonstrated consistent quality, potency, purity, and safety, with observed differences deemed inconsequential to product efficacy or safety. The comprehensive development and comparability assessments ensure the finished product meets predefined criteria, supporting patient safety and therapeutic effectiveness.

The primary container closure systems for the 1 mg/vial and 10 mg/vial finished products consist of ISO Type I glass vials (2R and 6R, respectively) paired with elastomeric stoppers and aluminum seals with flip-off caps. Both systems underwent comprehensive physical, chemical, and functional testing to ensure safety, suitability, and compliance with USP, Ph. Eur., and JP standards. Pre-washed and sterilized stoppers were tested for penetrability, fragmentation, and self-sealing, confirming their reliability. Chemical resistance testing verified the vials met Type I glass requirements, while the stoppers complied with physicochemical standards for elastomeric closures. Stopper compatibility was demonstrated. Appropriate information on sterilisation has been provided. Non-compendial extractables testing and 24-month leachable testing identified no toxicological concerns, with targeted organic leachables below toxicological thresholds. Compatibility testing confirmed no interaction between the closure systems and finished products, with sorption studies showing negligible loss of deliverable doses. Hold-up volumes ensured accurate labeled protein delivery. Container closure integrity testing and secondary packaging in solid paperboard cartons protect the finished products from light-induced degradation.

Container closure integrity (CCI) testing for the tarlatamab finished product presentations was conducted evaluating the quality of fit between container closure components (ISO 2R and ISO 6R glass vials, elastomeric stoppers, and aluminum seals) and the processes used to assemble them. Testing was performed on vials stoppered and capped at the commercial manufacturing site, with samples evaluated under variable capping settings and across the entire filling operation. Results confirmed robust CCI for both vial systems, demonstrating that the filling, stoppering, and capping processes do not compromise container closure integrity). CCI testing methodology, qualification, and results, supporting the integrity of the container closure system.

Tarlatamab underwent two compatibility studies to evaluate its stability and storage conditions. The first study supported storage for 7 days at 2°C to 8°C and IV administration for 8 hours at 25°C, demonstrating physical stability in 0.9% saline with 5% IVSS in EVA IV bags. Compatibility was confirmed with commonly used tubing and catheter materials during infusion at ambient temperatures.

The second study extended the allowable storage to 35 days at 2°C to 8°C and 1 day at 30°C, testing additional materials like polyolefin (PLF), polyvinyl chloride (PVC), and polybutadiene (PB). Tarlatamab remained stable under these conditions. Based on the findings, tarlatamab can be stored for up to 28 days at 2°C to 8°C and 8 hours at 25°C. The prescribing information includes instructions to warm refrigerated IV bags to room temperature prior to administration. These results confirm the finished product's stability and compatibility with commonly used IV materials under recommended conditions. Compatibility has been adequately described.

3.3.2. Manufacture of the product and process controls

Manufacturers

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

Manufacturing process and process controls

The tarlatamab finished product manufacturing process is adequately described. The tarlatamab finished product manufacturing process is appropriately controlled and consists of formulation, sterile filtration, aseptic filling, and lyophilisation operations. The active substance is thawed, diluted with a formulation buffer to the target concentration, and mixed under defined conditions to produce the formulated bulk solution. The bulk solution undergoes filtration and aseptic filling into vials with appropriate in-process controls. Filled vials are fully stoppered, capped, and visually inspected.

The manufacturing process is supported by validated process parameters, environmental controls, and appropriate in-process and release testing to ensure consistent product quality. Labelling and packaging operations are performed with verification of batch-specific information. The finished product batch sizes have been sufficiently described.

Process controls

The IPCs and microbial control strategies for finished product manufacturing are presented. The microbial control strategy is provided and is adequate. Bioburden action limits are set. Filters demonstrate excess microbial retention capacity under worst-case conditions, and is considered acceptable.

Process validation

The process validation for the finished product manufacturing covered formulation to filling, aseptic processing, sterilization validation, filter validation, and transportation qualification. Validation demonstrated that the manufacturing process for both 1 mg/vial and 10 mg/vial presentations is controlled, consistent, and reproducible, meeting predefined acceptance criteria for process performance and product quality.

The approach for establishing process validation strategies based on prior knowledge and clinical manufacturing experience is presented. Filter validation confirmed the compatibility, microbial retention, and safety of the membrane used. Aseptic process validation ensured sterility throughout the filling process, while sterilization validation confirmed the effectiveness of sterilization and depyrogenation cycles for product-contact materials and equipment. Transportation qualification demonstrated that the finished product maintains quality attributes under transport stresses within the temperature range of 2°C to 8°C.

Overall, the validation activities confirm that the finished product manufacturing process is robust, reliable, and in a state of control. The finished product manufacturing process is considered appropriately validated.

3.3.3. Product specification

The methods applied for finished product release and shelf-life testing include appearance, osmolality, pH, water content, reconstitution time, visible and sub-visible particles, uniformity of dosage unit, protein content, purity, biological activity, microbiological aspects and container integrity.

The proposed acceptance limits are appropriately defined. Acceptance criteria for in-process controls and specifications were justified using manufacturing experience, product and process characterisation, analytical method performance, and clinical data, with tolerance intervals applied to predict long-term process behaviour and set release and stability specifications.

A risk assessment of N-nitrosamine contamination covering both active substance and finished product has been performed and it is agreed that the risk of N-nitrosamine impurities is negligible.

A risk assessment of elemental impurities in the finished product has been performed, and it is agreed that the residual quantity of elemental impurities is very low, and all meet the requirements specified in ICH Q3D. This is found acceptable.

The finished product specifications are considered appropriate.

Analytical procedures

Analytical methods used for finished product release testing have been adequately described or refer to Ph. Eur. Methods common for active substance and finished product are described in the dossier. In-house developed analytical methods are appropriately validated. Method performance parameters are addressed adequately in the presented validation reports. The information provided is sufficient and adequate.

Batch analysis

Batch analyses data are provided for the Process 2 and Process 2 (Commercial) finished product lots for clinical and commercial development. This includes different presentations of lyophilized finished product lots. Each lot was tested to the specification in place at the time of testing.

All lots representative of the commercial process, meet the proposed commercial specification.

Reference standards

The same reference standards are used for both tarlatamab active substance and finished product testing. Please refer to the active substance section.

Container closure

The primary container closure systems for tarlatamab consist of ISO Type I glass vials paired with elastomeric stoppers and aluminium seal flip-off caps. For the 1 mg/vial dosage, an ISO 2R vial with a 13 mm stopper is used, while the 10 mg/vial dosage utilizes an ISO 6R vial with a 20 mm stopper.

The selection of these components was based on extensive physical, chemical, and functional testing, including assessments of leachables and container closure integrity.

Both the vials and stoppers comply with Ph. Eur. standards, with appropriate specifications outlined in the dossier. Secondary packaging consists of labelled finished product vials placed in solid paperboard cartons, which provide light protection.

The container closure system is considered sufficiently justified and appropriate.

3.3.4. Stability of the product

A shelf life of 4 years is claimed for the finished product (1 mg/vial and 10 mg/vial presentations) when stored at the recommended storage conditions of (2°C to 8°C).

Stability studies for the finished product were conducted to determine shelf life and assess the impact of various storage conditions, including elevated temperatures and experimental conditions such as photostability, temperature cycling, and transportation.

The Applicant states that the two presentations, 1 mg/vial and 10 mg/vial single-use lyophilized vials, can be considered to have equivalent stability profiles, differing only in protein concentration and container size. Stability data from Process 2 for both presentations were combined to support the proposed shelf life, with at least one lot from each presentation evaluated comprehensively which is supported. The stability program includes several lots stored at the recommended condition of 5°C, encompassing supporting, primary, and production lots. Comparability between clinical and commercial manufacturing processes has been demonstrated.

Stability data under long term storage conditions was presented. The stability of finished product lots was also evaluated under accelerated storage conditions and stressed storage conditions. Results demonstrated no meaningful changes in relevant CQAs, including moisture content, sterility, container closure integrity, protein concentration, bioassay, pH, and subvisible in the stability lots. Relative potency and pH remained stable under both storage conditions, and subvisible particles met acceptance criteria. Overall, it is agreed the data support the stability of the finished product under accelerated and stressed conditions.

The photostability, temperature cycling, and transportation evaluations, demonstrate the stability of the product under various stress conditions. Photostability studies confirm that the secondary packaging effectively protects the finished product from photodegradation, underscoring the importance of protecting tarlatamab from light during storage. Temperature cycling studies show that the finished product remains stable and maintains its quality attributes after exposure to significant temperature fluctuations, validating its stability during transport and handling. Transportation studies simulate worst-case conditions, including elevated temperature, shock, vibration, and pressure, and confirm that the product retains its quality attributes, with minor differences in subvisible particles remaining within acceptable limits. These findings support the conclusion that tarlatamab finished product is very stable and well-suited for commercial distribution, storage, and handling under real-world conditions.

The available stability data at 5°C comply with stability acceptance criteria, with no significant changes observed with statistical analyses using confidence bounds, indicating that the parameters will remain within stability specifications up to 48 months. The data available supports a 48 month shelf life.

The secondary packaging effectively protects the product from light exposure. Stability profiles for the two presentations are equivalent, differing only in protein concentration and container size. The stability program includes several lots stored at 5°C, with additional evaluations under accelerated and stressed conditions to assess degradation rates and temperature stress effects. Comparability has been demonstrated between clinical and commercial manufacturing processes, ensuring consistency. The container closure system used in the stability program matches the one proposed for commercial distribution.

Based on the stability data provided the claimed shelf life of 4 years for the finished product when stored at 2°C to 8°C, is acceptable. Based on the compatibility studies summarised, the in-use stability for up to 28 days at 2°C to 8°C and 8 hours at 20°C to 25°C is supported.

From a microbiological point of view, the product should be used immediately. If not used immediately,

in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless the method of reconstitution and dilution has taken place in controlled and validated aseptic conditions.

Intravenous (IV) solution stabilizer (IVSS)

Description of the product

The IVSS is supplied with the finished product for administration via intravenous infusion. The IVSS is supplied as a sterile solution in a 10R glass vial containing 7 mL of deliverable solution. The IVSS is a buffered, preservative-free, colorless to slightly yellow, and clear solution.

Pharmaceutical development

The container closure system for the IVSS is a 10R Type I borosilicate glass vial, with elastomeric stopper, and aluminum seal with flip-off cap. The formulation for IVSS has stayed the same throughout the development of tarlatamab and has the same formulation in the commercial presentation.

The IVSS presentation was optimized by changing the fill volume to a 7 mL fill in a 10R glass vial. The commercial presentation, otherwise, is unchanged throughout development.

A process design approach was used to develop a comprehensive understanding of the IVSS manufacturing process that consistently delivers IVSS of the required quality.

The comprehensive process understanding obtained from these evaluations was used to establish process parameters for each process step and IPCs to demonstrate acceptable process performance during routine manufacturing operations.

The overall process history to the 7 mL/10R IVSS lots, has been described in terms of scale, process steps, and product presentations. The changes made throughout development have been described, evaluated and shown to result in an acceptable final product for commercial manufacture.

A process design approach was used to develop a comprehensive understanding of the IVSS manufacturing process that consistently delivers IVSS of the required quality. Prior knowledge, which includes process development studies, manufacturing experience, and the results of process risk assessments, was leveraged to support the process design of 7 mL/10R IVSS.

Manufacture of the product and process controls

The IVSS 7 mL/10R vial is manufactured in accordance with current Good Manufacturing Practices (cGMP). The facilities involved in the manufacturing and testing of IVSS are GMP compliant.

The 7 mL/10R IVSS manufacturing process consists of the following unit operations: formulation, bioburden reduction filtration, filtered IVSS hold, sterile filtration, filling, stoppering, capping, and inspection and storage.

Process parameters for these IVSS manufacturing unit operations were established and classified. The IVSS commercial process has been characterised, through process development studies both at laboratory and commercial scale. Process characterisation demonstrated that the IVSS manufacturing process is robust and can deliver the required product quality and process consistency when operated within acceptable ranges.

The IVSS primary container closure system consists of an ISO 10R Type I glass vial with an elastomeric stopper and an aluminum seal with a flip-off cap. The selection of the commercial primary container closure system is based on the results of physical, chemical, and functional tests. Suitability of the container closure system for product storage and transportation has been demonstrated.

Process validation

Sufficient and adequate process validation data has been provided demonstrating robustness and good control of the manufacturing process. The process validation is considered acceptable.

Product specification

The IVSS specifications cover methods for appearance, general tests, identity, sterility, bacterial endotoxins. IVSS does not contain an active ingredient. It is manufactured from compendial components. The proposed specifications are acceptable.

Analytical procedures

The analytical procedures used to test IVSS for release and/or stability are described and have been appropriately validated.

Batch analysis

Batch analyses data are provided. All lots meet the proposed commercial specification. The batch analyses data demonstrate that IVSS can be manufactured reproducibly to a high level of quality.

Container closure

The primary container closure system selected for use with the IVSS consists of an ISO 10R Type I glass vial with an elastomeric stopper and an aluminium seal with flip-off cap. A description of each component has been provided in the dossier. The labelled finished product and IVSS vials are placed into a carton together. Each carton is constructed of solid paperboard that serves to shield the product from light.

Stability of the product

The IVSS stability program includes data from primary lots, data from supporting lots, and data from production lots. Stability studies confirm that the test methods effectively detect changes in product quality attributes, and experimental evaluations demonstrate that IVSS remains stable under worst-case conditions, including light exposure, temperature cycling, transportation, storage, handling, and use.

Based on the stability data available and provided the claimed shelf life for the IVSS at the recommended storage condition is acceptable.

3.3.5. Post approval change management protocol(s)

Not applicable

3.3.6. Adventitious agents

An adventitious agents risk assessment and cell bank and viral clearance study reports have been provided. The master cell bank was characterised for viral and non-viral adventitious agents. The

working cell bank and end of production cells at the LIVCA were also characterised. Retrovirus-like particles were detected in the cell banks, which is typical for CHO cells. This is acceptable. Taking the estimated maximum retrovirus-like particles per dose into account, the Applicant presented calculations which conclude that there is an excess retrovirus clearance in the manufacturing process. Thus, this is considered sufficiently addressed. Apart from the retrovirus-like particles, no adventitious agents were detected, and thus the adventitious agent evaluations of the cells are considered acceptable.

The unprocessed bulk is tested for mycoplasma, bioburden and adventitious viruses using indicator cell lines and several positive control viruses. The process was evaluated for viral clearance with both new and used resins. The unprocessed bulk testing is considered acceptable.

In line with ICH Q5A, the Applicant presents a viral clearance assessment. For this purpose, small scale models were qualified and used which is considered acceptable. Four model viruses were used. The panel includes enveloped and non-enveloped viruses and both RNA and DNA viruses, a range of sizes, and a range in resistance to inactivation. The choice of model viruses is considered appropriate. The information on the virus clearance studies provided is sufficient and appropriate.

The presented transmissible spongiform encephalopathy (TSE) risk assessment, concluding negligible risk, is considered acceptable.

The information provided is sufficient and ensures adventitious agents safety of the product.

3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Active substance

Tarlatamab is a bispecific T-cell engager (BiTE) antibody derivative targeting DLL3 on cancer cells and CD3 on T cells, enabling T-cell-mediated cytotoxicity. It is engineered to be aglycosylated and includes a half-life extension moiety. The manufacture of the active substance follows a standard process consisting of CHO cell culture expansion, harvest and purification of tarlatamab.

The manufacturing process is well described in the dossier and details of in-process controls are listed for each manufacturing step. The critical process parameters and critical in-process controls are also indicated.

Process validation acceptance criteria and process parameter results, including critical process parameters and non-critical process parameters have been provided for each manufacturing step. All active substance release results met acceptance criteria in place at the time of process validation and additionally meet the proposed commercial specification. All process parameters were within the registered acceptable range and all performance indicators were within the validation acceptance criteria.

The development of the active substance manufacturing process was sufficiently described.

The tarlatamab active substance has been extensively characterised in terms of biological function and impurity profile. Stability studies support the claimed shelf life. The active substance specification and analytical procedures are adequate.

Overall, the manufacturing process and control strategy for the active substance are considered robust.

Finished product

The finished product is supplied in two presentations: 1 mg/vial and 10 mg/vial, both formulated as sterile, white lyophilized powders for reconstitution. The reconstituted product is clear to opalescent, colourless to slightly yellow, and intended for intravenous administration following dilution with normal saline and an intravenous solution stabilizer (IVSS). The IVSS, supplied as a buffered, preservative-free solution, prevents adsorption of the product to infusion bag and tubing surfaces. The container closure systems for both presentations consist of ISO Type I glass vials with elastomeric stoppers and aluminium seals. Comprehensive testing has confirmed the safety, compatibility, and suitability of container closure system.

Development studies demonstrate the robustness and stability of the finished product formulation under variations in pH, protein concentration, and excipient composition. The formulation includes sucrose, L-glutamic acid, and polysorbate 80, designed for sterile, single-use intravenous administration. Stability studies under long-term, accelerated, and stressed conditions confirm the product's stability. Based on the stability data provided the claimed shelf life of 4 years for the finished product when stored at 2°C to 8°C, is acceptable. Based on the compatibility studies summarised, the in-use stability for up to 28 days at 2°C to 8°C and 8 hours at 20°C to 25°C is supported.

Process validation activities, including aseptic processing, sterilization, and transportation qualification, confirm that the manufacturing process is validated. The analytical methods for release and shelf-life testing are appropriately validated, with batch analyses confirming compliance with commercial specifications.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Imdylltra is considered approvable from the quality point of view.

3.5. Recommendation(s) for future quality development

N/A

4. Non-clinical aspects

4.1. Introduction

Non-clinical testing strategy and regulatory framework

The nonclinical testing strategy for tarlatamab adhered to a development pathway typical for biopharmaceutical products. Specifically, the nonclinical development of tarlatamab followed the guidelines for anti-cancer pharmaceuticals outlined in ICH S9, 2010, and ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers, 2018, as well as the Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (ICH S6 (R1), 2011). Studies covering pharmacology, pharmacokinetics, exploratory toxicology, and GLP-compliant toxicity were conducted at scientific and contract research laboratories in the European Union and the United States. Pivotal studies were carried out in accordance with FDA and/or OECD GLP regulations.

Analytical methods

The quantification of tarlatamab in cynomolgus monkey serum and cerebrospinal fluid (CSF) utilized ligand binding assays with high sensitivity and specificity. In the non-GLP 121985 study, biotinylated DLL3-human Fc protein and ruthenylated mouse clone 3E5.E1 anti-anti-human CD3 monoclonal antibody were used. The assay had a LLOQ of 0.035 ng/mL, indicating high sensitivity.

In Study 121424, a mouse monoclonal antibody against anti-CD3 and biotin-conjugated recombinant human DLL3-Fc were used, with validated ELISA methods achieving LLOQs of 15.0 ng/mL for serum and 1.50 ng/mL for CSF. The ADA testing employed a validated ECL immunoassay with a sensitivity of 6.2 ng/mL.

In the 3-month GLP toxicology study (122516), a mouse monoclonal antibody against anti-CD3 was used as a capture reagent, while HRP-conjugated anti-human IgG Fc was used for detection. The validated method had a LLOQ of 15.0 ng/mL. ADA testing applied the same validated method as study 121424.

Study 157064 explored three assay configurations with uniform LLOQ (0.61 ng/mL), indicating consistent performance across setups.

For muS757 quantification in mouse serum, the ECL-based ligand binding assay showed variable LLOQs across studies. The GLP complied EFD toxicology study applied a validated method.

4.2. Pharmacology

4.2.1. Pharmacodynamics

4.2.1.1. Primary pharmacodynamics

Primary pharmacology was investigated in in vitro binding and functional studies, in vivo mouse tumour models, and with a murine surrogate molecule developed for additional non-clinical evaluation. The activity of tarlatamab was characterized using nonclinical models of SCLC. The cell lines used to assess tarlatamab activity in vitro were generated from human SCLC tumours. The in vitro binding affinity studies demonstrated comparable binding of tarlatamab to human and cynomolgus monkey DLL3 and CD3ε, with less than a 10-fold difference in KD values. The specificity of tarlatamab for DLL3 was confirmed, with selective binding to DLL3-expressing cells and limited cross-reactivity to murine DLL3. Furthermore, the CD3-binding arm exhibited species-specific binding to human and cynomolgus monkey T cells, without cross-reactivity to CD3 from other species.

Functional studies demonstrated tarlatamab-induced T cell activation and cytotoxicity in co-cultures with DLL3-positive target cells. Competitive binding by physiological levels of human IgG was shown to mitigate target-independent T cell activation.

The DLL3 binding domain of tarlatamab also cross-reacts to murine DLL3 and was used to generate a murine surrogate molecule, muS757, for additional nonclinical safety assessment. muS757 bound to murine DLL3 and murine CD3 with similar affinity as tarlatamab bound to human DLL3 and human CD3. In addition, muS757 co-cultured with murine T cells and target cells expressing murine DLL3 induced T cell activation and T cell-dependent lysis of target cells.

Anti-tumour activity of tarlatamab was examined across multiple mouse tumour models, including orthotopic and patient-derived xenograft models of small cell lung cancer (SCLC) and a neuroendocrine prostate cancer model. Due to the lack of binding to murine CD3, the studies utilized immunodeficient mice supplemented with human PBMCs or T cells to evaluate the therapeutic effects of tarlatamab.

In orthotopic SCLC models, tarlatamab induced significant tumour regression and enhanced T cell infiltration into tumours. Complete tumour regression was observed in certain models. Enhanced expression of T cell activation markers (e.g., CD25, PD-1, and 4-1BB) was also observed in T cells isolated from treated animals.

Dose-dependent tumour regression was observed in the neuroendocrine prostate cancer xenograft model, with near-complete or complete responses observed at higher tarlatamab doses.

4.2.1.2. Secondary pharmacodynamics

DLL3 is typically intracellular in normal cells but is upregulated and found on the surface of neuroendocrine tumour cells like SCLC. DLL3 expression was analysed in normal human and cynomolgus monkey tissues.

RNA sequencing (RNA-seq) was conducted to measure the mRNA levels of DLL3 in normal tissues from humans and cynomolgus monkeys. In addition to the canonical full-length DLL3 transcript, previously uncharacterized variants lacking certain exons were identified. Some of these variants were detected at higher levels than the canonical DLL3 transcript in multiple tissues. The presence of these novel DLL3 transcripts was confirmed through qPCR and in situ hybridization studies. Transcripts containing the tarlatamab-recognized region were detected at levels ≥ 1 transcript per cell in the optic nerve of cynomolgus monkeys and the brain of humans and cynomolgus monkeys. The expression pattern appears to be restricted to the cytoplasm.

DLL3 IHC staining was detected in neurons in the human cerebrum, cerebellum, hypothalamus, and hippocampus. In addition, DLL3 protein was detected by Western blot and IHC staining in the basophil pituicytes of the anterior pituitary and the pancreatic islets in both humans and cynomolgus monkey tissues. IHC staining in normal human and cynomolgus monkey tissues generally had weak (1+) and occasionally mild (2+) intensity and had a cytoplasmic pattern of localization**.**

No evidence of platelet activation was observed in either human or cynomolgus monkey whole blood at any of the tested concentrations after a single administration of tarlatamab.

4.2.1.3. Safety pharmacology

Safety pharmacological endpoints were evaluated in repeat-dose toxicity studies with cynomolgus monkeys and mice. In cynomolgus monkeys, electrocardiographic changes were limited to a slight increase in heart rate and corresponding decreases in PR, RR, and QT intervals, observed after the first dose at medium and high doses on day 2, but not on day 23. No tarlatamab-related neurological observations or alterations in body temperature or respiratory rate were noted in cynomolgus monkeys, and no muS757-related effects on respiratory or central nervous system function were observed in mice.

4.2.1.4. Pharmacodynamic drug interactions

Pharmacodynamic interaction studies were conducted in cell culture systems and in an SCLC xenograft model. The effect of dexamethasone on tarlatamab- mediated T cell activation and redirected lysis was tested in cell culture experiments, showing that dexamethasone reduces cytokine release and suppresses the expression of activation markers CD69 and CD25 on T cells, increasing their EC50 values by up to 3.7-fold (CD69) and 3.3-fold (CD25). Additionally, dexamethasone affected tarlatamab-mediated redirected lysis of cancer cells, with its impact varying between cell types. For SHP-77 cells, dexamethasone almost completely blocked redirected lysis, increasing EC50 values up to 6.6-fold, while its effect on DMS 79 cells was less pronounced, with EC50 values increasing approximately 3-fold.

The impact of immune checkpoint blockade on tarlatamab cytotoxic activity was assessed in vitro. SHP-77 cells overexpressing PD-L1 were treated with tarlatamab and human T cells, with or without

the anti-PD-1 antibody AMG 404. Co-treatment with AMG 404 enhanced tarlatamab cytotoxicity, lowering EC50 values across 4 T cell donors. In COR-L279 cells engineered to express PD-L1, co-treatment reduced EC50 values by 1.3-fold, though the difference was not statistically significant (P=0.06).

The combination of tarlatamab with platinum and etoposide chemotherapy was evaluated in SCLC cell lines in vitro and in a SCLC xenograft model in vivo. It was demonstrated that all treatments reduced T cell viability to some extent. Etoposide treatment had the strongest effect on T cell viability, with half-maximal inhibitory concentrations (IC50) of 34 μM after 48 hours and 16 μM after 72 hours.

4.2.2. Pharmacokinetics

Absorption

The pharmacokinetics of tarlatamab were assessed in cynomolgus monkeys after single IV bolus injection, short IV infusion, slow IV bolus administration and SC administration. A biphasic decline in serum concentrations was observed after a single IV bolus administration. Measured half-life was 119–140 hours in mice, 234 hours in monkeys, and 10.6 days in humans. Accumulation was observed in mouse and cynomolgus monkey studies. In repeated-dose toxicokinetic evaluations, tarlatamab exposure increased with dose and repeated administration. No marked sex-based differences in exposure were observed in most dosing groups. Anti-drug antibodies were detected in most animals. In the 28-day repeat-dose toxicity study in cynomolgus monkeys, one low-dose animal had vascular changes in the heart and lung, and the Applicant attributed these findings to immune complexes formed by ADA with tarlatamab. The murine surrogate muS757 was studied in mice, and repeated weekly dosing resulted in observable drug accumulation.

Distribution

No non-clinical distribution studies were conducted. The Applicant stated that bispecific antibodies are generally distributed in the circulatory system and extracellular fluids because of their large molecular weights.

Metabolism

No in vitro metabolism studies were performed for tarlatamab. The Applicant stated that tarlatamab is expected to be broken down into small peptides and individual amino acids.

Excretion

No excretion studies were performed. The Applicant referred to publications indicating that glomerular filtration is restricted to molecules <60 kD, whereas larger molecules are taken up by the reticuloendothelial system and catabolised by the liver. Tarlatamab is approximately 105 kD. No specific studies were conducted to examine excretion of tarlatamab in the milk of lactating animals. The Applicant referred to published studies showing that IgG antibodies can be transferred into the milk of lactating animals.

PK-related drug-drug interaction

Literature indicates that cytokines can alter CYP enzyme expression. In non-clinical in vitro study 122717, tarlatamab caused dose-dependent cytokine release, including IL-6, TNF-α and IFN-γ, from effector cells. Elevations in serum cytokines were also observed within 24 to 48 hours after the first infusion of tarlatamab in patients in clinical study 20160323.

4.3. Toxicology

4.3.1. Overview of the non-clinical toxicology program

Cynomolgus monkeys were selected for the non-clinical toxicology assessment because tarlatamab showed cross-reactivity with cynomolgus monkey DLL3 and CD3 in cell binding and bioactivity assays, and DLL3 expression profiles were similar between cynomolgus monkeys and humans. The non-clinical safety evaluation of tarlatamab included exploratory 10-day studies and 28-day and 3-month GLP repeat-dose toxicology studies in cynomolgus monkeys using once-weekly IV doses up to 4500 µg/kg. The physicochemical characteristics of tarlatamab determined the maximum feasible dose for administration to cynomolgus monkeys. To facilitate embryofoetal development assessment, a murine surrogate of tarlatamab, muS757, was developed with the same DLL3 binding domain as tarlatamab and murine CD3-binding and Fc domains. The bioactivity of muS757 in co-cultures of murine T cells and murine DLL3-expressing target cells was found to be comparable to that of tarlatamab in the human system. Pharmacokinetic and toxicokinetic studies with tarlatamab and muS757 showed similar PK characteristics in terms of C_{max} and AUC_{last}.

4.3.2. Single-dose toxicity

Single-dose toxicity studies have not been conducted.

4.3.3. Repeat-dose toxicity

The non-clinical safety evaluation included a 28-day toxicology study and a 3-month GLP toxicology study in cynomolgus monkeys, and a 4-week repeat-dose study in mice with muS757.

In the 28-day study, tarlatamab-related changes were limited to a minor decrease in lymphocyte populations and minimal to mild mixed cell infiltrates in the pituitary at low and medium dose levels. One animal in the low-dose group exhibited vascular changes in the heart and lung. Granulomatous inflammation was observed in the coronary groove around a coronary artery in the heart, and two small organised thrombi were found in pulmonary arteries in the lung. The Applicant stated that these changes were consistent with secondary effects from immune complexes formed by ADA with tarlatamab. A slight increase in heart rate was observed on Day 2 at the medium and high dose levels, but not on Day 23. All tarlatamab-related effects showed full or partial reversibility. HNSTD was 4500 µg/kg.

In the 3-month study, tarlatamab-related findings consisted of minimal decreases in lymphocytes and mononuclear and/or mixed cell infiltrates in multiple tissues, including heart, gallbladder, brain, lung and pituitary gland. The anatomic pathology report stated that the findings were directly related to administration of tarlatamab and/or due to formation of anti-drug antibodies. ADAs were detected in the majority of animals administered tarlatamab in the two pivotal monkey studies. NOAEL was 4500 µg/kg.

Pituitary gland findings were observed in all repeat-dose toxicity studies in cynomolgus monkeys and consisted of minimal to mild mixed cell inflammatory infiltrates without signs of cellular damage. These infiltrates were mainly composed of lymphocytes with varying numbers of eosinophils and were confined to the interface between the pars intermedia and pars nervosa. In recovery animals in the 28-day study, reduced distribution of the finding and a shift from mixed cell infiltrates to mononuclear cell infiltrates were observed.

In the 4-week repeat-dose mouse study, muS757 was well tolerated, with minimal decreases in white blood cells and triglycerides in males on Day 29 at doses ≥500 µg/kg. The NOAEL was 4500 µg/kg.

4.3.4. Genotoxicity

No studies have been conducted to evaluate the genotoxic or mutagenic potential of tarlatamab.

4.3.5. Carcinogenicity

No carcinogenicity studies with tarlatamab have been conducted or are planned.

4.3.6. Developmental and reproductive toxicity

Developmental and reproductive toxicity assessment was limited to a single embryo-foetal development study in mice using the murine surrogate muS757. MuS757 was well tolerated, and no test article-related adverse effects were observed. The NOAEL for muS757 was 4500 µg/kg.

4.3.7. Toxicokinetics and exposure margins

The toxicokinetics of tarlatamab were evaluated in cynomolgus monkeys following weekly intravenous administration at doses of 50, 500 and 4500 µg/kg for up to three months. Tarlatamab exposure increased proportionally with dose and frequency of administration. No significant gender-related differences in exposure, measured by AUC_{last} and C_0, were observed between male and female subjects. Anti-drug antibodies were detected in most animals receiving tarlatamab by the conclusion of the studies. A tenfold difference in mean exposure (AUC_{last}) was noted at Day 22 between the high-dose groups in the pivotal one-month and three-month repeat-dose toxicity studies in cynomolgus monkeys. The pharmacokinetic characteristics and potential immunogenicity of muS757 were evaluated through repeated weekly intravenous bolus injections in BALB/c mice in study 154480. Following the final administration, muS757 accumulation was observed, with an accumulation ratio of 2.1, and no ADA formation was detected in this study. The presence of ADAs was not assessed in two other toxicology studies in mice (studies 153960 and 122517). Safety margins were derived from exposure levels observed in the key repeat-dose toxicity studies and from data presented in the Summary of Clinical Pharmacology Studies.

4.3.8. Local tolerance

The non-clinical local tolerance assessment was based on the 4-week and 3-month repeat-dose IV toxicology studies, in addition to a SC local tolerance study in cynomolgus monkeys.

4.3.9. Other toxicity studies

Anti-drug antibodies were investigated in the pivotal 4-week and 3-month repeat-dose toxicity studies in cynomolgus monkeys and in a mouse immunogenicity study. In both cynomolgus studies, nearly all animals were ADA positive at the end of the study. In the 4-week study, one animal had vascular injury-associated changes in the heart and lung that were described as consistent with secondary effects likely mediated by ADA-related immune complexes. Potential immunogenicity of muS757 was also assessed in a mouse study, and no ADA formation was detected. No studies to investigate dependency were conducted.

4.3.10. Ecotoxicity/environmental risk assessment

The Applicant stated that tarlatamab is a natural substance and is not expected to pose a risk to the environment.

4.4. Overall discussion and conclusions on non-clinical aspects

4.4.1. Discussion

Pharmacology

Tarlatamab is a bispecific molecule engineered to activate and direct T cells towards the elimination of tumour cells expressing DLL3. The biological activity and pharmacological mechanisms of tarlatamab were investigated through various nonclinical models of SCLC, both in vitro and in vivo.

Tarlatamab showed comparable binding to human and cynomolgus monkey DLL3 and CD3, supporting the selection of cynomolgus monkey as the relevant non-clinical species. The modified Fc domain showed low or no relevant interaction with Fc receptors and no binding to C1q, indicating low potential for Fc-mediated effector functions such as ADCC and CDC. Tarlatamab induced target-dependent T-cell activation, cytotoxicity and cytokine release in human and cynomolgus monkey systems, consistent with its intended mechanism of action. At high concentrations, some target-independent T-cell activation and cytokine release were observed, but these effects were blocked by physiological concentrations of human IgG. Nevertheless, uncertainties remain regarding the translational relevance of these findings, as the in vitro systems may underestimate the potential for cytokine release or immune activation in humans. Overall, the in vitro data support the pharmacological activity of tarlatamab, while also identifying a clinically relevant need to consider cytokine-related effects.

In vivo, tarlatamab showed antitumour activity across several xenograft models of small cell lung cancer and neuroendocrine prostate cancer, with evidence of tumour regression and inhibition of tumour growth. These findings support the mechanism demonstrated in vitro, including T-cell activation and infiltration into tumours. However, dose-response consistency was not fully demonstrated in all models. Overall, the in vivo efficacy package provides convincing support for the pharmacological activity of tarlatamab. In addition, the observed upregulation of the PD-1/PD-L1 axis provides a rationale for combination with immune checkpoint inhibitors.

Dedicated safety pharmacology studies were not performed, which is acceptable in the context of ICH S9 and is supported by the evaluation of safety pharmacology endpoints within repeat-dose toxicity studies. In cynomolgus monkeys, only slight and transient electrocardiographic changes were observed after the first dose, consisting of increased heart rate with corresponding interval changes, and these were considered non-adverse. No tarlatamab-related effects on neurological observations, body temperature or respiratory rate were seen in cynomolgus monkeys, and no muS757-related effects on respiratory or central nervous system function were observed in mice. Overall, the safety pharmacology findings do not indicate a major non-clinical concern for clinical use.

Evaluation of DLL3 expression in normal tissues was performed to assess the potential for on-target off-tumour effects. Although DLL3-related transcripts and protein were detected in selected normal tissues, including brain, pituitary and pancreatic tissues, expression was generally low and predominantly cytoplasmic. This supports a low risk of on-target off-tumour toxicity in normal tissues. However, some inconsistencies were noted between the different RNA-based methods,

which introduce uncertainty in the interpretation of the expression data. In addition, no evidence of platelet activation was observed in human or cynomolgus monkey whole blood. Overall, the secondary pharmacology data do not indicate a major unexpected off-target risk.

The interaction studies are clinically relevant because dexamethasone is used to mitigate tarlatamab-induced cytokine release. In vitro, dexamethasone reduced cytokine release and T-cell activation, but it also impaired tarlatamab-mediated cytotoxicity, with variable effects across tumour cell lines. These findings indicate that while dexamethasone may improve tolerability, it may also reduce pharmacological activity. In addition, combination with PD-1 blockade showed signs of enhanced activity in vitro, although further in vivo confirmation would be needed. Combination with platinum and etoposide reduced T-cell viability, particularly with etoposide, but increased cytotoxic activity of tarlatamab together with chemotherapy was also observed. Overall, these findings suggest that concomitant treatments may influence both the efficacy and tolerability profile of tarlatamab in clinical use.

Pharmacokinetics

The analytical methods used for quantification of tarlatamab and muS757 were considered adequate. The pharmacokinetic profile of tarlatamab, including biphasic decline after intravenous administration and extended half-life, was in line with the two-compartment model observed clinically. The prolonged exposure may support sustained therapeutic effects, but the observed accumulation in animal studies is also relevant for clinical use. Anti-drug antibodies were detected in most animals, indicating immunogenicity that may affect the interpretation of exposure and toxicity findings. Transplacental transport of muS757 was demonstrated, confirming foetal exposure in the embryofoetal development study. The absence of dedicated distribution, metabolism and excretion studies is acceptable for a bispecific antibody of this type. Potential cytokine-mediated effects on CYP enzyme expression are addressed in section 4.5 of the SmPC.

Toxicology

Cynomolgus monkey was an appropriate species for the toxicology evaluation because of cross-reactivity with DLL3 and CD3 and similarity in DLL3 expression patterns to humans. Overall, the repeat-dose toxicology studies showed that tarlatamab was generally well tolerated, with mainly limited findings such as small decreases in lymphocyte populations and minimal inflammatory infiltrates in selected tissues. Pituitary findings were consistently observed in monkeys but were not considered adverse, as they were limited in extent and not associated with cellular damage or endocrine dysfunction; moreover, long-term clinical safety analysis indicated a low incidence of pituitary dysfunction events. Anti-drug antibodies were detected in most animals and were considered relevant to some limited vascular findings. The NOAEL and HNSTD were identified as 4500 µg/kg. The use of the murine surrogate muS757 for embryofoetal development was accepted, although the limitations of surrogate antibodies were acknowledged. No maternal toxicity or test article-related malformations were observed in the embryofoetal development study, but a risk to the foetus cannot be excluded given the potential for T-cell activation, cytokine release and inflammatory effects, and this is reflected in sections 4.6 and 5.3 of the SmPC. The absence of genotoxicity, carcinogenicity, and dedicated fertility studies was considered acceptable in light of applicable ICH guidance and has been reflected in the SmPC. Local tolerance findings were related to the injection procedure rather than to tarlatamab itself. One remaining uncertainty is that the cause of the marked exposure difference between the high-dose groups in the pivotal studies could not be conclusively determined.

Tarlatamab is considered exempt from an environmental risk assessment because, as a natural substance, it is not expected to alter environmental concentrations or distribution and is not expected to pose a risk to the environment according to the "Guideline on the Environmental Risk

Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00).

4.4.2. Conclusions

In conclusion, the non-clinical pharmacology, pharmacokinetic and toxicology package for tarlatamab is considered acceptable in support of the marketing authorisation application.
The pharmacology studies adequately support the proposed mechanism of action and demonstrate DLL3-specific, T-cell-mediated antitumour activity in relevant in vitro and in vivo models.
The pharmacokinetic and toxicokinetic package is considered adequate and identifies prolonged exposure, accumulation and immunogenicity as relevant considerations.
The toxicology programme, including the use of cynomolgus monkey as the relevant species and muS757 as a surrogate for developmental toxicity assessment, is considered acceptable. The observed toxicology findings were largely non-adverse and reversible, and the pituitary findings seen in monkeys were not considered adverse and appear of limited clinical relevance.
Although some uncertainty remains regarding the difference in exposure between the high-dose groups in the pivotal repeat-dose studies, this is not considered to preclude an overall positive non-clinical conclusion.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 3.4.3).

5.1.2. Tabular overview of clinical trials

Table 3. Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)
Phase 1 FIH					
20160323	Non-randomized First in human Dose exploration Dose expansion Open-label Multicentre	**Part A1:** Monotherapy dose exploration; Tarlatamab 0.003 to 100 mg IV or eIV Q2W **Part A2:** Monotherapy dose expansion; Tarlatamab 10 or 100 mg IV or eIV Q2W **Part C:** Combination dose exploration with fixed dose of	Participants ≥ 18 years with SCLC who progressed or recurred following at least 1 platinum-based regimen	PK, safety, tolerability. MTD or RP2D and preliminary antitumor activity Primary endpoint:	269 randomised of 392 planned as of 18 October 2024 ≤ 3 mg N = 35 1->10 mg N = 88

		pembrolizumab; Tarlatamab 0.1 or 0.3 mg IV Q2W; Pembrolizumab 200 mg IV Q3W **Part D:** Monotherapy dose with additional CRS mitigation strategies; Tarlatamab 100 mg IV Q2W **Part E:** Monotherapy administration with 24-hour monitoring; Tarlatamab 100 mg IV Q2W **Part F:** Monotherapy administration with 8-hour monitoring; Tarlatamab 10 mg IV Q2W **Part G:** Monotherapy alternative dosing schedule; Tarlatamab 100 mg IV day 1/day or 200 mg IV Q3W		Objective response by investigator	1->30 mg N = 8 1->100 mg N = 76 eIV Cohorts N = 32 Alternative Dosing Cohorts N = 19 Combination Cohorts N = 8
Phase 2					
20200491	Randomized dose evaluation Non-randomised dose expansion Open-label (BICR endpoint) Multicentre	**Part 1:** Tarlatamab 1 mg on Day 1, then 10 or 100 mg on Day 8, Day 15 and Q2W IV thereafter **Part 2 and 3**: Tarlatamab 1 mg on Day 1, then 10 mg (based on an interim analysis of Part 1) on Day 8 , Day 15 and Q2WIV thereafter	Adult participants ≥ 18 years of age with confirmed SCLC who have progressed after 1 prior treatment with platinum containing therapy, and at least 1 additional line of therapy	Efficacy, safety, tolerability, PK Primary endpoint: Objective response by BICR	222 randomised 100 were in the 10 mg target dose group across Parts 1 and 2, 88 in the 100 mg target dose group in Part 1, and 34 in the Part 3 modified safety monitoring 10 mg target dose group.
Phase 3 Therapeutic confirmatory					
20210004 (DeLLphi-304)	Randomized Active-controlled Open-label Multicentre Treatment until progression or unacceptable toxicity	<u>Tarlatamab</u> 1 mg on Day 1, then 10 mg on Day 8, Day 15, and Q2W IV thereafter; <u>SOC</u> Lurbinectedin 3.2 mg/m2 IV Q3W; or topotecan 1.5 mg/m2 IV or 2.3 mg/m2/day PO (1.2 mg/m2 IV or 2.3 mg/m2/day PO in China) on Days 1 to 5 Q3W cycles; or amrubicin 40 mg/m2 IV days 1 to 3 Q3W	Adult participants ≥ 18 years of age with SCLC who have progressed after 1 prior line of platinum containing therapy	Efficacy, safety, tolerability, PROs, PK Primary endpoint: Overall survival	509 participants randomised: 254 participants in the tarlatamab arm, 255 participants in the SOC arm

BICR = blinded independent central review; CSR = clinical study report; DCO = data cut-off; eIV = extended intravenous; ES = extensive stage; IV = intravenous; LS = limited stage; LTFU = long term follow up; MTD = maximum tolerated dose; PK = pharmacokinetics; PO = oral; PRO = patient-reported outcome; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; RP2D = recommended phase 2 dose; SCLC = small cell lung cancer; SOC = standard of care

5.2. Clinical pharmacology

Tarlatamab is a half-life extended bispecific T-cell engager (BiTE) indicated for monotherapy treatment of adult patients with previously treated small-cell lung cancer (SCLC).

Tarlatamab is presented as reconstitutable powder for intravenous (IV) infusion supplied as 1 mg/vial and 10 mg/vial. The recommended dose of tarlatamab is an initial step dose of 1 mg on day 1 and 10 mg on days 8 and 15 and Q2W thereafter. Tarlatamab is administered as a 1-hour intravenous infusion.

Clinical pharmacology data are available from 3 ongoing clinical trials, a phase 1 study, a phase 2 study and a phase 3 study. In addition, the Applicant has undertaken a population PK analysis, using data from these three studies.

5.2.1. Methods

Bioanalytical methods were utilized in clinical studies of tarlatamab to determine serum concentrations of the drug, as well as to detect antidrug and neutralizing antibodies. For PK assessment, an electrochemiluminescence (ECL)-based ligand-binding assay (MET-406436) was developed and fully validated according to ICH M10. The assay demonstrated high sensitivity, appropriate calibration range and regression models, and was thoroughly evaluated for accuracy, precision, selectivity, specificity, dilution linearity, stability, and parallelism. Interference testing confirmed no impact from commonly co-administered therapeutics, and stability was demonstrated for extended periods at both −20 °C and −80 °C. The method was subsequently transferred and re-validated at CRO laboratories in India (Syngene) and China (Labcorp), with cross-validation confirming acceptable agreement across laboratories, thereby supporting its use in global phase 2 and pivotal phase 3 studies.

For immunogenicity assessment, a validated ECL-based bridging immunoassay (MET-406516) was employed to detect binding antibodies. This assay followed a two-tiered approach of screening and confirmatory testing, demonstrated sensitivity in the low nanogram per millilitre range, and showed adequate tolerance to circulating drug. The method was transferred and re-validated at CRO sites for use across different clinical regions, with inclusion of titre determination in later studies to better characterize the magnitude of immune responses. Samples confirmed positive for binding antibodies were subsequently evaluated in a cell-based luciferase reporter bioassay (MET-407730) designed to detect neutralizing activity against tarlatamab. This assay reflected the biological mode of action, demonstrated adequate sensitivity and drug tolerance, and was successfully transferred to a CRO laboratory with confirmatory validation.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Pharmacokinetics of tarlatamab were investigated in all three studies (20160323, 20200491 and 20210004) in patients with small-cell lung cancer. No clinical studies with tarlatamab have been conducted in healthy volunteers. In the phase 1 study 20160323 and in a Chinese cohort of the phase

3 study 20210004 intensive PK sampling was done after the first dose and at steady state to generate full PK profiles. In the phase 2 study 20200491 and the main cohort of the phase 3 study, sparse sampling was used. PK parameters in the phase 1 study (t_{max}, C_{max}, AUC_{tau}, $t_{1/2,z}$, and accumulation ratio) and the phase 3 study (t_{max}, C_{max}, AUC_{tau}, $t_{1/2,z}$, and C_{trough}) were estimated by non-compartmental analysis (NCA). Where sparse sampling was used, summary statistics was provided. Population PK was used to characterise the pharmacokinetics, identify potential covariates which may impact the exposure of tarlatamab and to provide post-hoc predictions for use in exposure-response analyses.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

Tarlatamab PK was characterized by a 2-compartment model with first order elimination. Estimated parameters were CL, V1, Q and V2. Covariates for clearance were bodyweight, hepatic dysfunction categories and number of prior anti-cancer therapies. In addition, presence of anti-drug antibodies was a time-varying covariate for clearance. Covariates for central volume of distribution were bodyweight and race.

The popPK analysis was based on 11672 tarlatamab serum concentration samples from 702 patients (including 437 patients who were administered the 10 mg Q2W dose regime). Excluded samples comprised 34 post-dose samples below quantification limit (0.3%), 39 records with sample date/time issues (0.3%) and 60 samples inconsistent with logical PK profile (0.5%).

Model development, performance evaluation and reporting of the popPK model was in line with the guideline.

5.2.2.3. Absorption

As tarlatamab is administered by the IV route, it is 100% bioavailable by definition. Absolute bioavailability, in vitro-in vivo correlation and the effect of food on PK are not relevant for drug products that are administered by IV route, and no such studies have thus not been conducted.

5.2.2.4. Bioequivalence

Different drug product presentations were developed at ATO in conjunction with drug substance manufacturing process development for use in clinical studies and for future commercialisation.

- Process 1 (Clinical) drug product: 5 mg/vial lyophilised powder for reconstitution for intravenous (IV) administration was used in the first-in-human Study 20160323.
- Process 2 drug product: Three new presentations, 1, 10 and 25 mg/vial lyophilised powder for reconstitution for IV administration were used in phase 2 Study 20200491, pivotal phase 3 Study 20210004, and the other studies. The drug substance formulation composition remained the same from Process 1 to Process 2 drug product development.

Process 2 (Commercial) drug product: Minor changes were incorporated into Process 2 to accommodate the commercial process and referred to as Process 2 (Commercial) drug product (change in manufacturing site and a scale increase). Process 1 (Clinical) and Process 2 drug substance were demonstrated as analytically comparable. Due to the low concentration of drug product administered to patients, an intravenous solution stabilizer (IVSS) is included in the drug product intravenous

infusion solution preparation to prevent adsorption of drug product to the surfaces of the infusion bag and tubing.

No PK comparisons between processes have been performed, and the different drug presentations were not a covariate in the popPK analyses. As the processes essentially are identical across studies, only varying the strength, this is acceptable.

5.2.2.5. Distribution

Neither V_d nor V_{ss} are reported from any of the clinical studies. PK sampling appears to have been too sparse to generate V_d or V_z based on the observed data. Using popPK, tarlatamab PK was described by a two-compartment model with first-order elimination. Based on the final model, tarlatamab volume of distribution at steady state (V_{ss}) for a typical 72.6 kg Caucasian subject with SCLC was estimated to be 8.19 L. The typical parameter estimates of V_c and V_p were 3.23 L and 4.96 L, respectively.

5.2.2.6. Metabolism

Tarlatamab is to be administered parenterally. Like other biologic therapeutics, owing to its large molecular size (~105 kDa), tarlatamab is expected to be degraded into small peptides and amino acids via catabolic pathways. Tarlatamab is neither expected to be metabolized by hepatic drug metabolizing enzymes nor undergo renal glomerular filtration and excretion.

5.2.2.7. Elimination

Elimination was examined in the first-in-human/phase 1 study 20210004, where mean terminal half-life ($t_{1/2,z}$) at steady state was reported for all dose levels and dose regimens. However, for the dose levels 0.003-0.1 mg Q2W a single patient was included only. Mean terminal half-life at steady state for the 0.3 mg and 1.0 mg Q2W dose levels were 4.28 (3.76-5.31) and 4.85 (3.78-5.75) days, respectively. After step-dose regimen of tarlatamab 1 mg IV (day 1) and 3-100 mg IV (day 8/15 and Q2W thereafter), mean terminal half-life at steady state was 5.51 (2.43-9.40) days in the 1 mg (day 1) + 3 mg (day 15) cohort, 5.31 (1.26-9.76) days in the 1 mg (day 1) + 10 mg (day 15) cohort, 4.08 (2.84-5.34) days in the 1 mg (day 1) + 30 mg (day 15) cohort, and 5.80 (1.63-15.9) days in the 1 mg (day 1) + 100 mg (day 15) cohorts.

Based on the popPK model, the estimated systemic clearance (inter-subject %CV) for tarlatamab was 0.728 L/day (34%). The terminal half-life was estimated to be 10.6 days (31%).

5.2.2.8. Dose proportionality and time dependency

Dose proportionality and time dependency were examined in the first-in-human (FIH)/phase 1 study 20210004 and the phase 2 study 20200491. Across the evaluated target dose range (0.003 mg to 100 mg Q2W) in the FIH/phase 1 study, the serum tarlatamab exposures increased in an approximately dose-proportional manner with mean (SD) estimated terminal phase terminal elimination half-life ($t_{1/2,z}$) of 5.4 (2.0) days. Steady state in serum exposures was achieved by approximately cycle 2 day 15. Descriptive statistics after the different dose regimens are presented in Table 4 and Table 5.

Table 4. Descriptive statistics of serum tarlatamab pharmacokinetic parameter estimates after every Q2W IV administration (cycle 2)

	Cycle 2 Day 1				Cycle 2 Day 15						
Dose (mg)	N	C_{max} (µg/mL)	AUC_{336hr} (hr•µg/mL)	C_{trough} (µg/mL)	N	C_{max} (µg/mL)	AUC_{336hr} (hr•µg/mL)	C_{trough} (µg/mL)	$t_{1/2,z}$ (day)	Dose Normalized C_{max}	Dose Normalized AUC_{336hr}
0.003	1	0.000838	0.0607	0.0000986	1	0.000693	0.0576	0.0000816	6.80	0.231	19.2
0.01	1	0.00404	0.453	0.000747	1	0.00320	0.407	0.000691	6.17	0.320	40.7
0.03	1	0.0190	1.68	0.00169	1	0.0180	1.51	-	4.23	0.600	50.4
0.1	1	0.0183	1.49	-	-	-	-	-	-	-	-
0.3	5	0.0557 (63%)	8.88 (34%)[a]	0.0102 (30%)[b]	3	0.118 (26%)	10.8 (37%)	0.0176[d]	4.28 (3.76-5.31)	0.393 (26%)	35.9 (37%)
1.0	7	0.228 (36%)	23.8 (66%)	0.0142 (72%)[c]	6	0.233 (79%)	40.2 (57%)[a]	0.0310 (67%)[a]	4.85 (3.78-5.75)[a]	0.236 (83%)	41.0 (60%)[a]

AUC_{336hr} = area under the concentration-time curve from time 0 to 336 hours postdose; C_{max} = maximum observed drug concentration; CV = coefficient of variation; C_{trough}= trough concentration; IV = intravenous; PK = pharmacokinetic; Q2W = every 2 weeks; $t_{1/2,z}$ = terminal elimination half-life; - = not applicable.
Pharmacokinetic parameters estimated using actual time/dose and presented as geometric mean (% CV), except for $t_{1/2,z}$, which is presented as mean (min - max).
% CV is not presented where N < 3. Individual PK parameters are presented for dose groups with data from only one subject.
Values are reported to 3 significant figures except for % CV, which is reported to the nearest integer.
[a] N = 4
[b] N = 3
[c] N = 6
[d] N = 1

Table 5. Descriptive statistics of serum tarlatamab pharmacokinetic parameter estimates (in cycle 2) after step-dose regiment of tarlatamab 1 mg IB (day 1) and 3 to 100 mg IV (day 8/15 and Q2W thereafter)

	Cycle 2 Day 1				Cycle 2 Day 15						
	N	C_{max} (µg/mL)	AUC_{336hr} (hr•µg/mL)	C_{trough} (µg/mL)	N	C_{max} (µg/mL)	AUC_{336hr} (hr•µg/mL)	C_{trough} (µg/mL)	$t_{1/2,z}$ (day)	Dose Normalized C_{max}	Dose Normalized AUC_{336hr}
1.0 (D1) and 3.0 (D15)-Cohort 7	5	0.975 (17%)	107 (28%)	0.110 (30%)	5	1.05 (29%)	104 (32%)	0.147 (27%)[b]	5.51 (2.43-9.40)	0.349 (29%)	34.7 (32%)
1.0 (D1) and 10.0 (D15)-Cohort 8 and 32 combined	42	3.00 (31%)	289 (44%)[a]	0.268 (46%)[g]	41	2.82 (31%)	299 (45%)[g]	0.306 (40%)[i]	5.31 (1.26-9.76)[d]	0.282 (31%)	29.9 (45%)[g]
1.0 (D1) and 30.0 (D15)-Cohort 9	5	8.50 (41%)	731 (61%)[b]	0.678 (46%)[b]	4	8.08 (21%)	813 (55%)	1.65[j]	4.08 (2.84-5.34)	0.269 (21%)	27.1 (55%)
1.0 (D1) and 100.0 (D15)-Cohort 10, 11, and 30 combined	41	25.4 (40%)	3190 (43%)[c]	4.09 (54%)[h]	36	27.7 (41%)	3890 (43%)[e]	4.36 (69%)[k]	5.80 (1.63-15.9)[f]	0.277 (41%)	38.9 (43%)[e]

AUC_{336hr} = area under the concentration-time curve from time 0 to 336 hours postdose; C_{max} = maximum observed drug concentration; CV = coefficient of variation; C_{trough} = trough concentration; IV = intravenous; PK = pharmacokinetic; Q2W = every 2 weeks; $t_{1/2,z}$ = terminal elimination half-life
Pharmacokinetic parameters are estimated using actual time/dose and presented as geometric mean (% CV), except for $t_{1/2,z}$, which is presented as mean (min - max).
% CV is not presented where N < 3. Individual PK parameters are presented for dose groups with data from only 1 subject.
Values are reported to 3 significant figures except for % CV, which is reported to the nearest integer.
[a] N = 41
[b] N = 4
[c] N = 39
[d] N = 31
[e] N = 28
[f] N = 24
[g] N = 37
[h] N = 27
[i] N = 29
[j] N = 1
[k] N = 23

The observed steady state maximal serum concentrations for tarlatamab at the end of infusion (cycle 2 day 15, cycle 3 day 1 and cycle 4 day 1) and trough serum concentrations (cycle 2 day 15, cycle 3 day 1 through cycle 6 day 1) for the 2 evaluated target dose levels of 10 and 100 mg in the phase 2 study are summarized in Table 6 and Table 7. Overall, tarlatamab demonstrated approximately dose-proportional increases in serum exposures. Steady state in serum tarlatamab exposures was achieved by approximately cycle 2 day 15.

Table 6. Descriptive statistics of steady state tarlatamab peak serum concentrations (µg/mL) at 10 mg or 100 mg Q2W regimen with step dosing

Dose	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 4 Day 1
10 mg	4.61 (38%) [93]	4.57 (36%) [87]	4.73 (34%) [73]
100 mg	43.3 (35%) [46]	49.3 (50%) [39]	46.8 (29%) [39]

CV = coefficient of variation; Q2W = every 2 weeks
Data are presented as Mean (%CV) [N]

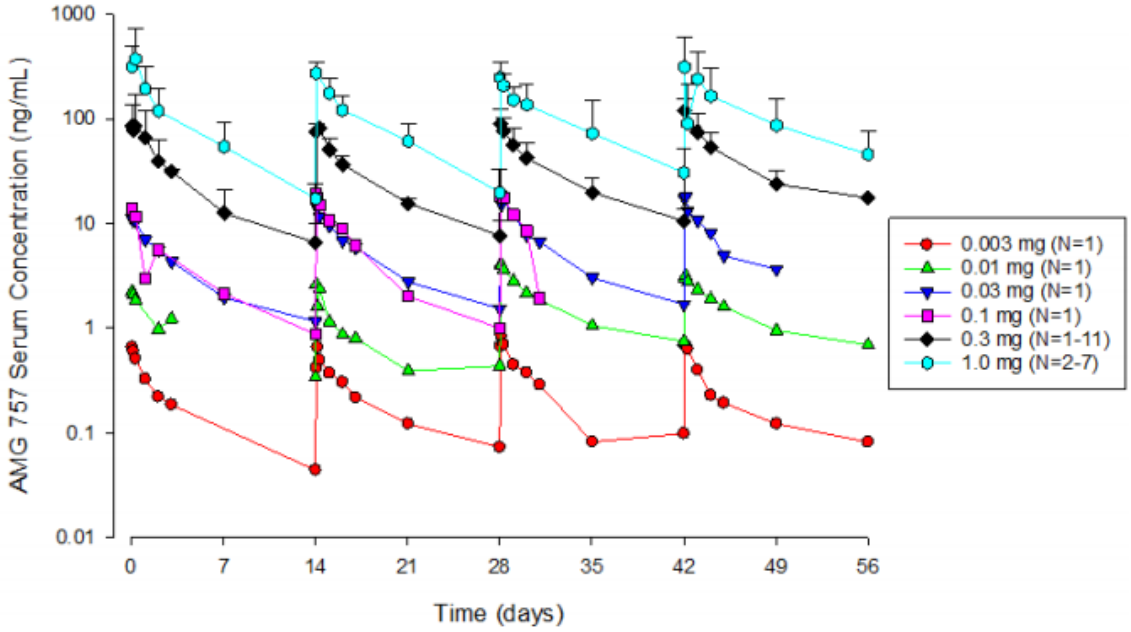
Table 7. Descriptive statistics of steady state tarlatamab trough serum concentrations (µg/mL) at 10 mg or 100 mg Q2W regiment with step dosing

Dose	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 6 Day 1
10 mg	0.514 (42%) [95]	0.525 (90%) [89]	0.604 (63%) [79]	0.600 (47%) [63]	0.666 (53%) [59]
100 mg	8.03 (85%) [47]	7.30 (70%) [42]	7.58 (53%) [41]	7.15 (47%) [35]	7.39 (56%) [29]

CV = coefficient of variation; Q2W = every 2 weeks
Data are presented as Mean (%CV)[N]

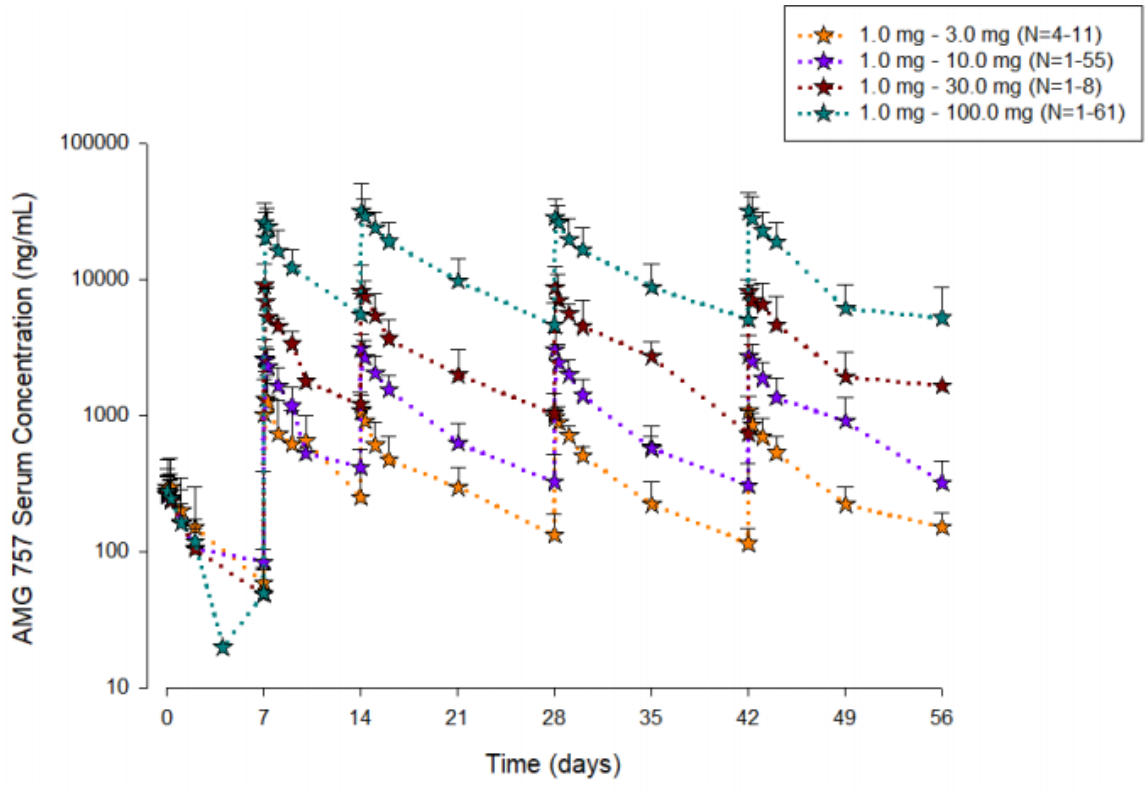
Time dependency was examined in the FIH/phase 1 study 20160323. Mean (+SD) observed serum tarlatamab concentration-time profiles after Q2W dosing regimen (dose range 0.003 mg to 1 mg with no step dose) and after 1-step dosing regimen (target dose range 3 mg to 100 mg) over cycle 1 and cycle 2 of the study are presented in Figure 1 and Figure 2, respectively. Following IV dosing, tarlatamab serum concentrations declined with time in a biphasic manner. Across the evaluated target dose range (0.003 mg to 100 mg Q2W and 200 mg Q3W), the serum tarlatamab exposures increased in an approximately dose-proportional manner with mean (SD) estimated terminal phase elimination half-life of 5.5 (1.6) days. Steady state in serum tarlatamab exposures were achieved approximately cycle 2 day 15.

Figure 1. Mean (±SD) serum tarlatamab concentration-time profiles after administration of tarlatamab using Q2W IV regimen in cycle 1 and cycle 2 (cohorts 1-6)



IV = intravenous; Q2W = every 2 weeks.

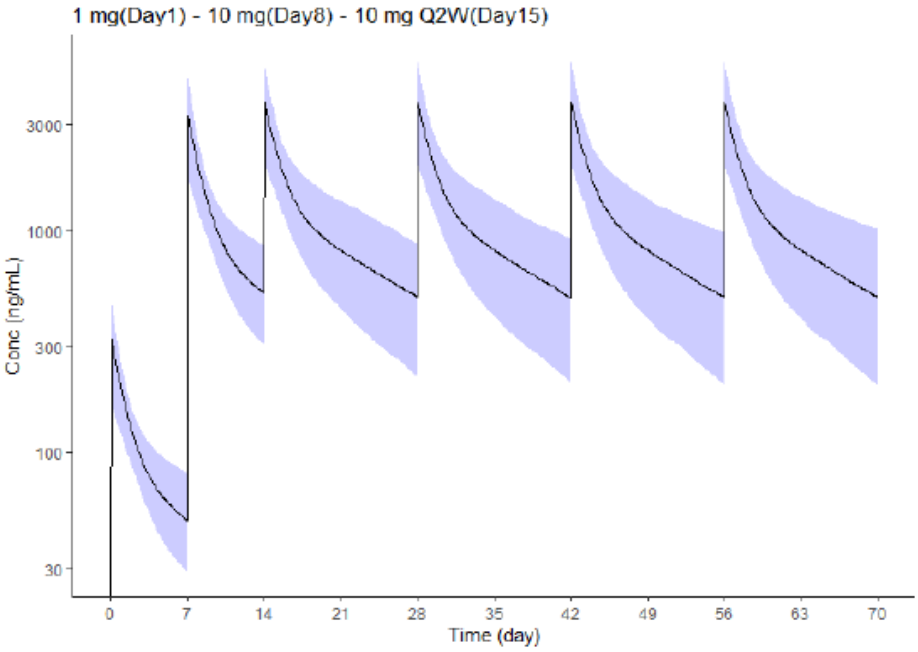
Figure 2. Mean (±SD) serum tarlatamab concentration-time profiles after administration of tarlatamab 1 mg IV (day 1) and 3 to 100 mg IV (days 8/15 and Q2W thereafter) in cycle 1 and cycle 2



IV = intravenous; Q2W = every 2 weeks.

Based on simulated tarlatamab serum concentration-time profiles, tarlatamab exposures after the third dose (D15) were comparable to exposures achieved at steady-state (Figure 3). The effect of ADA on tarlatamab CL is addressed in section 5.2.3.5.

Figure 3. Typical pharmacokinetic profile of tarlatamab following the clinical regimen on 1 mg D1, 10 mg D8/15 and Q2W thereafter



Median is represented by solid black line. 90% prediction interval is represented by the shaded blue area.

5.2.2.9. Pharmacokinetics in the target population

PK has only been documented in patients with SCLC and not in healthy subjects. Descriptive statistics after the different dose regimens in the FIH/phase I study **20160323** are presented in Table 4 and Table 5. Descriptive statistics in the pivotal phase III study **20210004** is presented in table below.

Table 8. Descriptive statistics of steady state tarlatamab serum concentrations following multiple dose IV administration of 10 mg tarlatamab to subjects with relapsed SCLC after platinum-based first-line chemotherapy

Dose (mg)	C_{trough} (µg/mL)	Cycle 2 Day 1	Cycle 4 Day 1	Cycle 6 Day 1
10	Mean	0.515	0.492	0.493
	CV%	75	51	65
	N	186	131	109

Descriptive statistics are presented to 3 significant figures except for CV% and N, which are presented to the nearest integer.

Pharmacokinetics of tarlatamab following multiple dosing was characterized in Study 20160323 (FIH), Study 20200491 (phase 2), and Study 20210004 (pivotal) in subjects with SCLC. Serial intensive samples were collected in the FIH study, while in phase 2 and pivotal study sparse PK samples were collected. Table 9 shows a summary of tarlatamab peak and trough serum concentrations across the 3 studies for the clinical regimen of 10 mg Q2W.

Table 9. Summary of observed tarlatamab steady state peak and trough serum concentration (µg/mL) following the clinical regimen of 10 mg Q2W based on data pooled across studies 20160323, 20200491 and 20210004

	Mean (%CV) [N]			
	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 6 Day 1
C_{max}	3.83 (45%) [N=166]	3.94 (43%) [N=166]	4.15 (43%) [N=136]	--
C_{trough}	0.429 (51%) [N=170]	0.429 (51%) [N=186]	0.542 (77%) [N=251]	0.521 (54%) [N=196]

C_{max} = maximum observed drug concentration; C_{trough} = trough concentration CV = coefficient of variation; Q2W = every 2 weeks
End of infusion samples were not collected after cycle 4.
Data from subjects receiving the 10 mg Q2W regimen (Cohorts 8, 32, and 35) in Study 20160323 were pooled with those from Study 20200491 and 20210004

ECOG and tumour burden were investigated as potential covariates in the popPK model but were not statistically significant. Number of prior anti-cancer therapies was a significant covariate on CL in the final popPK model, but the effect on tarlatamab exposure was not considered clinically meaningful. No dose adjustment based on disease status is recommended. Geometric mean (%CV) of first-dose and steady state PK parameters from the popPK model simulations are presented in Table 10.

Table 10. Pharmacokinetic parameter values of tarlatamab following the clinical regiment 1 mg D1, 10 mg D8/15 and Q2W thereafter

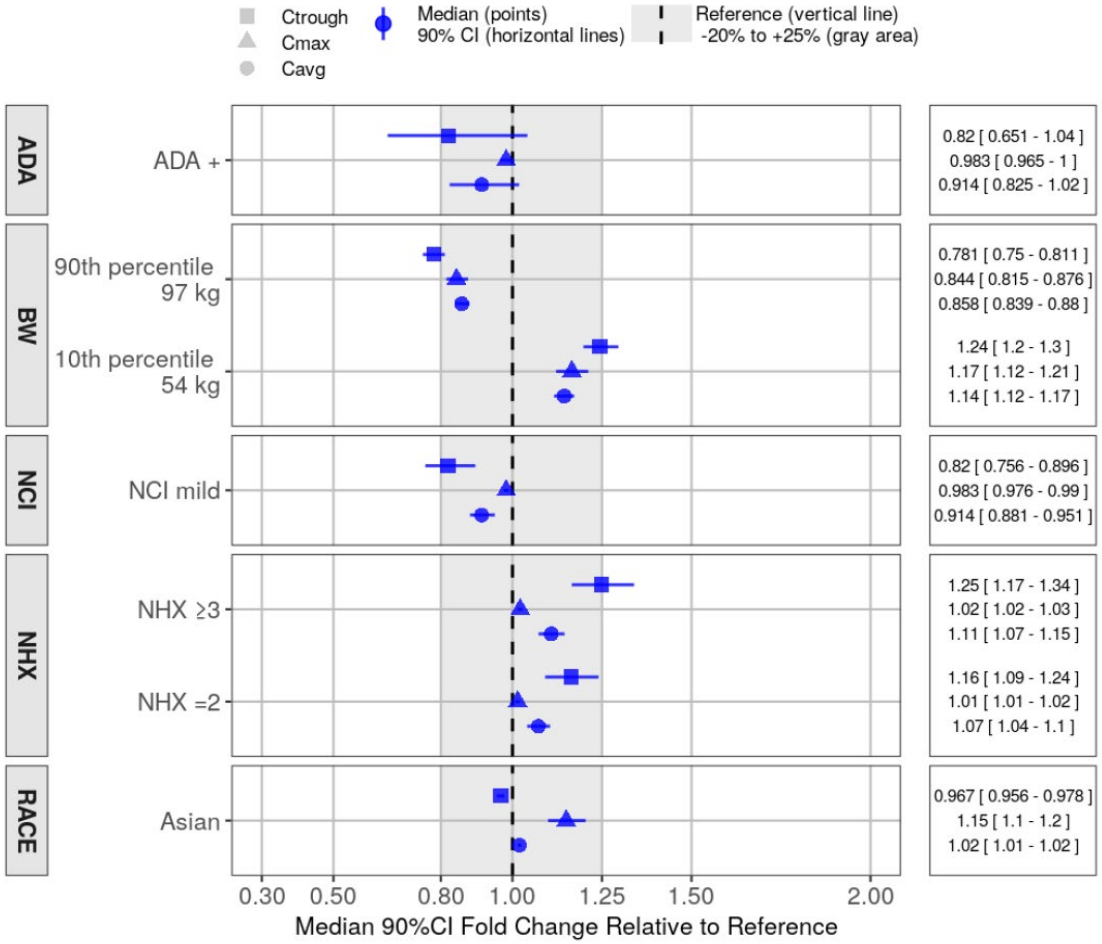
	Parameter*		
	Cavg (ng/mL)	Cmax (ng/mL)	Ctrough (ng/mL)
First step up dose 1mg	106 (26%)	314 (35%)	49 (35%)
First treatment dose 10mg	1100 (26%)	3190 (35%)	517 (36%)
Steady state 10mg every 2 weeks	1040 (37%)	3640 (35%)	472 (62%)

*Parameters are reported as geometric mean (CV%).

5.2.2.10. Special populations

No dedicated studies were performed in special populations. PopPK analysis was used to assess the PK in special populations. Significant covariates in the popPK model included bodyweight, hepatic dysfunction categories, number of prior anti-cancer therapies and presence of anti-drug antibodies as covariates for clearance. Covariates for central volume of distribution were bodyweight and race. In the forest plot below, the influence of covariates on tarlatamab exposures is shown.

Figure 4. Forest plot to demonstrate the impact of statistically significant covariates on tarlatamab exposure metrics (C_{max}, C_{trough}, and $C_{avg, first\ cycle}$) following the clinical regimen



* The simulation was performed with the estimates of the final model using RxODE package in R. The parameters comprising 1,000 samples were generated from normal distributions with the respective estimated parameters and standard errors.

* Tarlatamab exposure metrics are defined as follows: C_{avg} is defined as Cycle 1 C_{avg} (average concentration over the first cycle), C_{max} (maximum concentration over the first cycle), C_{trough} (trough concentration at the end of first cycle)

* The impacts of covariate on C_{avg}, C_{max}, and C_{trough} were shown as % (model-predicted C_{avg}, C_{max}, and C_{trough}) relative to the model-predicted C_{avg}, C_{max} and C_{trough} in the reference subject. The solid horizontal lines represent the 90%CI of the covariate effect. The dashed vertical line represents the reference and shaded gray region represents 80%/125% of the reference.

* The reference subject is defined as a caucasian subject receiving tarlatamab 1 mg D1, 10 mg on D8, D15 and Q2W thereafter with the following covariates: RACE: Caucasian; ADA: negative; BW: 73 kg, NCI: normal; Prior anti-cancer therapy (NHX): 1

* RACE was assessed as a categorical covariate (Asian, Caucasian, Black, Other). Black race and Other race are retained in the model but not shown above; the effect of Black race on exposure is not significant due to small sample size; the effect of Other race on exposure is not interpretable

Gender had no significant effect on the PK of tarlatamab.

Although Asian race was a statistically significant covariate on Vc in the popPK model, the effect on estimated tarlatamab exposures was not considered clinically relevant.

When compared to the tarlatamab concentration in subjects with the median body weight of 72.6 kg, subjects with a bodyweight of 54 kg (representing 10th percentile of observed data) were estimated to have 14% increase in $C_{avg, first\ cycle}$ and subjects with bodyweight of 97 kg (representing 90th percentile of observed data) were estimated to have 14% decrease in $C_{avg, first\ cycle}$. The effect of body weight on

tarlatamab exposures was not considered clinically relevant.

Studied age range was 20-86 years (65-74 years: n=263, 75-84 years: n=57, ≥85 years: n=1). Population PK analysis showed that age had no significant effect on the PK of tarlatamab.

In the population PK analyses, number of prior anti-cancer therapies and antidrug antibody status were significant covariates on the clearance of tarlatamab, but the effect on tarlatamab exposure was not considered clinically relevant.

Positive binding ADA status was identified as significant time-varying covariate on tarlatamab clearance. In total, 82 individuals with evaluable PK and positive ADA binding status at any time during the study. The effect of ADA on tarlatamab exposure was not considered clinically relevant.

5.2.2.11. Pharmacokinetic interaction studies

Drug-drug interactions (DDI) studies were not performed due to lack of relevance with protein therapeutics.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Tarlatamab is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager that binds to DLL3 expressed on the surface of tumour cells and CD3 expressed on the surface of T-cells. The bispecific binding of tarlatamab to T-cells and DLL3-positive tumour cells triggers T-cell activation, production of inflammatory cytokines, and release of cytotoxic proteins, which results in redirected lysis of tumour cells.

The selected pharmacodynamic (PD) markers are deemed relevant to the MoA, and the description in the SmPC appears adequate.

5.2.3.2. Primary and secondary pharmacology

Primary pharmacology

Pharmacodynamic (PD) biomarker analyses were conducted across Phase 1 (study 20160323), Phase 2 (DeLLphi-301, study 20200491), and Phase 3 (DeLLphi-304, study 20210004) studies demonstrating immune activation through T-cell redistribution, activation, and cytokine secretion.

Tarlatamab induced transient declines in peripheral CD3+ T-cell levels shortly after infusion, followed by varying degrees of recovery in all 3 studies (data not shown) In the Phase 3 study, T-cell levels normalized in subsequent cycles, indicating transient effects. Similarly, in the Phase 1 study, non-extended intravenous (non-eIV) cohorts showed recovery to baseline levels by Day 8 and Day 15, while extended IV infusion (eIV) cohorts demonstrated sustained reductions below baseline during continuous infusion periods. In the Phase 2 study dose-dependent effects were observed, with the 100 mg group exhibiting a greater and statistically significant reduction in T-cell levels compared to the 10 mg group. T-cell levels in the 100 mg group did not fully recover to baseline in subsequent cycles.

Activation of CD8+ T-cells, was consistently observed across all studies, peaking within 6–24 hours post-infusion.

Cytokine analyses revealed transient elevations in inflammatory markers, including interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-8 (IL-8), and interleukin-2 (IL-2) within 24–48 hours post-infusion.

Secondary pharmacology

Effect on QTc interval

The PK time-matched QTcF analysis dataset consisted of 295 patients who had time-matched PK and triplicate QTcF measurements, and a predose baseline QTcF measurement on day 1. A linear mixed-effect model with inter-subject variability on intercept and slope best described the relationship between tarlatamab exposure and change in QTcF from baseline (ΔQTcF). A significant shallow trend between tarlatamab concentration and QTcF was observed (slope = 7.10e-05, p-value = 0.0112). However, the model-predicted mean change in QTcF at the model-estimated steady state C_{max} of 3780 ng/mL following the proposed clinical regimen of 10 mg Q2W of tarlatamab was +0.268 milliseconds (90% CI: 0.0947, 0.442), suggesting that tarlatamab exposure is not associated with clinically significant increases in QTc interval (e.g., > 20 ms).

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Dedicated DDI studies of tarlatamab have not been performed.

5.2.3.4. Genetic differences in PD response

Not applicable.

5.2.3.5. Immunological events

Immunogenicity, including ADA against tarlatamab, was assessed across all the three clinical studies (20160323, 20200491, and 20210004), while neutralising antibodies (Nab+) were assessed in the phase 2 and phase 3 studies but not in the phase 1 study.

Across all clinical studies utilising the proposed 10 mg target dose of tarlatamab, the overall incidence of treatment-emergent ADA (TE-ADA) was low, observed in 7.7% (34/444) of the subjects. Among these, 9 subjects (26.5%) had "transient" antibody responses that reverted to an ADA negative status by the last on-study assessment. In addition, 36 of 468 subjects (7.7%) with results at baseline had pre-existing antitarlatamab binding antibodies at baseline before administration of tarlatamab. In the phase 2 and phase 3 studies, 7.5% (27/359) of patients developed TE-ADA, of which 3.1% (11/359) were positive for Nab+. No subject had Nab+ at baseline.

Impact of Immunogenicity on PK, Efficacy and Safety

Among patients receiving the proposed regimen of 10mg Q2W, tarlatamab peak and trough serum concentrations (central tendency and distribution) were comparable between subjects who were ADA-positive and ADA-negative over time. In the popPK analysis, 12% (82/702) of the patients were registered as ADA positive (including 36 patients who were ADA positive at baseline). The effect of ADA on tarlatamab CL was statistically significant, and ADA-positive subjects were estimated to have approximately 9% lower $C_{avg,first\ cycle}$. These results indicate that ADA development does not result in a clinically relevant impact on tarlatamab exposure.

The potential impact of ADA development on the clinical efficacy and safety of tarlatamab was assessed using data from the three clinical studies (20160323, 20200491, and 20210004). The analysis included efficacy endpoints such as objective response rate (ORR), disease control rate (DCR),

duration of response (DOR), progression-free survival (PFS), and overall survival (OS), as well as treatment-emergent adverse events (TEAEs) to evaluate safety.

Across the studies, some variability in efficacy endpoints, including ORR, DOR, and PFS, was observed between ADA-positive and ADA-negative subjects. However, these variations were inconsistent, and the overall efficacy outcomes appeared comparable between the two groups. Subgroup analyses further confirmed that the presence of ADA, including Nab+, did not have a clinically relevant impact on efficacy across the three studies.

Safety analyses revealed no significant differences in the frequency or severity of AEs between ADA-positive and ADA-negative subjects. The incidence of TEAEs, serious AEs, and grade ⩾3 AEs was similar across the groups. Furthermore, no distinct safety signals were identified in subjects who developed Nab+.

In conclusion, the reporting of immunogenicity was conducted in accordance with the *Guideline on Immunogenicity assessment of therapeutic proteins* (EMEA/CHMP/BMWP/14327/2006 Rev 1). The clinical ADA analyses indicate that the incidence of TE-ADA was low (<10%) in the target patient population at the proposed posology, with 26.5% of these being transient responses. The available data suggest no clinically relevant impact of ADA, including Nab+, on the PK, efficacy, or safety of tarlatamab. However, the limited number of ADA-positive subjects imposes constraints on the robustness of the conclusions, and the data should be interpreted with caution.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Exposure-response (ER) analyses were performed to characterize the relationships between tarlatamab serum exposures and key efficacy and safety endpoints and to identify potential covariates affecting the ER relationships.

A Cox proportional hazards regression model was used to characterize the ER relationships for time-to-event endpoints (overall survival [OS], progression-free survival [PFS], and duration of response [DOR]). A log-linear logistic model and an Emax model were evaluated to characterize the ER relationships for probability of achieving objective response (partial response [PR] or complete response [CR]) and disease control (stable disease [SD], PR, or CR)), and a log-linear model and an Imax model were evaluated for continuous efficacy endpoints (best tumor size response [BTSR]).

Significant ER relationships were identified for OS, PFS, objective response rate (ORR), disease control rate (DCR) and BTSR across the evaluated dose range of 0.003 mg to 100 mg Q2W or 200 mg Q3W. Higher tarlatamab exposure was associated with lower hazard of OS and PFS events, and higher magnitude of anti-tumor activity as measured by ORR, DCR and BTSR. The ER relationships for these efficacy endpoints reached a plateau at the 2nd exposure quartile for tarlatamab (corresponding to 10 mg Q2W exposure).

To evaluate ER relationships for safety endpoints, including probability of experiencing grade ≥ 3 treatment emergent adverse event (TEAE), grade ≥ 3 treatment related adverse event (TRAE), grade ≥ 3 TEAE of interest (neutropenia, neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS)), log-linear logistic regression models were used.

No significant positive ER relationship was identified for grade ⩾ 3 TEAE, grade ⩾ 3 TRAE, grade ⩾ 3 neurologic toxicity including ICANS, or grade ⩾ 3 CRS. A significant ER relationship was identified for neutropenia with a higher percentage of patients experiencing grade ⩾ 3 neutropenia with increasing tarlatamab exposures (6-7% in exposure quartiles 1-2, 14% in exposure quartiles 3-4).

5.2.5. Dose selection and therapeutic window

The clinical dose and dosing regimen for tarlatamab for the treatment of adult subjects with extensive stage (ES)-SCLC with disease progression on or after platinum-based chemotherapy is an initial 1 mg dose on day 1, followed by 10 mg on day 8, day 15, and Q2W thereafter, all doses administered via a 1-hour IV infusion. This selection was based on an interim analysis of Study 20200491, in which 10 mg and 100 mg doses were evaluated following dose exploration in study 20160323.

Selection of 10 mg and 100 mg dose levels administered as Q2W regimen evaluated in part 1 of phase II study 20200491

The totality of data from the dose exploration and expansion parts of Study 20160323 supported the selection of 2 target dose levels of 10 and 100 mg Q2W to be further characterized in Study 20200491. Within the evaluated target dose range, a numerical benefit associated with 10 mg Q2W exposures relative to lower target doses of 3 mg or 1 mg administered as a Q2W regimen was observed. The analysis also displayed numerical benefit in disease control rate (DCR) with exposures associated with 100 mg Q2W regimen, relative to 10 mg Q2W regimen, and therefore supported the selection of 100 mg as the higher dose level (in addition to 10 mg) to be evaluated in Study 20200491. Importantly, from a safety and tolerability perspective, a maximal tolerated dose level was not achieved in Study 20160323, within the evaluated target dose range of 0.003 to 100 mg administered Q2W (or 200 mg Q3W). In summary, these analyses, in addition to the overall manageable safety and tolerability profile of tarlatamab, supported the selection of 10 and 100 mg Q2W target doses to be further evaluated in Part 1 of Study 20200491.

Selection of 10 mg Q2W regimen at the prespecified interim analysis in study 20200491

Of the two target dose levels assessed in Part 1 of Study 20200491, 10 mg Q2W regimen was selected for further evaluation in Part 2 and Part 3 and subsequent monotherapy studies. Part 1 of the Study 20200491 was designed to evaluate the safety and efficacy of 10 and 100 mg doses of tarlatamab. A prespecified interim analysis was conducted to select 1 of the 2 doses for further evaluation after 30 subjects per arm were enrolled and had received at least 1 dose of tarlatamab and had the opportunity to confirm objective response after the first post-treatment scan (or had up to 13 weeks of follow-up). At the time of interim analysis, a total of 127 subjects had enrolled in Part 1 of Study 20200491. Of these, 125 subjects received at least 1 dose of tarlatamab and were included in the Safety Analysis Set, and 63 subjects met the criteria for inclusion in the Interim Efficacy Analysis Set. Briefly, measures of efficacy response were similar between the 10 mg and 100 mg groups. In the 10 mg group, the confirmed objective response rate (ORR) (assessed by the Investigator) was 34.4% (95% CI: 18.6, 53.2), and the DCR was 75.0% (95% CI: 56.6, 88.5). In the 100 mg group, the confirmed ORR was 35.5% (95% CI: 19.2, 54.6), and the DCR was 64.5% (95% CI: 45.4, 80.8).

Compared with the 100 mg group, subjects in the 10 mg group experienced fewer treatment-emergent adverse events leading to discontinuation of tarlatamab, fewer serious adverse events, and fewer fatal adverse events. Consistent with the dose-response data, exposures with the 10 mg target dose regimen were associated with improved tolerability but comparable efficacy relative to the 100 mg dose. Data from the pivotal study (20210004) confirms the selection of 10 mg Q2W as the optimal dose with regards to safety and efficacy.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioanalytical methods

Both the PK determination method and the immunogenicity assays for tarlatamab are considered robust, validated, and compliant with ICH M10 and the EMA immunogenicity guideline. The overall bioanalytical strategy is appropriate and provides confidence that pharmacokinetics as well as binding and neutralizing antibodies are reliably assessed, supporting the adequacy of the clinical development program.

Both ADA assays, the electrochemiluminescence (ECL)-based and the cell-based neutralising antibody (NAb) assay formats, rely on the inhibition of tarlatamab binding to its two targets: DLL3 and CD3. While this approach is suitable for detecting antibodies that directly interfere with the target-binding function of the molecule, it may fail to detect neutralising or binding antibodies directed against other non-humanised or immunogenic regions of the molecule. However, since the entire tarlatamab molecule was used both as the detection reagent (biotin- and ruthenium-labelled) and as the spiking reagent in the confirmatory assay, all anti-drug antibodies (ADAs), including those binding to non-target domains, could be detected by the method.

In conclusion, the PK and immunogenicity assays for tarlatamab were developed and validated in line with ICH M10 and EMA/FDA immunogenicity guidance. The methods were robust, fit for purpose, and reliably supported the assessment of pharmacokinetics, binding antibodies, and neutralizing antibodies across phase 1, 2, and pivotal phase 3 clinical studies.

Population PK analysis

The PopPK analysis dataset included 11,805 post–first-dose PK samples from 702 patients, of which 99.7% were measurable and 0.29% were below the limit of quantitation (BLQ); while exclusion of the 34 BLQ samples was considered acceptable, an additional 99 measurable samples (0.84%), including 60 flagged as "illogical" based on visual inspection, were excluded, 81 of which originated from Study 20160323. However, Study 20160323 was a large and complex first-in-human (FIH) study with multiple dosing regimens and sampling schemes, which may account for the higher number of exclusions, and a cross-study review of these exclusions did not indicate the presence of systematic issues, including study-site-related systematic deviations. Tarlatamab PK was characterized by a 2-compartment model with first order elimination. Estimated parameters were CL, V1, Q and V2. The covariates included on CL in the model were baseline bodyweight, mild hepatic dysfunction, number of prior lines of anticancer therapies and presence of anti-drug antibodies, and the covariates included on V1 were bodyweight and ethnicity.

PopPK parameters were in general estimated with acceptable precision. Goodness-of-fit plots showed an acceptable fit. The η-shrinkage was acceptable for CL and V1 (11-16%). Overall, the prediction-corrected VPCs indicate that the model captures both the central tendency and variability of observed data, suggesting no significant trends over time or over included body weight ranges.

The popPK model appears fit for purpose to estimate PK parameters and to evaluate clinical relevance of covariates on the PK of tarlatamab in SCLC patients.

Bioavailability

As tarlatamab is administered by the IV route, it is 100% bioavailable by definition. Absolute bioavailability, in vitro-in vivo correlation and the effect of food on PK are not relevant for drug

products that are administered by IV route and no such studies have thus not been conducted.

Distribution

PK sampling appears to have been too sparse to generate V_d or V_z based on the observed data and no such values are reported. PopPK analysis provided a volume of distribution (8.19 L) that is consistent with what is known for larger proteins where V_{ss} generally is similar to the distribution of albumin (0.1 L/kg).

Metabolism

Tarlatamab is to be administered parenterally and expected to be cleared by protein catabolism, thus, metabolism does not contribute to its clearance.

Elimination

Estimated clearance derived from popPK analysis was 0.728 L/day and terminal half-life estimated from the popPK model was 10.6 days.

The terminal half-life reported from NCA analyses was approximately 5 days for the recommended dose regimen and is probably under-estimated due to sparse sampling. The Applicant has not provided any data on CL; however, this is probably also related to sampling being too sparse to generate such a parameter.

Dose proportionality and time dependency

Tarlatamab exhibited approximate dose proportional PK among the evaluated IV dosing regimens at steady state (0.003-1 mg Q2W [only a single subject included for the 0.003-0.1 mg dose range]; 1 mg day 1 + 3-100 mg day 8/15 and Q2W thereafter). Furthermore, there was no indication of time-dependent kinetics. Dose proportionality and time dependency after single dosing was not studied; however, this is considered acceptable given administration of 1 mg step-dose at treatment initiation to reduce the risk for CRS. However, it is difficult to draw conclusions due to the sparse sampling.

Pharmacokinetics in target population and therapeutic window

All clinical studies were performed in patients with SCLC. Disease-related factors (type and state of the disease) are known drivers of variability in mAb clearance, but neither ECOG status nor tumour burden were significant covariates for tarlatamab CL in the popPK model.

No no-effect boundary in terms of dose/exposure or dosing interval was detected in humans in vivo. From a safety and tolerability perspective, a maximal tolerated dose level was not achieved in Study 20160323, within the evaluated target dose range of 0.003 to 100 mg administered Q2W. Therefore, no therapeutic window can be determined.

Special populations

Renal function

The degree of renal impairment was classified in accordance with the EMA guideline on PK in renal impairment (EMA/CHMP/83874/2014). As tarlatamab is a large protein (~105kDa), elimination is not expected to be affected by renal impairment. Based on popPK analysis tarlatamab clearance is not affected by mild or moderate renal impairment. This is agreed. No data was available in patients with severe renal impairment.

Hepatic function

Based on popPK analysis mild hepatic impairment was a statistically significant covariate on tarlatamab clearance, but the effect on tarlatamab serum concentration was not clinically relevant.

Very limited data are available in patients with moderate hepatic impairment, and no data are available in patients with severe hepatic impairment.

Gender

Based on popPK analysis there was no difference in CL or Vc between genders.

Ethnic factors

The Applicant has provided observed PK data from the Chinese cohort included in the phase 3 study. However, the submission contained little to no description of the data or the associated statistical methods used in the Chinese substudy. No comparative analysis of PK exposures between ethnic groups has been provided.

Although Asian race was a statistically significant covariate on Vc in the popPK model, the effect on estimated tarlatamab exposures was not considered clinically relevant. This is agreed.

A limited number of patients with African origin were included.

Weight

The effect of BW on tarlatamab PK was evaluated by popPK analysis. The range of BW (34.9 kg to 149 kg) included in the popPK dataset appears sufficient for this purpose.

The final popPK model included BW as a significant predictor of both clearance and volume of distribution (Vc), but the effect of BW on tarlatamab exposures was not considered clinically relevant.

Elderly

Based on popPK analysis age was not a predictor of tarlatamab PK. It is not to be expected that the PK of tarlatamab in elderly patients is different compared to younger patients. There were sufficient subjects in the dataset older than 65 years (age 65-74 n=263, age 75-84 n=57, age ≥85 n=1).

Number of prior anti-cancer therapies

In the pop PK analyses, number of prior anti-cancer therapies was a significant covariate on the clearance of tarlatamab. The Forest plot in Figure 4 for tarlatamab exposures shows that the effect of prior anti-cancer therapies on C_{avg} was not clinically relevant.

Antidrug antibody status

In the pop PK analyses, ADA status was a significant covariate on the clearance of tarlatamab. The Forest plot in Figure 4 for tarlatamab exposures shows that the effect of ADA status on C_{avg} was not clinically relevant.

Pharmacokinetic interaction studies

No dedicated DDI studies were performed. However, in the SmPC it is stated in section 4.5: Initiation of IMDYLLTRA treatment causes transient release of cytokines that may suppress CYP450 enzymes and may result in increased exposures of concomitant CYP substrates. Patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, should be monitored for known adverse events. The dose of the concomitant drug should be adjusted as needed. This is agreed.

Pharmacodynamics

Primary pharmacology

The pharmacodynamic (PD) biomarker analyses conducted across Phase 1 (20160323), Phase 2 (DeLLphi-301 study 20200491), and Phase 3 (DeLLphi-304 study 20210004) studies demonstrated immune activation through T-cell redistribution, activation, and cytokine secretion. $CD3^+$ T cells represent the total T-cell population, $CD8^+$ cells identify the cytotoxic subset, and CD69 and PD-1 are markers of activation and potential exhaustion, respectively. Therefore, it was noted that in Study 20210004 PD-1 expression was significantly upregulated during the treatment period with the lower 10 mg dose schedule. However, these early biomarker observations (Cycle 2 Day 15 pre-dose and Cycle 4 Day 1 pre-dose) do not allow firm conclusions to be drawn regarding long-term clinical outcomes.

Tarlatamab induced transient declines in peripheral CD3+ T-cell levels shortly after infusion, followed by varying degrees of recovery in all 3 studies. In the Phase 3 study, T-cell levels normalized in subsequent cycles, indicating transient effects.

In the Phase 1 study, data from non-extended intravenous (non-eIV) administration showed rapid recovery of T-cell levels to baseline by Day 8 and Day 15. In contrast, extended intravenous (eIV) infusion cohorts exhibited sustained reductions in T-cell levels below baseline during continuous infusion periods, suggesting that the method of administration impacts the degree of T-cell redistribution.

In the Phase 2 study dose-dependent effects were observed, with the 100 mg group exhibiting a greater and statistically significant reduction in T-cell levels compared to the 10 mg group. Notably, T-cell levels in the 100 mg group did not fully recover to baseline in subsequent cycles, suggesting a prolonged PD effect. Activation of CD8+ T-cells, was consistently observed across all studies, peaking within 6–24 hours post-infusion.

Cytokine analyses revealed transient elevations in inflammatory markers, including interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-8 (IL-8), and interleukin-2 (IL-2) within 24-28 hours post-infusion, indicating that tarlatamab induces an immune response without sustained prolonged immunosuppression.

Secondary pharmacology

In general, monoclonal antibodies have a low likelihood of direct ion channel interactions, and the provided data do not suggest that tarlatamab exposure is associated with clinically significant increases in QTc interval.

Immunological events

The available data indicate that TE-ADA was commonly detected, with no evidence of clinically significant impact on the PK, efficacy, or safety of tarlatamab. However, the small number of ADA-positive patients makes it difficult to draw definitive conclusions. These findings have been reflected in section 5.1 of the SmPC.

Exposure-response relationships

Significant ER relationships were identified for several efficacy variables. Higher tarlatamab exposure was associated with lower hazard of PFS and OS events, and higher magnitude of anti-tumor activity as measured by ORR, DCR and BTSR. The exposure–response analysis confirms the findings of the dose-finding studies, demonstrating that the maximal therapeutic benefit of tarlatamab is achieved with the 10 mg Q2W dosing regimen; no further efficacy gains are observed at higher doses. The exposure–effect curve for best tumour size response reaches a plateau at the 10 mg dose, indicating that maximal tumour reduction is achieved. At higher exposures, an inverse trend is observed for

key clinical outcomes, including objective response rate (ORR) and disease control rate (DCR). However, these higher concentrations are primarily associated with the 100 mg dose regimen. While this trend may raise questions regarding the validity of the proposed PK/PD model at higher exposures, the observed deviation from the predicted response is of no practical relevance, as the 100 mg dose regimen is not proposed due to efficacy and safety considerations.

The product information does not recommend DLL3 testing to guide tarlatamab therapy, despite the presumed mode of action requiring the presence of DLL3 receptors on the surface of tumour cells. The absence of a requirement for DLL3 testing is justified by the observation that, although efficacy parameters were consistently lower in patients with DLL3 expression <25% compared with higher expression categories across datasets, some antitumour activity was still observed. However, in the absence of information on the performance characteristics of the applied DLL3 assay (e.g. sensitivity and specificity), it cannot be assessed how many patients enrolled in the clinical trials were truly DLL3-negative. While the Applicant stated that an industry-standard, certified DLL3 assay was used, no quantitative assay performance data were provided.

No significant positive ER relationship was identified for grade $\geqslant$ 3 TEAE, grade $\geqslant$ 3 TRAE, grade $\geqslant$ 3 neurologic toxicity including ICANS, or grade $\geqslant$ 3 CRS. A positive ER relationship was identified for neutropenia such that a higher percentage of patients experienced grade $\geqslant$ 3 neutropenia with increasing tarlatamab exposures. However, a more detailed quantitative analysis of the relationship between tarlatamab exposure and neutropenia was not feasible, as neutropenia events were actively managed as they emerged across all clinical studies.

An inverse relationship between cytokine release syndrome (CRS) and plasma concentrations was observed, with a lower probability of CRS at higher concentrations. This pattern may have been influenced by the inclusion of data from the initial 1 mg step-up dose in the analysis. A more detailed quantitative assessment of factors relevant to CRS was not feasible, as CRS events were actively managed as they emerged.

Dose selection and justification

Dose selection was based on an interim analysis of the phase II study 20200491, in which 10 mg and 100 mg doses were evaluated following dose exploration in the FIH/phase I study 20160323. From a safety and tolerability perspective, a maximal tolerated dose level was not achieved in Study 20160323, within the evaluated target dose range of 0.003 to 100 mg administered Q2W (or 200 mg Q3W). Further, the Applicant describes that compared with the 100 mg group, subjects in the 10 mg group experienced fewer treatment-emergent adverse events leading to discontinuation of tarlatamab, fewer serious adverse events, and fewer fatal adverse events. Consistent with the dose-response data, exposures with the 10 mg target dose regimen were associated with improved tolerability but comparable efficacy relative to the 100 mg dose. Data from the pivotal study (20210004) confirms the selection of 10 mg Q2W as the optimal dose with regards to safety and efficacy. Since the proposed posology was used in the pivotal study, the provided data can be acceptable.

The results of the pooled ER analysis across 20160323, 20200491 and 20210004 concludes that the proposed clinical regimen of 10 mg Q2W reached an efficacy plateau with a manageable safety profile. This is agreed.

5.2.6.2. Conclusions

The pharmacodynamic results supported the mechanism of action for tarlatamab as a bispecific T-cell engager. The ability to activate and mobilize both T-cells and a cytokine response was

demonstrated. The T-cell and cytokine effects were in general transient and did not lead to prolonged immunosuppression.

Overall, the pharmacokinetics of tarlatamab have been adequately investigated.

5.3. Clinical efficacy

5.3.1. Dose response studies

See section 5.2.5. Dose selection.

5.3.2. Main study

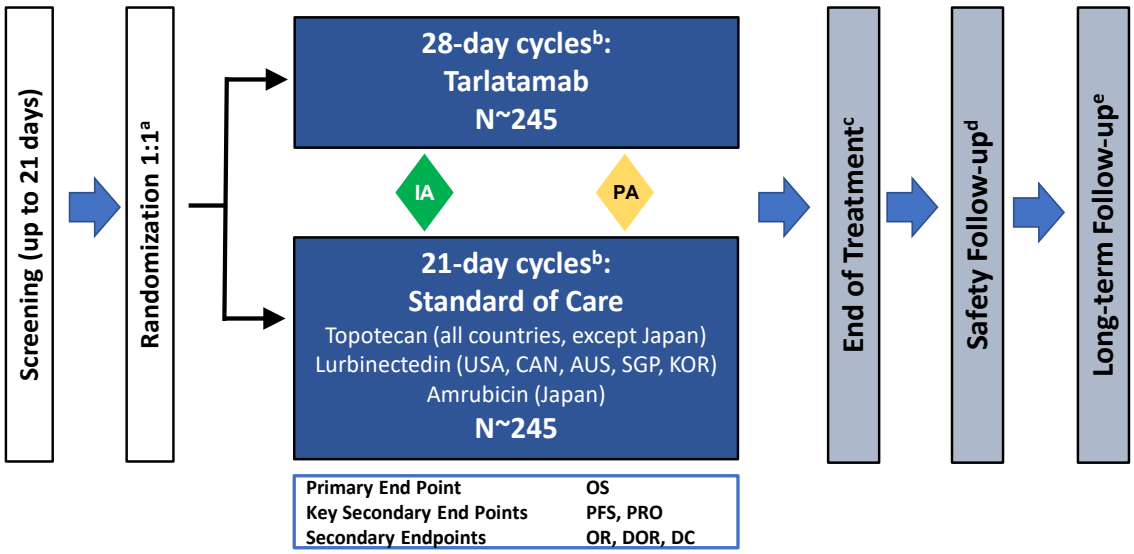
5.3.2.1. Study 20210004 (DeLLphi-304)

5.3.2.1.1. Study title

A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects with Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy

5.3.2.1.2. Study design

Figure 5. Study schema



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

imaging visit, whichever is later, for up to 3 years from last subject enrolled, or 1 year from the subject's last dose of study treatment, whichever is later.

Treatment

Tarlatamab was administered as a 60-minute intravenous (IV) infusion with a step dose (1 mg tarlatamab) on cycle 1 day 1 (C1D1) followed by 10 mg target dose on cycle 1 day 8 (C1D8) and C1D15, and every 2 weeks (Q2W) thereafter (i.e. D1/D15) in a 28-day cycle. Dexamethasone (8 mg IV or equivalent) was administered within 1 hour prior to tarlatamab infusion on C1D1 and C1D8. Intravenous hydration (1 L normal saline over 2 to 4 hours) was administered following tarlatamab doses on C1D1 and C1D8.

Standard of care was administered as follows in a 21-day cycle:

- Lurbinectedin (US, Canada, Australia, Singapore, and Korea) was administered as 3.2 mg/m2 IV on day 1 every 3 weeks
- Topotecan (all countries, except Japan and China) was administered as IV at 1.5 mg/m2 or oral at 2.3 mg/m2/day on days 1, 2, 3, 4, and 5 every 3 weeks
- Topotecan (China) was administered as IV at 1.2 mg/m2 or other locally approved dose or oral at 2.3 mg/m2 /day on days 1, 2, 3, 4, and 5 every 3 weeks
- Amrubicin (Japan) was administered as 40 mg/m2 IV on days 1 to 3 every 3 weeks

Subjects would receive study treatment until investigator-determined radiographic disease progression per RECIST 1.1, unacceptable toxicity, withdrawal of consent, death, or end of study.

Tumour assessments were performed every 6 weeks for the first 48 weeks and every 12 weeks thereafter.

Randomisation

Subjects were randomized in a 1:1 allocation ratio, to receive tarlatamab or SOC chemotherapy (lurbinectedin or topotecan in US, Canada, Australia, Singapore, Korea; amrubicin in Japan; or topotecan in all countries except Japan), respectively, in an open-label manner. For subjects randomized to the SOC chemotherapy group in US, Canada, Australia, Singapore, and Korea, lurbinectedin or topotecan was selected for treatment based on investigator discretion.

The stratification factors were:

- prior anti-PD-(L)1 exposure (yes vs no)
- chemotherapy-free interval (≥180 days, <180 to ≥90 days, or <90 days)
- presence (previous or current) of brain metastases (yes or no)
- standard of care (topotecan/amrubicin vs lurbinectedin)

Blinding

This is an open-label study. To maintain trial integrity of the study, post-baseline data analyses of primary and key secondary endpoints were not produced or reviewed by the study team prior to interim/primary analysis snapshot analysis.

Patient population

Main inclusion criteria

- Histologically or cytologically confirmed SCLC with demonstrated progression or relapse.
- Subject has progressed or recurred following 1 platinum-based regimen:
  - documented first disease progression must be during or following first-line platinum-based systemic chemotherapy for extensive stage (ES) or limited stage (LS) disease
  - patients who received treatment for LS disease who recur are eligible
  - patients who received adjuvant Platinum-Etoposide (EP) after resection of their SCLC who recur are eligible
  - in countries where SOC first-line systemic treatment for ES disease includes platinum containing chemotherapy in combination with PD-(L)1 inhibitor, it is required that patients have failed PD-(L)1 inhibitor as part of their first-line systemic treatment or are ineligible to receive PD-(L)1 inhibitor therapy
- Measurable disease as defined per RECIST 1.1 within the 21-day screening period.
- Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1.
- Minimum life expectancy of 12 weeks.

Main exclusion criteria

- Disease related symptomatic central nervous system (CNS) metastases:
- Prior history of immune checkpoint inhibitors resulting in any severe or life-threatening immune-mediated adverse event
- Active autoimmune disease that has required systemic treatment (except replacement therapy) within the past 2 years or any other diseases requiring immunosuppressive therapy while on study.
- Myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months prior to first dose of study treatment.
- History of arterial thrombosis within 12 months prior to first dose of study treatment.
- Presence/history of viral infection with some exceptions as specified in the protocol.
- Acute and/or uncontrolled active systemic infection as specified in the protocol.
- Evidence of interstitial lung disease or active, non-infectious pneumonitis.
- History of other malignancy within the past 2 years prior to first dose of tarlatamab
- Major surgery within 28 days of first dose of tarlatamab

5.3.2.1.3. Objectives and estimands

Primary objective

The primary objective of the study was to compare the efficacy of tarlatamab with SOC chemotherapy on prolonging OS. The protocol or Statistical Analysis Plan (SAP) does not state the hypothesis for the

primary objective. However, from the sample-size estimation and interim analysis plan it can be seen that superiority was intended to be tested.

Estimand for the primary objective

Table 11. Estimand for primary objective

	Subjects with relapsed small cell lung cancer (SCLC) after platinum-based first-line chemotherapy.
Treatment condition<s>	Assignment to Tarlatamab, regardless of discontinuation, compared to assignment to Standard of Care Chemotherapy, regardless of discontinuation.
Endpoint (variable)	Overall Survival (OS) defined as time from randomization until death from any cause.
Population-level summary	Hazard ratio (HR)
Intercurrent events and strategy to handle them	
Start of new anti-cancer	Treatment policy, OS will be estimated regardless of subsequent anti-cancer therapy.

The primary estimand was hazard ratio of OS between tarlatamab and SOC, for subjects with relapsed SCLC after platinum-based first-line chemotherapy, regardless of subsequent anti-cancer therapy.

Statistical methods for estimation and sensitivity analysis on primary estimand

Analysis sets

The ITT analysis set included all randomized subjects, analysed according to the randomized treatment arm. The ITT analysis set was used for primary and secondary efficacy endpoints, unless specified otherwise.

The safety analysis set included all subjects who took at least 1 dose of investigational product. Subjects were analysed according to the investigational product they actually received.

Planned analyses

The timing for the primary analysis of OS was event driven and planned to take place when approximately 345 OS events were reached cumulatively in the 2 treatment groups. An interim analysis was planned when 259 cumulative events had occurred. If OS achieved statistical significance at the interim analysis, key secondary endpoints (PFS and PRO) were to be tested hierarchically. The final analysis occured when enrolment was complete and each subject completed the study, including LTFU.

The analysis of the OS primary endpoint was made using a stratified log-rank test controlling for two of the four randomization stratification factors, presence (previous or current) of brain metastases (yes or no) and chemotherapy-free interval (collapsed into < 90 days and ≥ 90 days) using the intent-to-treat (ITT) analysis set. The HR and its 95% CI was estimated using a Cox proportional hazards model with the same stratification. The distribution of OS, including the median and quartiles was characterized using the Kaplan-Meier method and their corresponding 95% CIs presented (Brookmeyer and Crowley method). The OS rates for selected landmarks (e.g. 1 year and 2 years) was reported with the 95% CIs.

For OS, a sensitivity analysis was performed using stratification factors as recorded in CRF instead of

IVRS.

Secondary objectives

A secondary objective was to compare the efficacy of tarlatamab versus SOC as assessed by progression-free survival (PFS), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

A secondary objective was to compare the treatment effect of tarlatamab with SOC on Patient reported disease-related symptoms, Physical Function, and Quality of Life.

Estimands for the secondary objectives

The estimand for this secondary objective was HR of PFS between tarlatamab and SOC chemotherapy, for subjects with SCLC after platinum-based first-line chemotherapy, prior to the start of new anti-cancer therapy or in cases where assessments were missing for 14 weeks (hypothetical strategy).

Table 12. Estimand for secondary objective Progression-Free Survival

	Subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy who would not encounter the Intercurrent Events of New Anti-Cancer Therapy, or Missed assessments for 14 weeks, under any treatment assignment.
Treatment condition<s>	Assignment to Tarlatamab, regardless of discontinuation, compared to assignment to Standard of Care Chemotherapy, regardless of discontinuation.
Endpoint (variable)	Progression-Free Survival (PFS) defined as time from randomization until disease progression or death from any cause, whichever occurs first for all subjects, in the hypothetical scenario that new anti-cancer therapy is not started and no assessments are missed. Progression will be based on investigator assessment of disease response per RECIST 1.1.
Population-level summary	Hazard ratio (HR)
Intercurrent events and strategy to handle them	
Start of new anti-cancer therapy	Hypothetical strategy, PFS will be estimated censoring events after starting new anti-cancer therapy.
Missed assessments	Hypothetical strategy, PFS will be estimated censoring events occurring later than fourteen weeks after last assessment.

The estimand for a further key secondary objective was the change from baseline in PRO endpoints, assessed every 6 weeks up to 18 weeks, comparing tarlatamab with SOC in subjects with relapsed SCLC after platinum-based first-line chemotherapy. PRO measurements taken before or at discontinuation of treatment were used to estimate treatment effect, based on a hypothetical strategy.

Table 13. Estimand for secondary objective Patient-Reported Outcomes

	Subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy who would not encounter the Intercurrent Events of Discontinuation of treatment.
Treatment condition<s>	Assignment to Tarlatamab, until discontinuation, compared to assignment to Standard of Care Chemotherapy, until discontinuation.

Endpoints (variables)	Change from Baseline assessed 6-weekly over time to 18 weeks: • Chest Pain as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC-QLQ-LC13) • Cough as measured by EORTC-QLQLC13 • Dyspnea as measured by EORTC Cancer Quality of Life Questionnaire 30 (EORTC-QLQ-C30) and EORTC-QLQ-LC13 • Physical Function as measured by EORTC-QLQ-C30 • Global Health Status of life as measured by EORTC-QLQ-C30
Population-level summary	Change from Baseline assessed 6-weekly over time to 18 weeks.
Intercurrent events and strategy to handle them	
Discontinuation of treatment	Hypothetical strategy, PRO endpoints will be estimated using measurements until censoring events after starting new anti-cancer therapy.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

The analyses of PFS were according to the protocol planned to occur after OS could claim statistical significance and was to only be tested once. PFS was analysed using the same approach as OS. The PFS rate at 6 months, 9 months and 1 year was reported with the 95% CI. Events were assigned at the earliest of progression or death. If no event was registered data were censored at the last visit or date of randomization if none were registered. Data were censored at the last prior visit if the patient started new anti-cancer therapy or progression or death occurred more than 14 weeks after last visit. Sensitivity analyses for PFS included one using strata stratification factors recorded in CRF instead of IVRS, and a treatment policy strategy analysis where progressive disease and death were considered PFS events regardless of new anti-cancer therapy or missed visits.

The ordinal endpoints of change from baseline over time to 18 weeks in symptoms of chest pain, and cough were measured by a single question from EORTC-QLQ-LC13 and analysed using generalized linear mixed models for repeated measures with cumulative logit link. The model included intercept, time, baseline score, treatment arm, an interaction term between treatment arm and time, and randomization stratification factors (as for primary endpoint) as additional covariates for fixed effects. Odds ratios with 95% CIs and p-values were reported, and tests for the assumption of proportional odds were presented.

Change from baseline over time to 18 weeks in symptoms of dyspnoea, and of change from baseline over time to 18 weeks in physical functioning and global health status, were analysed using a mixed model for repeated measurement (MMRM) with 'unstructured (UN)' covariance structure. If MMRM models failed to achieve convergence due to complexity of model specification, 'compound symmetry (CS)' covariance structure could be used. The linear models included intercept, time, baseline score, treatment arms, an interaction term between treatment arm and time, and randomization stratification factors as additional covariates for fixed effects. LS mean of scores by treatment arm (standard error, 95 % CI), and difference in LS mean between treatment arms (95 % CI) and P-value for the difference in LS means between treatment arms was reported.

Missing data for the generalized linear mixed model and MMRM used for the PRO endpoints were handled under the assumption of missing at random (MAR).

The difference in ORR was tested using the Cochran Mantel Haenszel chi-square test, controlling for the same randomization stratification factors as for the primary endpoint. The ORR was calculated by treatment group and the associated 95% CI estimated using the Clopper-Pearson method. The odds ratio (95% CI) was estimated using the Mantel-Haenszel method.

Duration of Response, based on BOR by investigator assessed outcomes per RECIST 1.1., was analysed for subjects who achieve a confirmed best overall response of PR or CR. The methods were as described for PFS, including censoring conventions, as were the presentation of results.

5.3.2.1.4. Results

Participant flow and numbers analysed

Study Initiation Date: 31 May 2023 (first subject enrolled)

Study Completion Date: 29 January 2025 (data cutoff of the first planned OS interim analysis). The interim analysis serves as primary analysis for this study. The analyses presented are based on a database snapshot date of 13 March 2025. The median follow-up time for OS was 11.2 months (95% CI: 10.4, 12.1) in the tarlatamab group and 11.7 months (95% CI: 10.6, 12.3) in the SOC chemotherapy group.

A total of 688 subjects were screened for enrolment into this study and of those, 509 subjects (74.0%) were enrolled and randomized to tarlatamab (254 subjects) or SOC chemotherapy (255 subjects; 47 lurbinectedin, 185 topotecan, 23 amrubicin).

Thirteen enrolled subjects (13/509, 2.6%) never received investigational product. Two of these subjects were assigned to the tarlatamab group and had adverse events that prevented initial treatment, i.e. one subject suffered from disease progression, and one subject was considered unfit by the investigator to initiate study treatment. Eleven subjects were assigned to the SOC chemotherapy group; 2 subjects had adverse events prior to first dose and 9 patients elected to discontinue participation prior to first dose. Long-term survival data were collected for all 13 subjects and are included in the OS analysis.

There were 179 patients screened for the pivotal study who were excluded for meeting various exclusion criteria, the most common being untreated or symptomatic CNS metastases (20.1%) and inadequate organ function (15.6%). Based on the provided data, there is no indication of systematic exclusion of patients beyond those meeting exclusion criteria or not meeting inclusion criteria.

Table 14. Participant flow

	Standard of Care (N = 255) n (%)	Tarlatamab (N = 254) n (%)	Overall (N = 509) n (%)
Investigational product accounting			
Subjects who never received IP	11 (4.3)	2 (0.8)	13 (2.6)
Subjects who received IP	244 (95.7)	252 (99.2)	496 (97.4)
Subjects who completed IP	0 (0.0)	0 (0.0)	0 (0.0)
Subjects continuing IP	19 (7.5)	69 (27.2)	88 (17.3)
Subjects who discontinued IP	225 (88.2)	183 (72.0)	408 (80.2)
Ineligibility determined	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)
Noncompliance	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	15 (5.9)	5 (2.0)	20 (3.9)
Subject request	17 (6.7)	9 (3.5)	26 (5.1)
Disease progression	159 (62.4)	152 (59.8)	311 (61.1)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	19 (7.5)	16 (6.3)	35 (6.9)
Requirement for alternative therapy	4 (1.6)	0 (0.0)	4 (0.8)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Other	11 (4.3)	1 (0.4)	12 (2.4)
Study completion accounting			
Subjects who completed study	0 (0.0)	0 (0.0)	0 (0.0)
Subjects continuing study	102 (40.0)	143 (56.3)	245 (48.1)
Subjects who discontinued study	153 (60.0)	111 (43.7)	264 (51.9)
Withdrawal of consent from study	2 (0.8)	0 (0.0)	2 (0.4)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	151 (59.2)	111 (43.7)	262 (51.5)
Subjects who completed safety follow-up	89 (34.9)	73 (28.7)	162 (31.8)
Subjects started safety follow-up and ongoing	3 (1.2)	5 (2.0)	8 (1.6)
Subjects who discontinued safety follow-up	129 (50.6)	94 (37.0)	223 (43.8)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Subject request	35 (13.7)	33 (13.0)	68 (13.4)
Lost to follow-up	1 (0.4)	0 (0.0)	1 (0.2)
Death	36 (14.1)	22 (8.7)	58 (11.4)
Protocol specified criteria	7 (2.7)	5 (2.0)	12 (2.4)
Other	50 (19.6)	34 (13.4)	84 (16.5)

Deviations from study plan

Protocol amendments

Protocol amendment 1 (30 May 2023) was introduced before the first patient was enrolled (31 May 2023) and consisted mainly of an update of the eligibility criteria to specify that only subjects deemed candidates for the three SOC therapies, per investigator discretion, should be included.

With Amendment 2 (06 September 2023), the number of patients to be enrolled was reduced from 700 to 490. The recalculation of the required number of patients was based on findings from the phase 2 study 20200491. In addition, one of two planned interim analyses was removed from the protocol, specifically the first interim analysis, which would have been triggered when 60% OS events occurred. The removal of exploratory endpoints pertained to the evaluation of biomarkers relevant to SCLC biology and tarlatamab's MoA, their association with clinical outcomes, and the assessment of health resource utilization. It was also clarified that providing a tissue biopsy was not required for inclusion in the pivotal study.

Amendment 3 (11 Dec. 2023) primarily focused on clarifications of wording, in addition to amendments related to safety.

Amendment 4 (19 July 2024): The protocol is mainly being amended due to the evolving data and the availability of pooled population-pharmacokinetics (PK) analysis for tarlatamab to inform and updated half-life. The contraception and lactation washout period for tarlatamab was adjusted to align with the Food and Drug Administration (FDA)'s recommended language in the U.S Prescribing Information (USPI). The new duration is set to 5 half-lives, equivalent to 2 months (60 days), after the last dose of tarlatamab for both male and female participants. There were several further clarifications and language revisions in the protocol.

Baseline data

Baseline demographics and disease characteristics were generally well balanced between the treatment arms.

Table 15. Baseline demographics

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Overall (N = 509)
Sex - n (%)			
Male	169 (66.3)	182 (71.7)	351 (69.0)
Female	86 (33.7)	72 (28.3)	158 (31.0)
Race - n (%)			
Asian	107 (42.0)	97 (38.2)	204 (40.1)
Black or African American	3 (1.2)	2 (0.8)	5 (1.0)
White	139 (54.5)	152 (59.8)	291 (57.2)
Ethnicity - n (%)			
Hispanic or Latino	11 (4.3)	12 (4.7)	23 (4.5)
Not Hispanic or Latino	128 (50.2)	140 (55.1)	268 (52.7)
American Indian or Alaska Native	1 (0.4)	1 (0.4)	2 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (1.2)	1 (0.4)	4 (0.8)
Missing	2 (0.8)	1 (0.4)	3 (0.6)
Age (years)			
n	255	254	509
Mean	64.2	63.6	63.9
SD	9.2	9.4	9.3
Median	66.0	64.0	65.0
Q1, Q3	58.0, 70.0	58.0, 70.0	58.0, 70.0
Min, Max	26, 84	20, 86	20, 86
Age group - n (%)			
18 - 64 years	115 (45.1)	129 (50.8)	244 (47.9)

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Overall (N = 509)
65 - 74 years	115 (45.1)	95 (37.4)	210 (41.3)
75 - 84 years	25 (9.8)	28 (11.0)	53 (10.4)
≥ 85 years	0 (0.0)	2 (0.8)	2 (0.4)
Region - n (%)			
North America	15 (5.9)	13 (5.1)	28 (5.5)
Europe	113 (44.3)	127 (50.0)	240 (47.2)
Asia	110 (43.1)	97 (38.2)	207 (40.7)
Rest of the world	17 (6.7)	17 (6.7)	34 (6.7)

N = Number of subjects in the analysis set; n = Number of subjects with observed data; Q1 = first quartile; Q3 = third quartile; SD = standard deviation
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Table 16. Baseline disease characteristics

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Overall (N = 509)
ECOG status at baseline[a] - n (%)			
0	80 (31.4)	83 (32.7)	163 (32.0)
1	173 (67.8)	169 (66.5)	342 (67.2)
2	2 (0.8)	2 (0.8)	4 (0.8)
Weight (kg)			
n	255	254	509
Mean	70.1850	72.4266	71.3036
SD	15.0867	16.3474	15.7530
Median	68.0000	70.8000	69.6000
Q1, Q3	60.0000, 80.0000	61.0000, 82.0000	60.5000, 80.5500
Min, Max	40.200, 127.000	39.000, 156.500	39.000, 156.500
Smoking history - n (%)			
Never	31 (12.2)	23 (9.1)	54 (10.6)
Current	51 (20.0)	54 (21.3)	105 (20.6)
Former	173 (67.8)	177 (69.7)	350 (68.8)
Prior lines of therapy - n (%)			
1	248 (97.3)	249 (98.0)	497 (97.6)
≥2	7 (2.7)	5 (2.0)	12 (2.4)
Number of prior lines of therapy			
n	255	254	509
Mean	1.0	1.0	1.0
SD	0.2	0.1	0.2
Median	1.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 1.0
Time from initial cancer diagnosis to randomization (months)			
n	248	250	498
Mean	11.50	10.50	11.00
SD	8.54	6.85	7.75
Median	8.97	8.57	8.80
Q1, Q3	6.90, 12.48	6.80, 11.73	6.87, 12.19
Min, Max	2.3, 84.2	0.7, 54.5	0.7, 84.2
Sum of diameters of target lesions at baseline (mm) - based on investigator assessments			
n	255	254	509
Mean	85.367	86.652	86.008

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Overall (N = 509)
SD	52.923	56.790	54.837
Median	78.640	72.955	75.000
Q1, Q3	42.000, 128.000	42.000, 117.490	42.000, 121.000
Min, Max	11.10, 274.00	10.30, 269.50	10.30, 274.00
Prior PD-1 or PD-L1 inhibitor therapy - n (%)			
Yes	180 (70.6)	180 (70.9)	360 (70.7)
No	75 (29.4)	74 (29.1)	149 (29.3)
Reasons for non-exposure to PD-1 or PD-L1 inhibitor therapy - n (%)			
Not approved	29 (11.4)	38 (15.0)	67 (13.2)
Not funded or accessible	32 (12.5)	30 (11.8)	62 (12.2)
Contraindication anti-PD-(L)1 therapy	2 (0.8)	2 (0.8)	4 (0.8)
Other	12 (4.7)	4 (1.6)	16 (3.1)
Prior radiotherapy for current malignancy - n (%)			
Yes	161 (63.1)	159 (62.6)	320 (62.9)
No	94 (36.9)	95 (37.4)	189 (37.1)
Prior surgery for current malignancy - n (%)			
Yes	26 (10.2)	26 (10.2)	52 (10.2)
No	229 (89.8)	228 (89.8)	457 (89.8)
Disease stage at initial diagnosis - n (%)			
Stage 0	0 (0.0)	0 (0.0)	0 (0.0)
Stage I	4 (1.6)	5 (2.0)	9 (1.8)
Stage II	4 (1.6)	2 (0.8)	6 (1.2)
Stage III	57 (22.4)	59 (23.2)	116 (22.8)
Stage IV	190 (74.5)	187 (73.6)	377 (74.1)
Unknown/Missing	0 (0.0)	1 (0.4)	1 (0.2)
Disease stage at screening - n (%)			
Stage 0	0 (0.0)	0 (0.0)	0 (0.0)
Stage I	0 (0.0)	0 (0.0)	0 (0.0)
Stage II	2 (0.8)	0 (0.0)	2 (0.4)
Stage III	18 (7.1)	21 (8.3)	39 (7.7)
Stage IV	235 (92.2)	233 (91.7)	468 (91.9)
Metastatic at baseline - n (%)			
Yes	236 (92.5)	227 (89.4)	463 (91.0)
No	19 (7.5)	27 (10.6)	46 (9.0)
Chemotherapy-free interval - n (%)			
<90 days	114 (44.7)	109 (42.9)	223 (43.8)
≥90 days	141 (55.3)	145 (57.1)	286 (56.2)
≥90 and <180 days	78 (30.6)	85 (33.5)	163 (32.0)
≥180 days	63 (24.7)	60 (23.6)	123 (24.2)
Brain metastases (previous or current) at baseline - n (%)			
Yes	115 (45.1)	113 (44.5)	228 (44.8)
No	140 (54.9)	141 (55.5)	281 (55.2)
Liver metastases at baseline - n (%)			
Yes	95 (37.3)	84 (33.1)	179 (35.2)
No	160 (62.7)	170 (66.9)	330 (64.8)

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Overall (N = 509)
DLL3 positive - n/N1 (%)[b]	198/214 (92.5)	207/217 (95.4)	405/431 (94.0)
DLL3 cut points - n (%)			
<75% at 2+ and 3+ staining intensity	114 (44.7)	119 (46.9)	233 (45.8)
≥75% at 2+ and 3+ staining intensity	100 (39.2)	98 (38.6)	198 (38.9)
<25% at 2+ and 3+ staining intensity	52 (20.4)	52 (20.5)	104 (20.4)
≥25% at 2+ and 3+ staining intensity	162 (63.5)	165 (65.0)	327 (64.2)
Missing	41 (16.1)	37 (14.6)	78 (15.3)

N = Number of subjects in the analysis set; N1 = Number of subjects with nonmissing DLL3 results; n = Number of subjects with observed data; Q1 = first quartile; Q3 = third quartile; SD = standard deviation
[a] 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
Subjects with ECOG status of 2 were assessed at randomization/day 1 instead of screening
DLL3 positive is defined as subjects with 0+ staining intensity < 100
[b] The percentage for DLL3 positive is based on subjects with nonmissing DLL3 results as denominator
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

All randomized patients were considered to have ES-SCLC at the time of study enrolment. In retrospect, based on the following criteria, a total of 83 patients (39 randomized to tarlatamab, 44 randomized to SOC) are considered to have had LS-SCLC at the initial diagnosis:

- Patient did not have stage IV disease at diagnosis
- Initial radiation delivered to thoracic sites, to a total dose of 45Gy or greater

  Note: Prophylactic cranial irradiation (PCI, defined as brain radiation after thoracic radiation) was acceptable
- Platinum-based chemotherapy was delivered concurrently or sequentially with thoracic radiation therapy.

One patient in the tarlatamab arm had received prior platinum-based chemotherapy as adjuvant treatment.

Outcomes and estimation

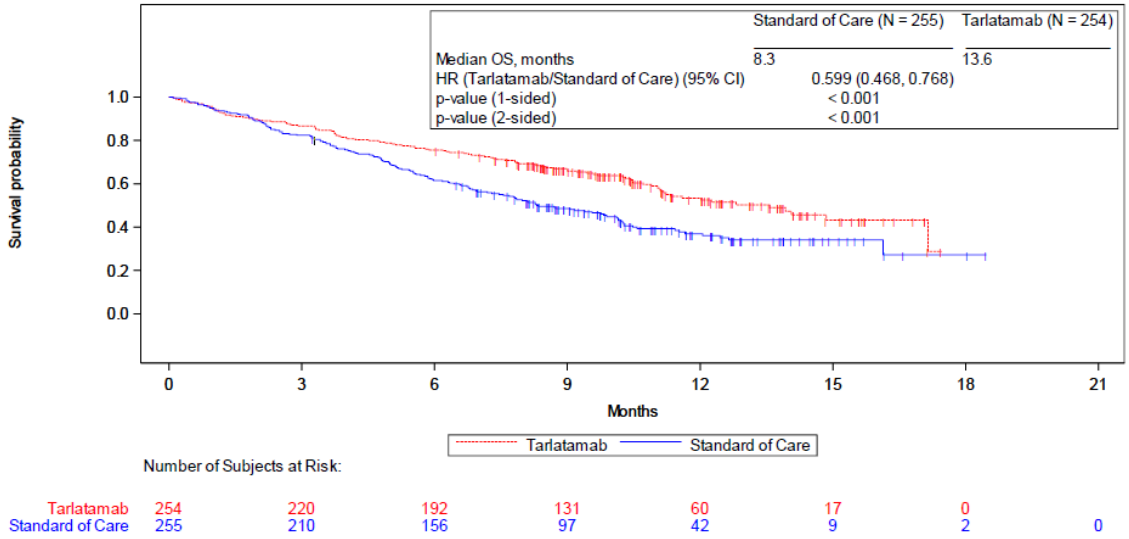
Primary endpoint: Overall survival

Table 17. Primary analysis of overall Survival (ITT Analysis Set)

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Treatment Difference
Subject status			
Events - n (%)			
Death	152 (59.6)	111 (43.7)	
Censored - n (%)	103 (40.4)	143 (56.3)	
Alive at last follow-up	102 (40.0)	143 (56.3)	
Withdrawal of consent from study	1 (0.4)	0 (0.0)	
Decision by sponsor	0 (0.0)	0 (0.0)	
Lost to follow-up	0 (0.0)	0 (0.0)	
Completed study without death	0 (0.0)	0 (0.0)	
Hazard ratio (95% CI)[a]			0.599 (0.468, 0.768)
P-value (1-sided)[b]			< 0.001
P-value (2-sided)[b]			< 0.001
Overall survival (KM) (months)[c]			
25th percentile (95% CI)	4.1 (3.3, 5.0)	6.3 (4.2, 7.9)	
Median (95% CI)	8.3 (7.0, 10.2)	13.6 (11.1, NE)	
75th percentile (95% CI)	NE (16.1, NE)	NE (17.1, NE)	
Min, Max (+ for censored)	0.1, 18.5+	0.1, 17.4+	
Follow-up time for OS (KM) (months)[c]			
25th percentile (95% CI)	9.4 (8.7, 9.9)	9.3 (8.7, 9.8)	
Median (95% CI)	11.7 (10.6, 12.3)	11.2 (10.4, 12.1)	
75th percentile (95% CI)	13.8 (12.7, 14.3)	13.9 (13.1, 14.5)	
Min, Max (+ for censored)	0.1+, 18.5	0.1+, 17.4	
Kaplan-Meier estimate (%) (95% CI)[d]			
At 6 months	61.5 (55.2, 67.1)	75.6 (69.8, 80.4)	
At 12 months	36.9 (30.3, 43.5)	53.4 (46.0, 60.2)	
At 18 months	27.2 (15.2, 40.8)	NE (NE, NE)	

IVRS=interactive voice response system; N=Number of subjects in the analysis set; n=Number of subjects with observed data; NE=not estimable
The follow-up time is measured by reversing the status indicator for censored and events. The randomization stratification factors used in stratified analysis includes chemotherapy-free interval (<90 days, ≥ 90 days), and presence (previous or current) of brain metastases (yes or no). This stratified analysis is based on IVRS data
[a] Hazard ratios and 95% CIs are estimated using a stratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
[b] P-value is calculated using a stratified log-rank test
[c] Median and quantiles are estimated using Kaplan-Meier method and 95% CI of median are estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method
[d] 95% CIs are estimated using Kalbfleisch and Prentice (1980) method
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Figure 6. Kaplan-Meier plot for overall survival (ITT Analysis Set)



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

Key secondary endpoints: Progression Free Survival and Patient Reported Outcome

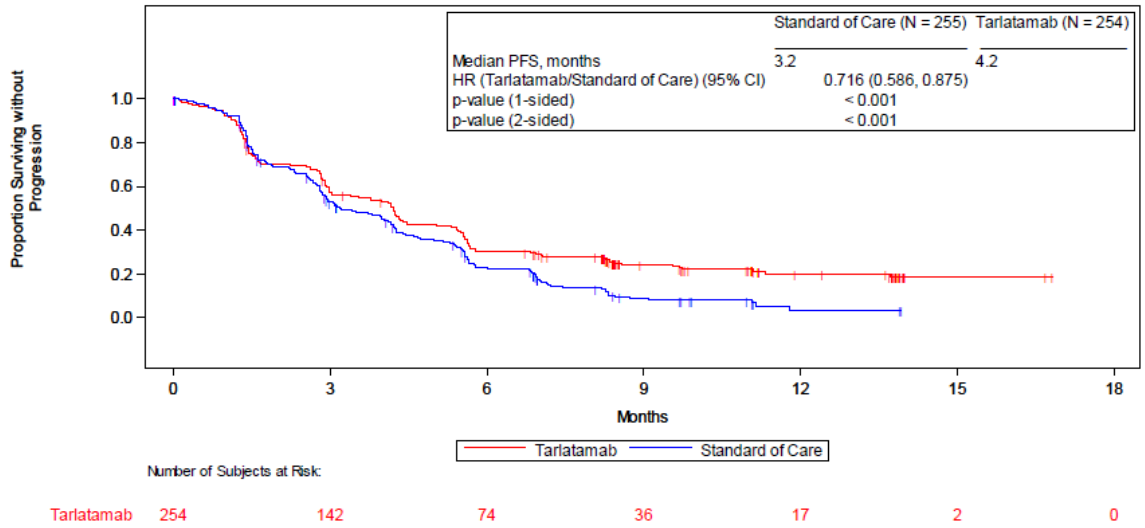
Table 18. Primary analysis of progression-free survival as assessed by investigator (ITT analysis set)

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Treatment Difference
Subject status			
Events - n (%)	205 (80.4)	191 (75.2)	
Death	41 (16.1)	25 (9.8)	
Disease progression	164 (64.3)	166 (65.4)	
Censored - n (%)	50 (19.6)	63 (24.8)	
On study without disease progression or death	20 (7.8)	56 (22.0)	
No evaluable postbaseline disease assessment	2 (0.8)	0 (0.0)	
Missed 2 or more consecutive assessments	7 (2.7)	4 (1.6)	
Started new anti-cancer therapy	21 (8.2)	3 (1.2)	
Withdrawal of consent from study	0 (0.0)	0 (0.0)	
Decision by sponsor	0 (0.0)	0 (0.0)	
Lost to follow-up	0 (0.0)	0 (0.0)	
Completed study without disease progression or death	0 (0.0)	0 (0.0)	
Hazard ratio (95% CI)[a]			0.716 (0.586, 0.875)
P-value (1-sided)[b]			< 0.001
P-value (2-sided)[b]			< 0.001
Progression-free survival (KM) (months)[c]			
25th percentile (95% CI)	1.5 (1.4, 1.9)	1.5 (1.4, 2.2)	
Median (95% CI)	3.2 (2.9, 4.2)	4.2 (3.0, 4.4)	
75th percentile (95% CI)	5.7 (5.5, 6.9)	8.4 (5.8, 13.7)	
Min, Max (+ for censored)	0.0+, 13.9+	0.0+, 16.8+	
Follow-up time for progression-free survival (KM) (months)[c]			
25th percentile (95% CI)	6.9 (5.6, 8.4)	8.3 (8.2, 8.5)	
Median (95% CI)	9.7 (8.4, 11.1)	11.0 (8.5, 11.2)	
75th percentile (95% CI)	11.1 (9.9, NE)	13.8 (11.2, 13.9)	
Min, Max (+ for censored)	0.0, 13.9	0.0, 16.8	
Kaplan-Meier estimate (%) (95% CI)[d]			
At 6 months	22.7 (17.4, 28.4)	30.4 (24.8, 36.2)	
At 9 months	8.8 (5.3, 13.4)	24.2 (18.9, 29.9)	
At 12 months	3.5 (0.9, 9.1)	20.1 (14.7, 26.0)	

IVRS=interactive voice response system; N=Number of subjects in the analysis set; n=Number of subjects with observed data; NE=not estimable
The follow-up time is measured by reversing the status indicator for censored and events
Event and censoring status are derived using RECIST 1.1 criteria
The randomization stratification factors used in stratified analysis includes chemotherapy-free interval (<90 days, ≥90 days), and presence (previous or current) of brain metastases (yes or no)
This stratified analysis is based on IVRS data
[a] Hazard ratios and 95% CIs are estimated using a stratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a longer PFS for tarlatamab arm
[b] P-value is calculated using a stratified log-rank test
[c] Median and quantiles are estimated using Kaplan-Meier method and 95□ CI of median are estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method
[d] 95% CIs are estimated using Kalbfleisch and Prentice (1980) method

Data snapshot date: 13MAR2025; *eCTD 5.3.5.1*

Figure 7. Kaplan-Meier plat for progression-free survival as assessed by investigator (ITT analysis Set)



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

Patient Reported Outcome

Table 19. EORTC QLQ-LC13 improved, stable, and worsened categories after 18 weeks from baseline

	SOC (n = 88 to 89)			Tarlatamab (n = 115 to 116)		
	Improved, m (%)	Stable, m (%)	Worsened, m (%)	Improved, m (%)	Stable, m (%)	Worsened, m (%)
Dyspnea (Composite)[a]	6 (6.8)	49 (55.7)	33 (37.5)	25 (21.6)	73 (62.9)	18 (15.5)
Cough	23 (25.8)	51 (57.3)	15 (16.9)	41 (35.3)	64 (55.2)	11 (9.5)
Chest Pain	9 (10.1)	64 (71.9)	16 (18.0)	22 (19.0)	85 (73.3)	9 (7.8)
Physical Functioning	7 (7.9)	61 (68.5)	21 (23.6)	15 (12.9)	97 (83.6)	4 (3.4)
GHS/QOL	13 (14.6)	44 (49.4)	32 (36.0)	26 (22.6)	61 (53.0)	28 (24.3)

Notes: m = subjects with responses; n = number of subjects with baseline score and after 18 weeks. The n for SOC Dyspnea (Composite) was 88 and the n for SOC Cough and Chest Pain was 89. The response "Improved" was defined as change from baseline ≤ −16 points for Dyspnea (Composite score), ≤ −33 each for Chest Pain and Cough, ≥ 20 points for Physical Functioning, and ≥ 16 points for GHS/QOL. The response "Stable" was defined as change from baseline of < ±16 points for Dyspnea (Composite score), ≤ ±33 each for Chest Pain and Cough, < ± 20 points for Physical Functioning, and < ±16 points for GHS/QOL. The response "Deteriorated" as defined as change from baseline of ≥ 16 points for Dyspnea (Composite score), ≥ 33 each for Chest Pain and Cough, ≤ −20 points for Physical Functioning, and ≤ −16 points for GHS/QOL.
[a] Dyspnea composite score represents the composite score of Items 3, 4, and 5 from the QLQ-LC13 and Item 8 from the QLQ-C30.

Table 20. GLMM analysis of change from baseline after 18 weeks for QLQLC13

	SOC (N = 255) n (%)	Tarlatamab (N = 254) n (%)	Odds Ratio (95% CI)	*P*-value[a] (2-sided)
Cough				
Improved	23 (9.0)	41 (16.1)		
Stable or Worsened	232 (91.0)	213 (83.9)		
Treatment Difference			2.041 (1.174, 3.549)	0.012
Chest Pain				
Improved	9 (3.5)	22 (8.7)		
Stable or Worsened	246 (96.5)	232 (91.3)		
Treatment Difference			1.841 (0.889, 3.811)	0.100

N = Number of subjects in the analysis set; n = Number of subjects with observed data CI = confidence interval; IVRS = interaction voice response system; LS = least squares; GLMM = generalized linear mixed model; QLQ-LC13 = lung cancer supplementary module; SE = standard error; SOC = standard of care
This stratified analysis is based on IVRS data. The randomization stratification factors used in stratified analysis includes chemotherapy-free interval (<90 days, ≥90 days), and presence (previous or current) of brain metastases (yes or no). The category 'Improved' is defined as at least 33 points decrease from baseline (equivalent to 1 level of improvement) and "Worsened" as at least 33 points of increase from baseline (equivalent to 1 level of worsening)
[a] GLMM is based on change from baseline as dependent variable, intercept, time, baseline score, treatment arms, interaction term between treatment arm and time and randomization stratification factors as fixed effects, and subject intercept and slope of time for the change from baseline as random effects
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Table 21. MMRM of change from baseline after 18 weeks in continuous key secondary PROs (ITT analysis set)

	SOC (N = 255)			Tarlatamab (N = 254)			Difference of LS means[a]	
Scales	**n**	**LS mean (SE) at week 19**	**95% CI**	**n**	**LS mean (SE) at week 19**	**95% CI**	**(95% CI)**	***P* Value[b]**
Dyspnea (Composite)	88	7.20 (1.33)	4.58 to 9.81	116	−1.94 (1.21)	−4.32 to 0.45	−9.14 (−12.64 to −5.64)	< 0.001
Physical Functioning	89	−11.57 (1.61)	−14.75 to −8.39	116	−1.23 (1.53)	−4.23 to 1.78	10.35 (6.00 to 14.69)	< 0.001
GHS/QOL	89	−10.60 (1.46)	−13.46 to −7.73	115	−1.66 (1.36)	−4.34 to 1.02	8.93 (5.04 to 12.83)	< 0.001

N = Number of subjects in the analysis set; n = Number of subjects with observed data CI = confidence interval; IVRS = interaction voice response system; LS = least squares; MMRM = mixed model for repeated measurements; QLQ-C30 = core questionnaire; QLQ-LC13 = lung cancer supplementary module; SE = standard error; SOC = standard of care
Dyspnea composite score represents the composite score of item # 3, 4, and 5 from QLQ-LC13 and item # 8 from QLQ-C30 questionnaires.
The randomization stratification factors used in stratified analysis includes chemotherapy-free interval (<90 days, ≥ 90 days), and presence (previous or current) of brain metastases (yes or no)
[a] Difference of LS Means is the difference of the least-squares mean change from baseline between tarlatamab and SOC
[b] P value from MMRM is based on change from baseline as the dependent variable; intercept, time, baseline score, treatment groups, interaction term between treatment group and time, and randomization stratification factors as fixed effects; and subject intercept and slope of time for the change from baseline as random effects.

Secondary endpoints: ORR and DOR

Table 22. Summary of objective response as assessed by investigator (ITT)

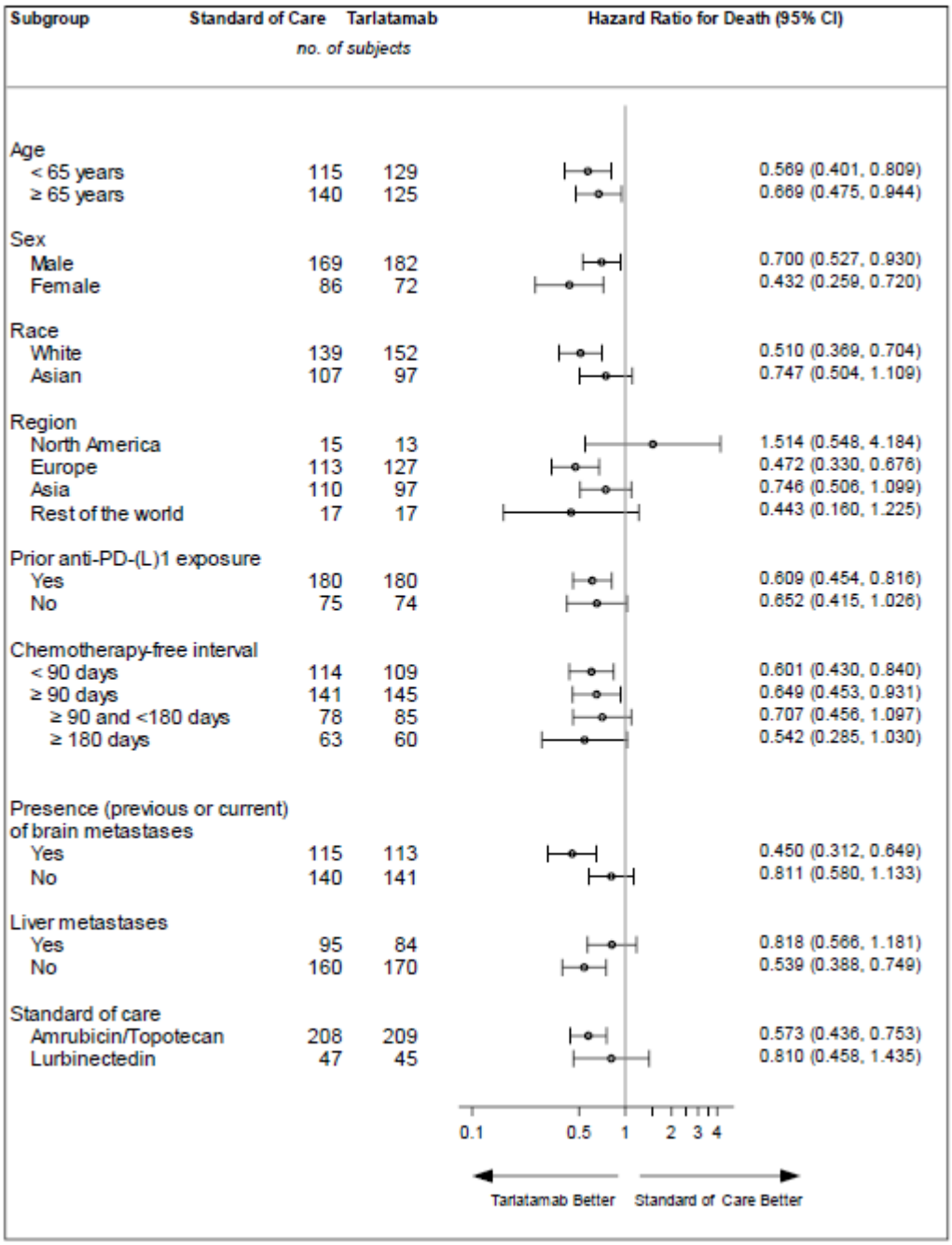
	Standard of Care (N = 255) n (%)	Tarlatamab (N = 254) n (%)	Treatment Difference
Best overall response[a] - n (%)			
Confirmed complete response	0 (0.0)	3 (1.2)	
Confirmed partial response	52 (20.4)	86 (33.9)	
Stable disease	112 (43.9)	84 (33.1)	
Progressive disease	50 (19.6)	56 (22.0)	
Not evaluable	1 (0.4)	1 (0.4)	
No post-baseline scan	40 (15.7)	24 (9.4)	
Objective response rate (ORR) per investigator			
Number of subjects who achieved objective response	52	89	
ORR (95% CI)[b]	20.4 (15.6, 25.9)	35.0 (29.2, 41.3)	
Odds ratio (95% CI)[c]			2.128 (1.425, 3.178)
P-value (1-sided)[c]			< 0.001
P-value (2-sided)[c]			< 0.001
Disease control rate (DCR)			
Number of subjects who achieved disease control	164	173	
DCR (95% CI)[b]	64.3 (58.1, 70.2)	68.1 (62.0, 73.8)	
Any tumor shrinkage - n (%)			
Yes[d]	158 (62.0)	159 (62.6)	
At least 30% tumor shrinkage[e]	76 (29.8)	110 (43.3)	
No	56 (22.0)	69 (27.2)	
Missing	41 (16.1)	26 (10.2)	

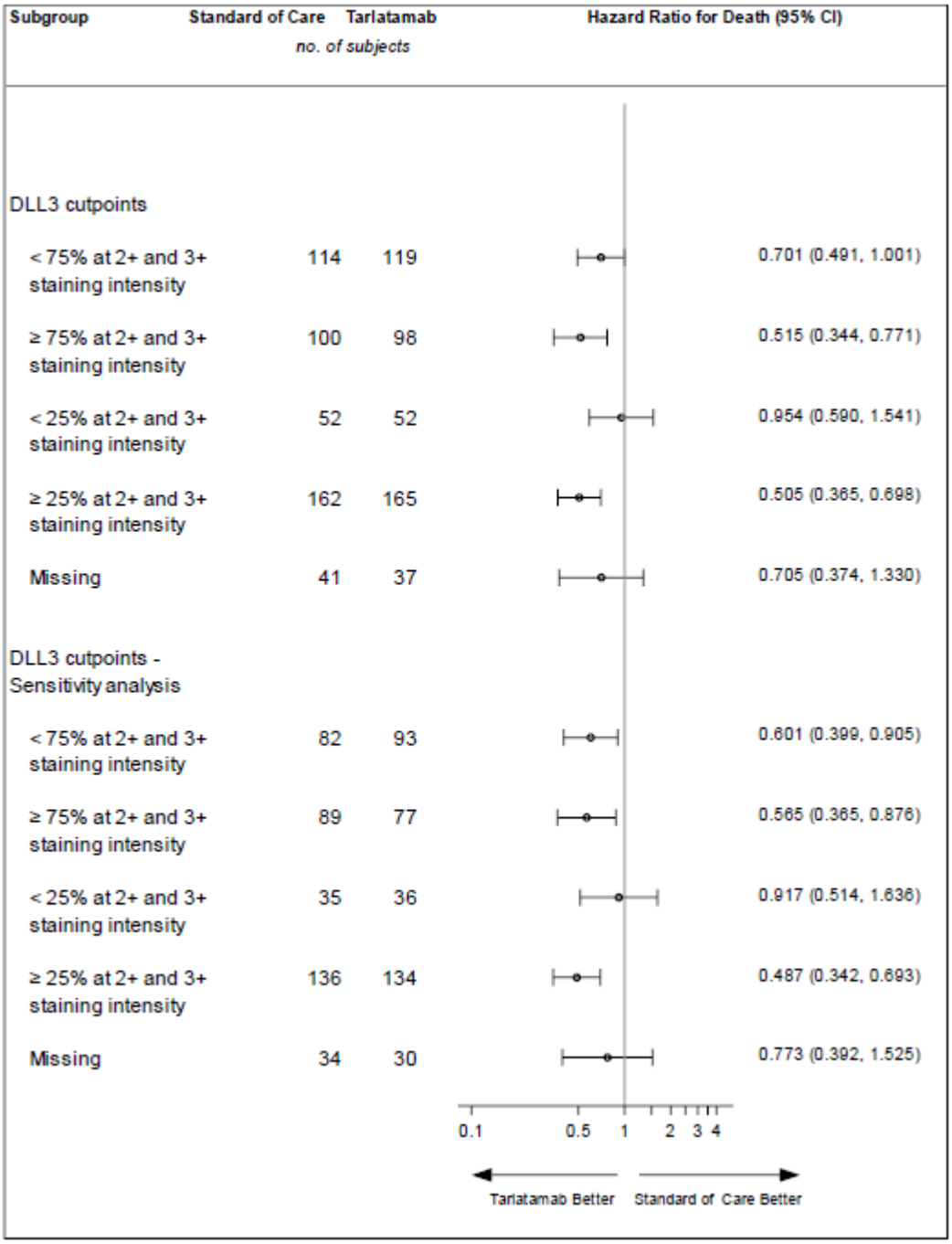
N = Number of subjects in the analysis set; n = Number of subjects with observed data IVRS = interactive voice response system
[a] Assessment of disease response is determined using RECIST 1.1 guidelines
[b] Exact confidence interval is calculated using Clopper Pearson method
[c] Odds ratio with 95% CI and p-value are estimated using the Cochran Mantel Haenszel Chi-square test controlling for the randomization stratification factors such as chemotherapy-free interval (<90 days, ≥90 days), and presence (previous or current) of brain metastases (yes or no); an odds ratio > 1.0 indicates a better objective response rate of tarlatamab arm
[d] Includes subjects who had any tumour shrinkage in the target lesions at postbaseline assessment
[e] Includes subjects who had at least 30% tumour shrinkage in the target lesions at postbaseline assessment
This stratified analysis is based on IVRS data
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Pre-defined and post hoc subgroup analyses

Pre-defined subgroup analyses of OS

Figure 8. Forest plot of subgroup analysis of OS (ITT)



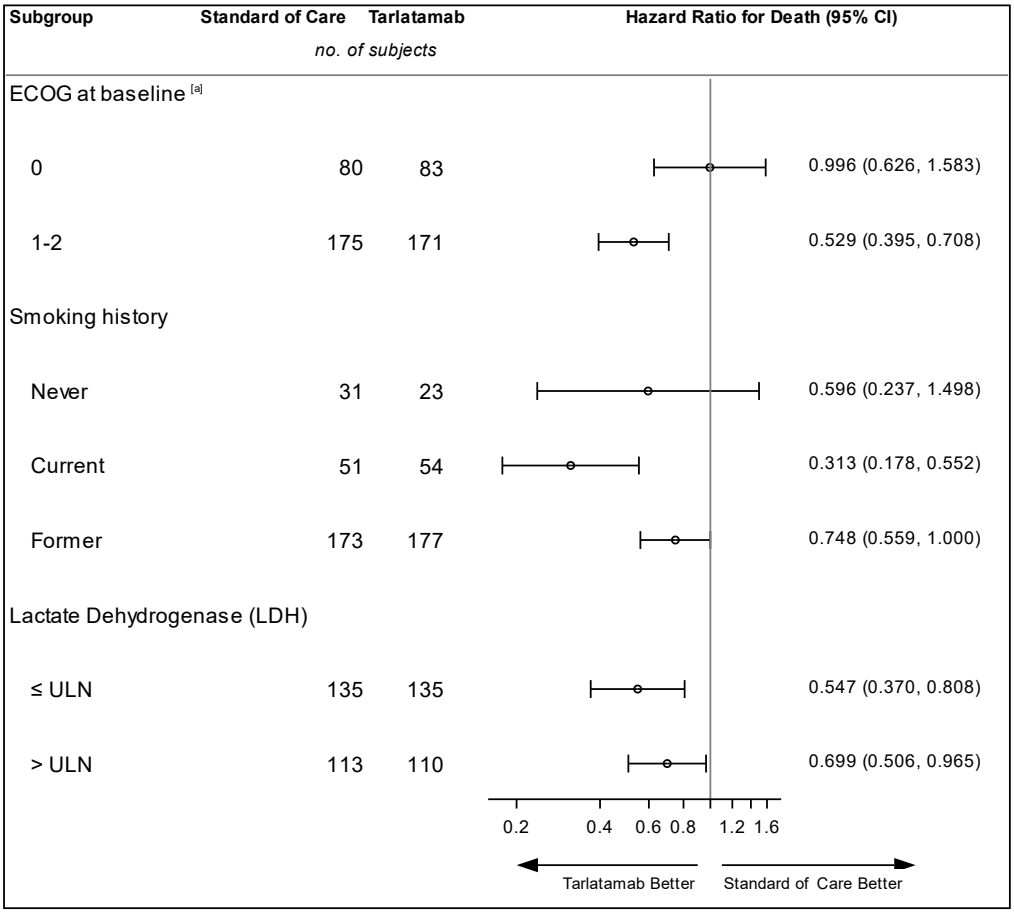


N = Number of subjects in the analysis set; NE = not estimable
Hazard ratios and 95% CIs are estimated using Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
For the subgroup categories with sample size of < 10 subjects, hazard ratios with corresponding 95% CIs are not displayed
The DLL3 cutpoints sensitivity analysis is applicable for samples tested with the primary vendor
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Post hoc subgroup analyses of OS

Additional subgroup analyses have been provided according to smoking history, LDH levels and ECOG performance status.

Figure 9. Additional Forest plot of subgroup analysis of OS (ITT)

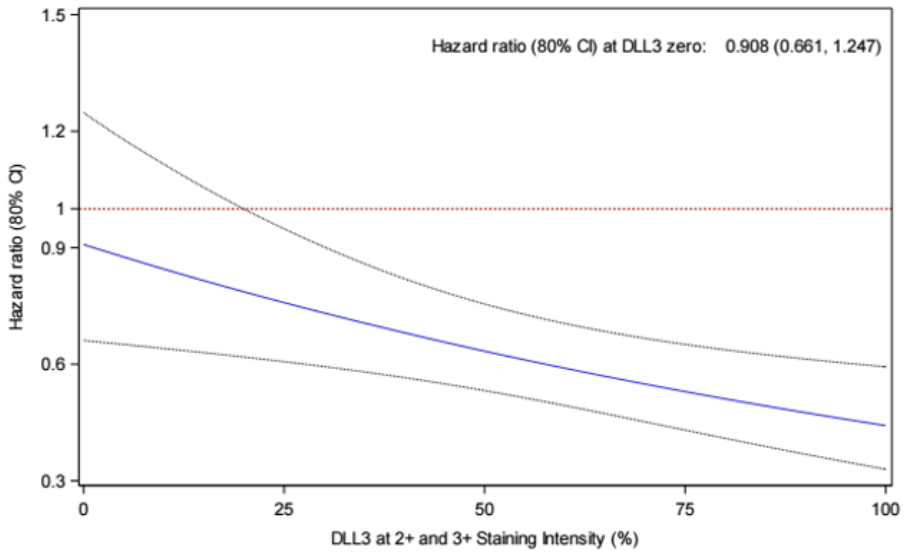


N = Number of subjects in the analysis set
[a] 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
Patients with ECOG status of 2 were assessed at randomization/day 1 instead of screening
Hazard ratios and 95% CIs are estimated using unstratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
For the subgroup categories with sample size of < 10 subjects, hazard ratios with corresponding 95% CIs are not displayed
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Post hoc analyses of OS according to DLL3 expression

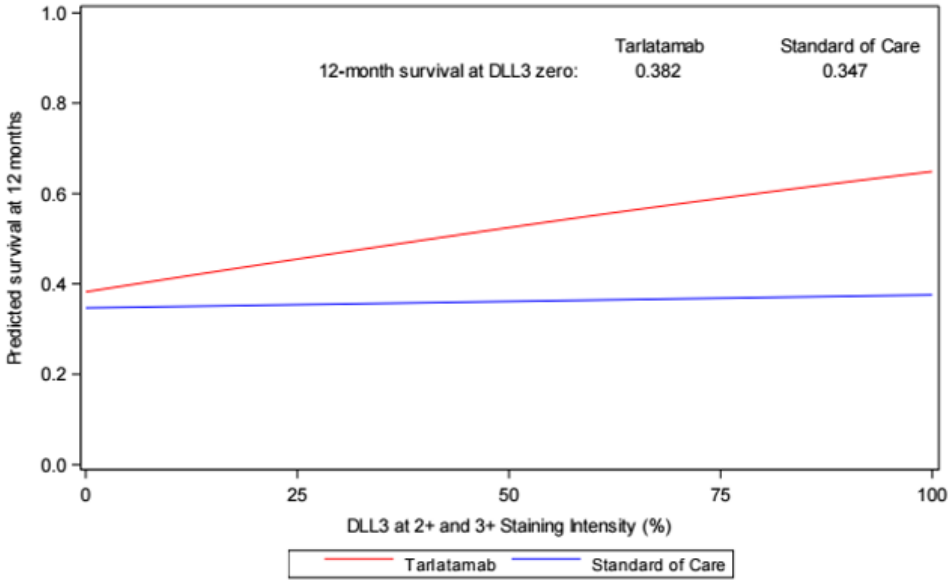
To investigate overall survival across DLL3 expression level (DLL3 staining intensity at 2+/3+), a post hoc analysis was performed using Cox proportional hazard model treating DLL3 as a continuous variable. The model included treatment, DLL3, and interaction between treatment and DLL3 level in order to obtain robust estimates of hazard ratio and survival probability across DLL3 levels. The model estimated hazard ratio at DLL3 zero is 0.91 (80% CI, 0.66, 1.25) and estimated 12-month survival probability at DLL3 zero is 38.2% for tarlatamab and 34.7% for SOC chemotherapy.

Figure 10. Hazard Ratio for overall survival based on Cox proportional Hazard model with treatment by DLL3 (continuous) interaction (ITT analysis set)



Hazard ratio and 80% CI are estimated using an unstratified Cox proportional hazards model with an interaction term between treatment and continuous DLL3 staining intensity at 2+/3+; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025;

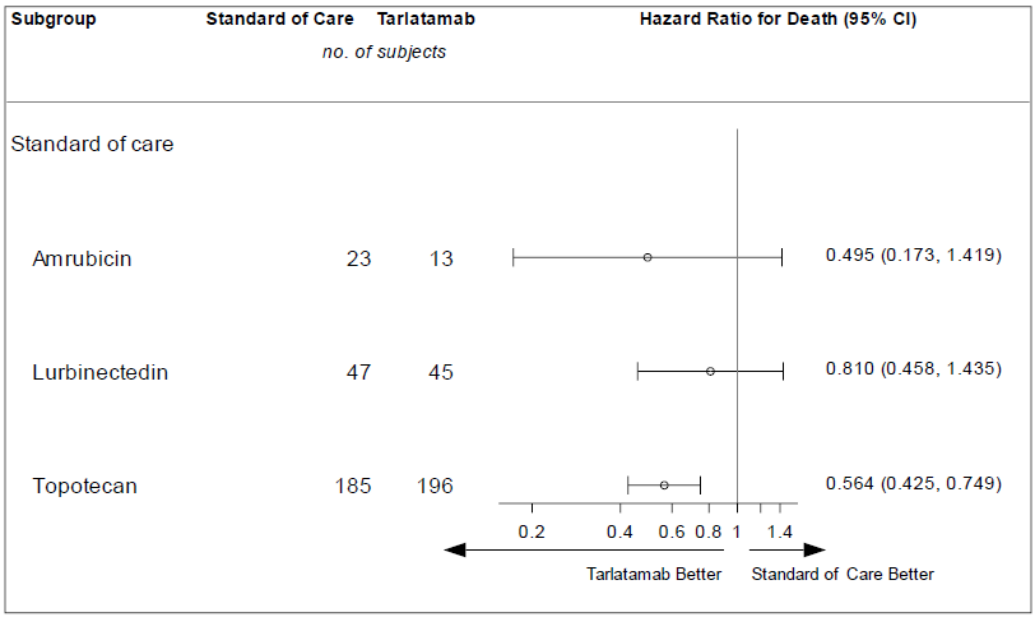
Figure 11. Predicted 12-month overall survival based on Cox proportional hazard model with treatment by DLL3 (Continuous) interaction (ITT analysis set)



Overall survival probability at 12 months is predicted from an unstratified Cox proportional hazards model with an interaction term between treatment and continuous DLL3 staining intensity at 2+/3+
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Post hoc subgroup analysis of OS for tarlatamab versus individual SOC

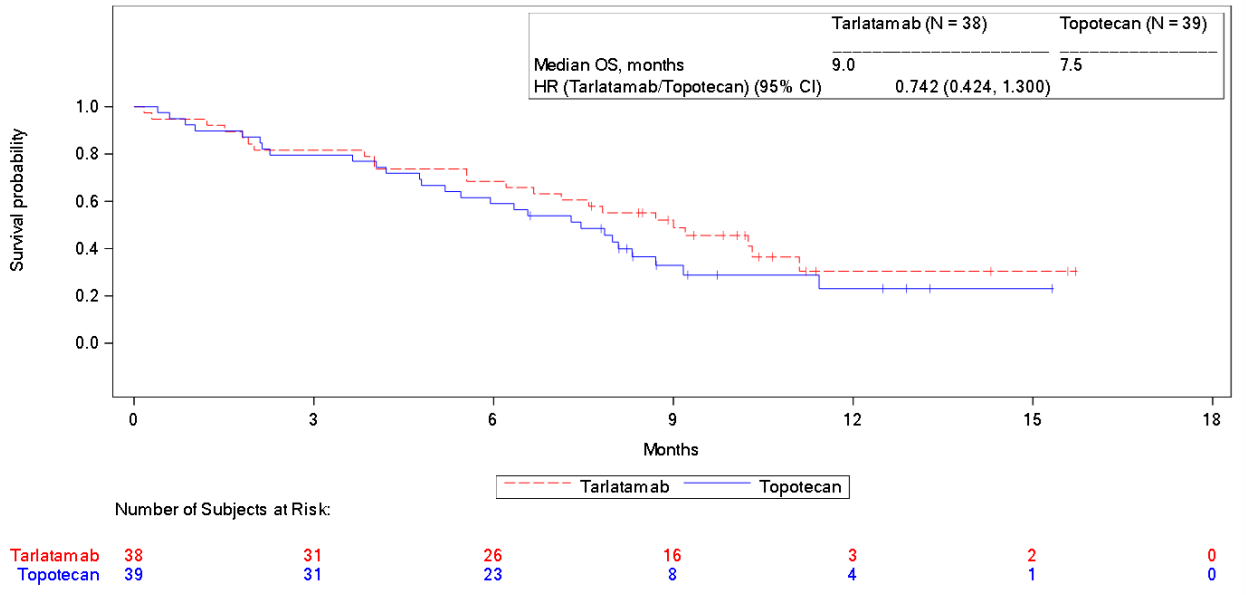
Figure 12. Forest plot of standard of care subgroup analysis of overall survival (ITT analysis set)



N = Number of subjects in the analysis set; NE = not estimable
Hazard ratios and 95% CIs are estimated using Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Post hoc subgroup analysis of OS for tarlatamab versus topotecan – DLL3 expression <25%

Figure 13. Kaplan-Meier plot for OS in subjects with DLL3 expression <25% (ITT)

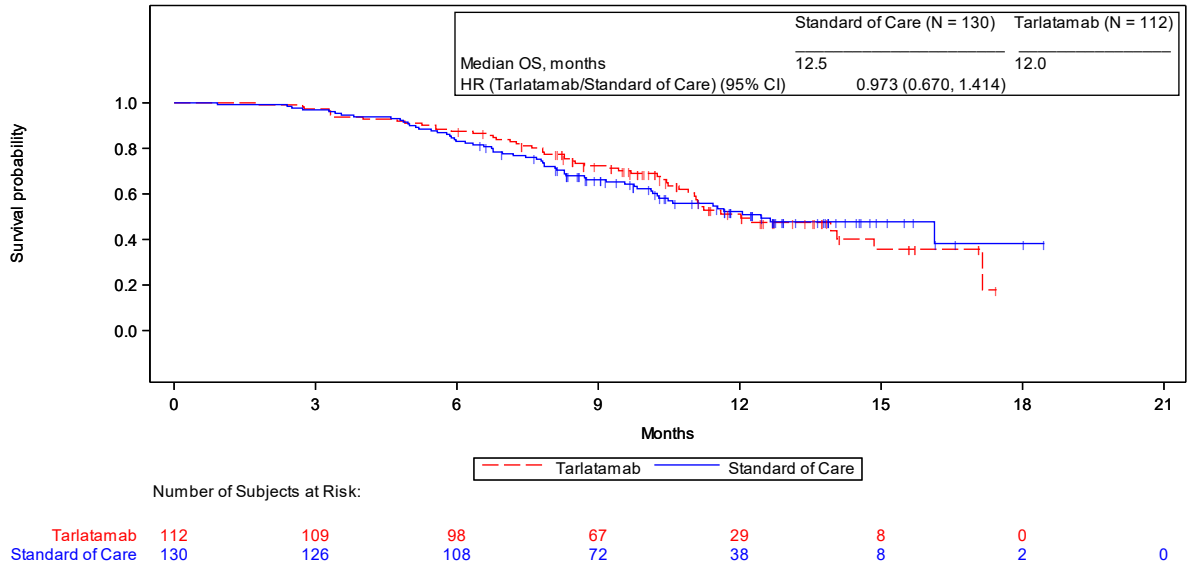


DLL3 tumour expression at 2+ and 3+ staining intensity
Topotecan treatment arm includes subjects who are randomized to the amrubicin or topotecan strata, and whose country is not Japan.
Censor indicated by vertical bar |
The survival curves and median overall survival are estimated using Kaplan-Meier method
Hazard ratio and 95% CI are estimated using an unstratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Post hoc analyses of OS according to subsequent therapy

Kaplan-Meier plots for OS for patients who had any subsequent therapy and patients who did not receive further anti-cancer therapies are shown in Figure 14 and Figure 15. The presented analyses indicate that the OS benefit for tarlatamab compared to SOC in the primary OS analysis is primarily driven by the group of patients who did not receive subsequent therapy (HR 0.427), whereas the group of patients who received subsequent therapy showed similar OS results for the two treatment arms (HR 0.973).

Figure 14. Kaplan-Meier plot for OS for subjects who had any subsequent therapy (ITT)

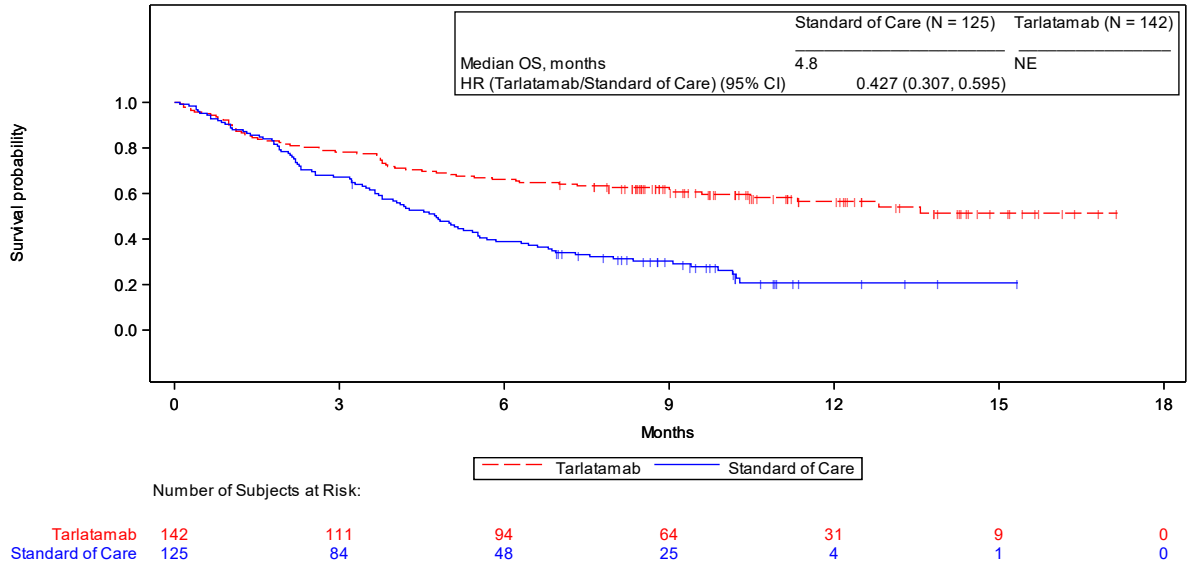


Number of Subjects at Risk:

Tarlatamab	112	109	98	67	29	8	0
Standard of Care	130	126	108	72	38	8	2	0

N = Number of subjects in the analysis set
Censor indicated by vertical bar |
The survival curves and median overall survival are estimated using Kaplan-Meier method
Hazard ratio and 95% CI are estimated using an unstratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Figure 15. Kaplan-Meier plot for OS for subjects without any subsequent therapy (ITT)



Number of Subjects at Risk:

Tarlatamab	142	111	94	64	31	9	0
Standard of Care	125	84	48	25	4	1	0

N = Number of subjects in the analysis set
The subjects without any subsequent therapy are considered regardless whether they discontinued or not.
Censor indicated by vertical bar |
The survival curves and median overall survival are estimated using Kaplan-Meier method

Hazard ratio and 95% CI are estimated using an unstratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Table 23. Descriptive analysis of overall survival by subsequent anti-cancer therapy

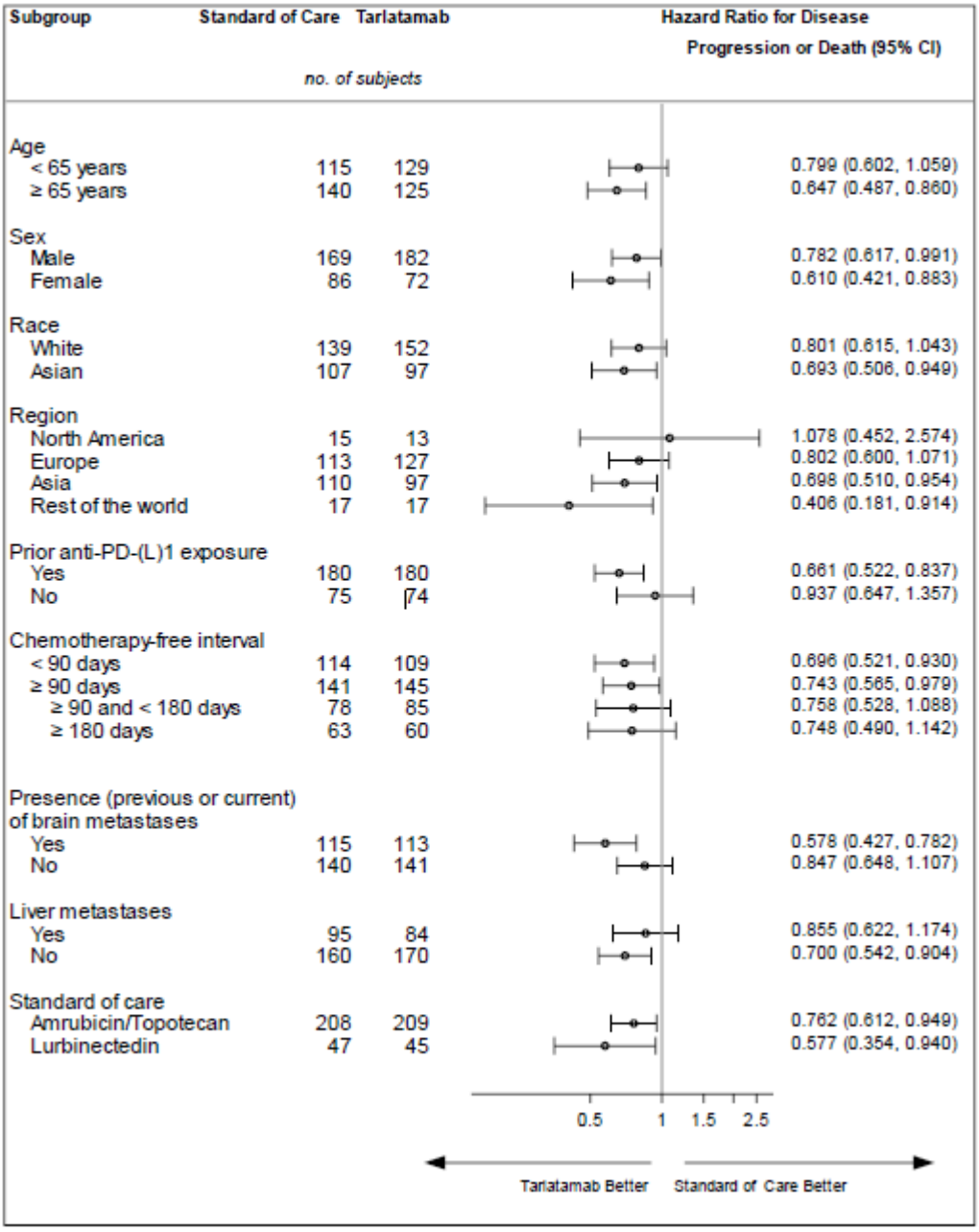
		Overall Survival - KM Estimate (months) (95% CI)[a]			Overall Survival Rates - KM Estimate (95% CI)[b]		
	n	25th Percentile	Median	75th Percentile	At 6 months	At 12 months	At 18 months
Standard of Care [N = 255]							
Subsequent therapy							
Randomized to SOC and received any subsequent therapy other than tarlatamab	115	7.2 (5.9, 8.3)	11.7 (9.8, NE)	NE (NE, NE)	81.7 (73.4, 87.7)	48.8 (38.5, 58.4)	45.0 (34.2, 55.2)
Randomized to SOC and received tarlatamab as subsequent therapy	15	12.1 (3.4, 16.1)	16.1 (10.6, NE)	NE (16.1, NE)	93.3 (61.3, 99.0)	77.0 (43.2, 92.2)	33.7 (1.7, 74.9)
Tarlatamab [N = 254]							
Subsequent therapy							
Randomized to tarlatamab and received any subsequent therapies	112	8.4 (7.1, 10.3)	12.0 (10.9, 14.9)	17.1 (14.9, NE)	87.5 (79.8, 92.4)	51.1 (39.7, 61.4)	NE (NE, NE)

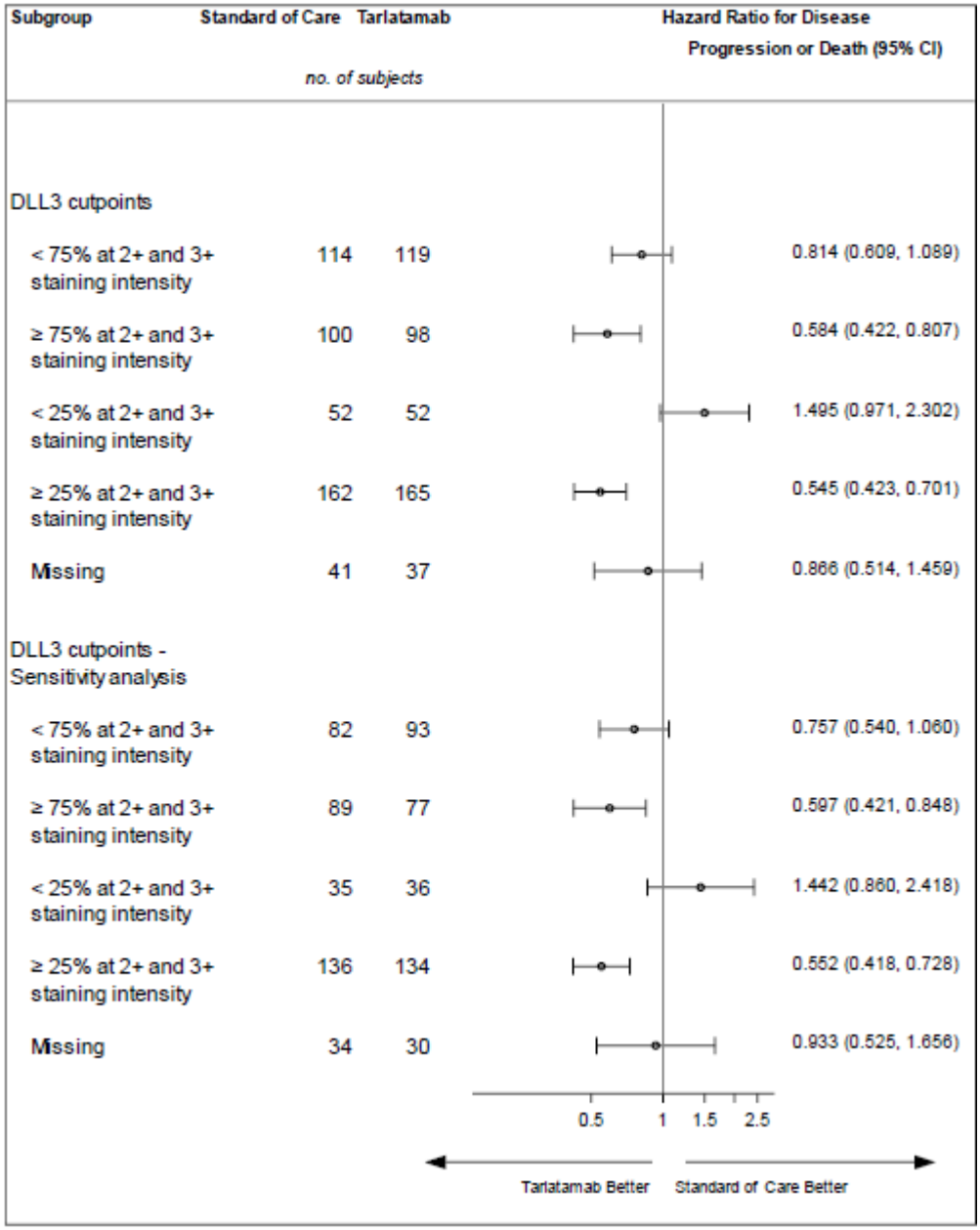
N = Number of subjects in the analysis set; n = Number of subjects with observed data
NE = not estimable; SOC = standard of care
[a] Median and quantiles are estimated using Kaplan-Meier method and 95% CIs of median are estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method
[b] 95% CIs are estimated using Kalbfleisch and Prentice (1980) method
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025; Table 14-4.6.4 eCTD 5.3.5.1.

In total, 44.4% (112/252) of the patients in the tarlatamab arm and 51.2% (125/244) of the patients in the SOC arm were treated with subsequent anti-cancer therapy after progression. Overall, there are no large deviations across treatment arms. The most commonly used treatments are checkpoint inhibitors (SOC arm: 8.6%, tarlatamab arm: 7.5%), TKI (catequentinib) (SOC arm: 10.2%, tarlatamab arm: 2.8%) and single agent chemotherapy (SOC arm: 38.9%, tarlatamab arm: 40.5%). The latter included topotecan (SOC arm: 3.3%, tarlatamab arm: 8.7%). In the SOC arm, 6.1% (15/244) received tarlatamab after progression.

Pre-defined subgroup analyses of PFS

Figure 16. Forest Plot of Subgroup analysis of PFS (ITT analysis set)



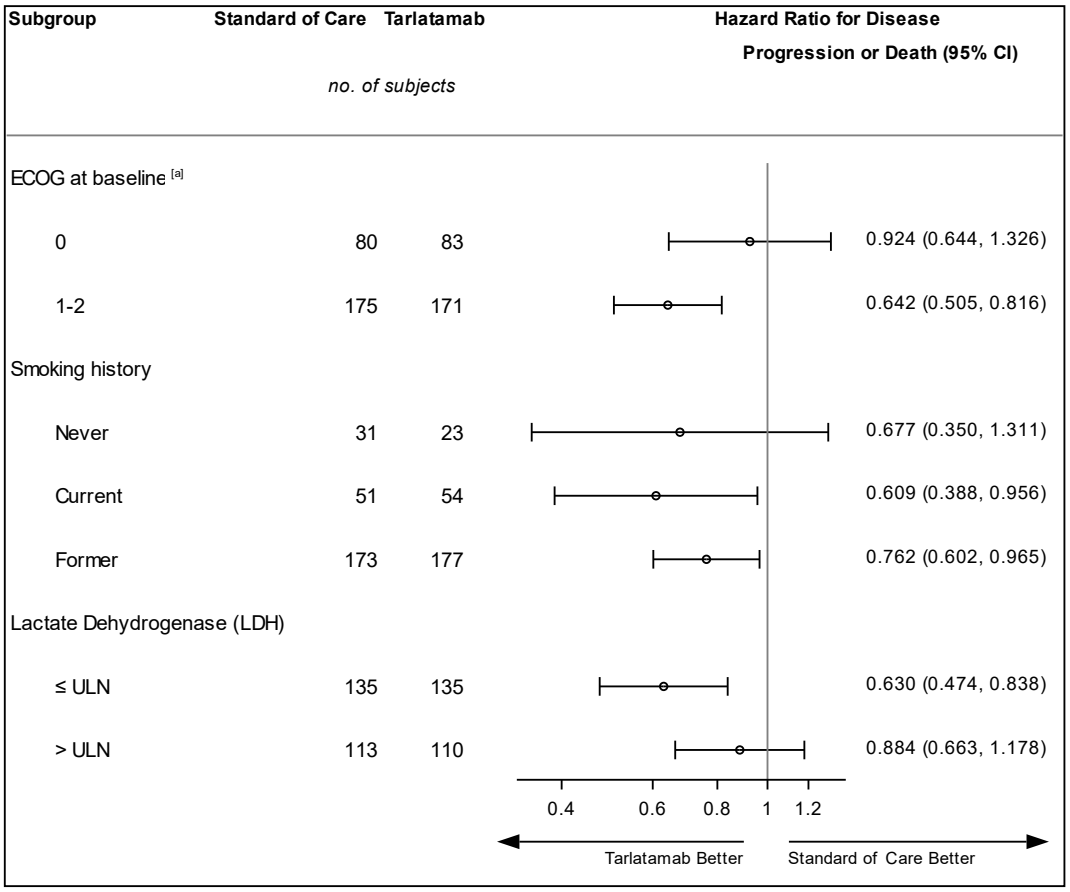


N = Number of subjects in the analysis set; NE = not estimable
Hazard ratios and 95% CIs are estimated using Cox proportional hazards model; a hazard ratio < 1.0 indicates a longer PFS for tarlatamab arm
For the subgroup categories with sample size of < 10 subjects, hazard ratios with corresponding 95% CIs are not displayed
The DLL3 cutpoints sensitivity analysis is applicable for samples tested with the primary vendor
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025;

Post hoc subgroup analyses of PFS

Additional subgroup analyses have been provided according to smoking history, LDH levels and ECOG performance status.

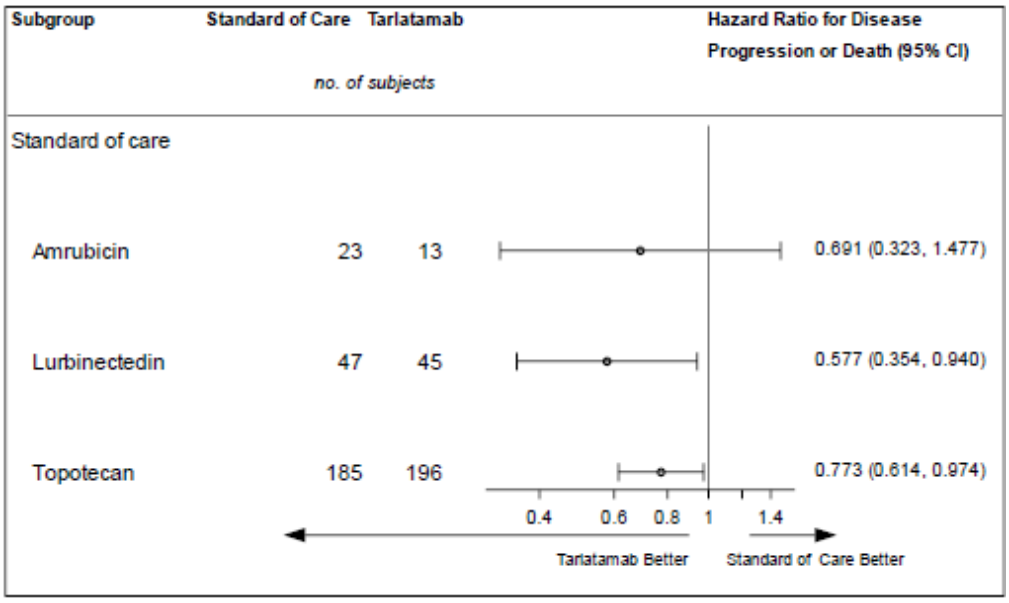
Figure 17. Additional Forest plot of subgroup analysis of PFS (ITT)



N = Number of subjects in the analysis set
[a] 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
Patients with ECOG status of 2 were assessed at randomization/day 1 instead of screening
Hazard ratios and 95% CIs are estimated using unstratified Cox proportional hazards model; a hazard ratio < 1.0 indicates longer PFS for tarlatamab arm
For the subgroup categories with sample size of < 10 subjects, hazard ratios with corresponding 95% CIs are not displayed
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Post hoc subgroup analysis of PFS for tarlatamab versus individual SOC

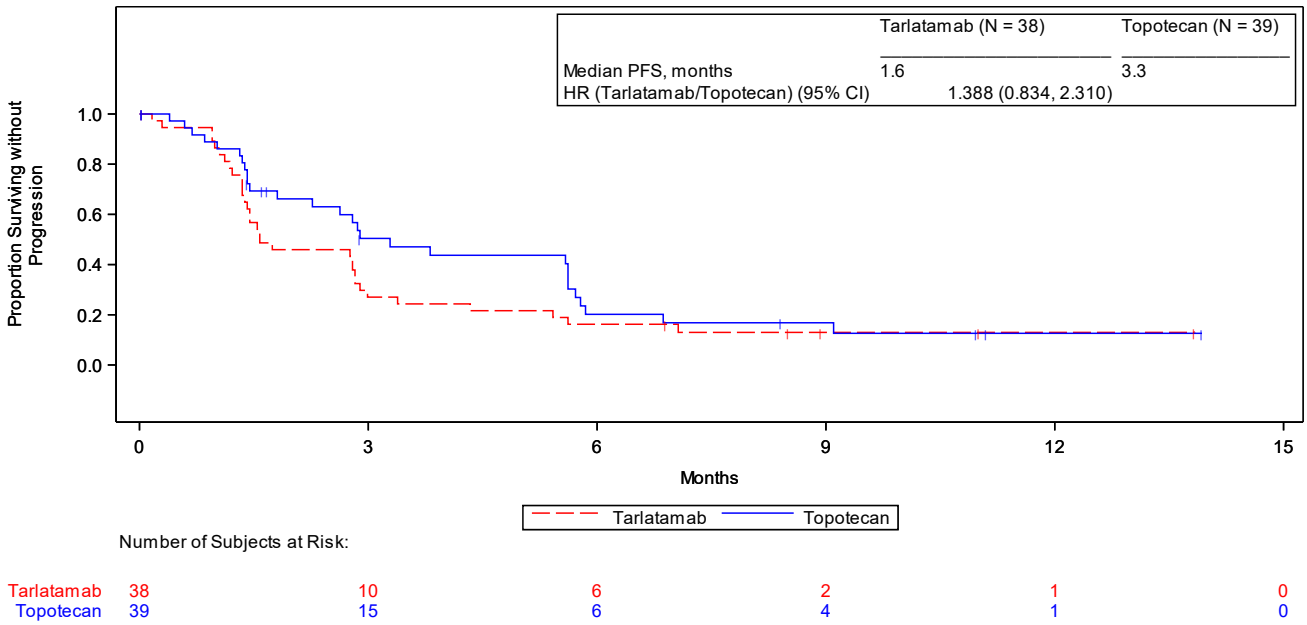
Figure 18. Forest plot of standard of care subgroup analysis of PFS as assessed by investigator (ITT analysis set)



N = Number of subjects in the analysis set; NE = not estimable
Hazard ratios and 95% CIs are estimated using Cox proportional hazards model; a hazard ratio < 1.0 indicates a longer PFS for tarlatamab arm
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Post hoc subgroup analysis of PFS for tarlatamab versus topotecan – DLL3 expression < 25%

Figure 19. Kaplan-Meier plot for PFS in subjects with DLL3 expression <25% (ITT)



Topotecan treatment arm includes subjects who are randomized to the amrubicin or topotecan strata, and whose country is not Japan.
Censor indicated by vertical bar |
The survival curves and median progression-free survival are estimated using Kaplan-Meier method
Hazard ratio and 95% CI are estimated using an unstratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a longer PFS for tarlatamab arm

Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025
Output: feu20251017-04-002-001-eff-km-pfs-inv-dll3-lt25-itt.rtf (Date Generated: 27OCT25 01:52)

Pre-defined and post-hoc sensitivity analyses

Table 24. Sensitivity analyses of overall survival

Analysis	Standard of Care		Tarlatamab		Hazard Ratio (95% CI)[c]	P-value (1-sided)[d]	P-value (2-sided)[d]
	Events[a]/ Subjects (%)	Median (months) (95% CI)[b]	Events[a]/ Subjects (%)	Median (months) (95% CI)[b]			
N	255	255	254	254			
Analysis based on true strata values	152/255 (59.6)	8.3 (7.0, 10.2)	111/254 (43.7)	13.6 (11.1, NE)	0.609 (0.476, 0.780)	< 0.001	< 0.001
N[e]	208	208	254	254			
Analysis based on excluding subjects planned to receive lurbinectedin	125/208 (60.1)	7.9 (6.6, 9.4)	111/254 (43.7)	13.6 (11.1, NE)	0.560 (0.432, 0.726)	< 0.001	< 0.001

The randomization stratification factors considered for first block of analysis are based on eCRF data, otherwise, IVRS data is used for rest of the analysis
[a] Events are death due to any cause
[b] Median and quantiles are estimated using Kaplan-Meier method and 95% CI of median are estimated using log-log transformation of KM survival estimate by
Brookmeyer and Crowley (1982) method
[c] Hazard ratios and 95% CIs are estimated using a stratified Cox proportional hazards model as specified; a hazard ratio < 1.0 indicates a better survival of
tarlatamab arm
[d] P-values are calculated using the stratified log-rank test as specified
[e] Excludes subjects planned to receive lurbinectedin in 'Standard of Care' treatment arm only
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025; eCTD 5.3.5.1

Table 25. Sensitivity analyses of progression-free survival as assessed by investigator

Analysis	Standard of Care		Tarlatamab		Hazard Ratio (95% CI)[c]	P-value (1-sided)[d]	P-value (2-sided)[d]
	Events[a]/ Subjects (%)	Median (months) (95% CI)[b]	Events[a]/ Subjects (%)	Median (months) (95% CI)[b]			
N	255	255	254	254			
Analysis based on true strata values	205/255 (80.4)	3.2 (2.9, 4.2)	191/254 (75.2)	4.2 (3.0, 4.4)	0.712 (0.582, 0.870)	< 0.001	< 0.001
N[e]	208	208	254	254			
Analysis based on excluding subjects planned to receive lurbinectedin	163/208 (78.4)	3.2 (2.9, 4.2)	191/254 (75.2)	4.2 (3.0, 4.4)	0.728 (0.589, 0.901)	0.002	0.003
N	255	255	254	254			
Analysis based on alternative censoring[f]	227/255 (89.0)	3.7 (2.9, 4.2)	197/254 (77.6)	4.2 (3.4, 4.5)	0.715 (0.590, 0.868)	< 0.001	< 0.001

N = Number of subjects in the analysis set; n = Number of subjects with observed data IVRS = interactive voice response system. The randomization stratification factors used in stratified analysis includes chemotherapy-free interval (<90 days, ≥90 days), and presence (previous or current) of brain metastases (yes or no). The randomization stratification factors considered for first block of analysis are based on eCRF data, otherwise, IVRS data is used for rest of the analysis
[a] Events are death or disease progression; event status of disease progression is derived using RECIST 1.1 criteria
[b] Median and quantiles are estimated using Kaplan-Meier method and 95% CI of median are estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method
[c] Hazard ratios and 95% CIs are estimated using a stratified Cox proportional hazards model as specified; a hazard ratio < 1.0 indicates a longer PFS for tarlatamab arm
[d] P-values are calculated using the stratified log-rank test as specified
[e] Excludes subjects planned to receive lurbinectedin in 'Standard of Care' treatment arm only
[f] This analysis is based on treatment policy strategy where progressive disease and death is considered as PFS event regardless of new anti-cancer therapy or missed visits
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

5.3.3. Clinical studies in special populations

Table 26: Clinical studies in special populations

	Controlled Trials[a]	***Non-controlled trials[b]***
Renal impairment* patients (Subjects number /total number)	Tarlatamab: 0/254 SOC 0/255	20200491: 0/133 20160323: 0/88

	Controlled Trials[a]	Non-controlled trials[b]
Hepatic impairment** patients (Subjects number /total number)	Tarlatamab: 0/254 SOC 0/255	20200491: 0/133 20160323: 0/88
Paediatric patients <18 years (Subjects number /total number)	Tarlatamab: 0/254 SOC 0/255	20200491: 0/133 20160323: 0/88
Older patients; Age 65-74 (Subjects number /total number)	Tarlatamab: 95/254 SOC: 115/255	20200491: 52/133 20160323: 41/88
Age 75-84 (Subjects number /total number)	Tarlatamab: 28/254 SOC: 25/255	20200491: 160/133 20160323: 7/88
Age 85+ (Subjects number /total number)	Tarlatamab: 2/254 SOC: 0/255	20200491: 0/133 20160323: 0/88
Other (Subjects number /total number)	N/A	N/A

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C
a: applicable Study 20210004
b: applicable studies 20160232 and 20200491

5.3.4. In vitro biomarker test for patient selection for efficacy

The applicant has not identified patients eligible for treatment with tarlatamab based on predictive biomarker testing.

5.3.5. Supportive studies

The applicant has provided two supportive studies, Phase 2 study 20200491 and FIH Phase 1 study 20160323. These studies are partly described in dose selection section as they form the basis for the dose finding of tarlatamab.

20200491 - Study Title: A Phase 2 Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of Tarlatamab in Subjects with Relapsed/Refractory Small-Cell Lung Cancer After Two or More Prior Lines of Treatment (DeLLphi-301)

The study is ongoing as of data cutoff date (18 October 2024). A total of 222 subjects were enrolled in this study, of which 100 were in the 10 mg target dose group across Parts 1 and 2, 88 in the 100 mg target dose group in Part 1, and 34 in the Part 3 modified safety monitoring 10 mg target dose group. Subjects were treated until disease progression, decision by sponsor, lost to follow-up, death, adverse event, subject request, ineligibility determined, protocol deviation, noncompliance, requirement for alternative therapy, or pregnancy.

Eligible subjects were men or women > 18 years of age with histologically or cytologically confirmed relapsed or refractory SCLC who progressed or recurred following 1 platinum-based regimen and at least 1 other prior line of therapy.

Baseline Demographics

Sex: 156 men (70.9%), 64 women (29.1%)

Median age: 64.0 years (range: 34 to 82)

Race: White (138 subjects [62.7%]), Asian (79 subjects [35.9%]), other (2 subjects [0.9%]), Black or African American (1 subject [0.5%])

Ethnicity: Not Hispanic/Latino (135 subjects [61.4%]), Hispanic/Latino (3 subjects [1.4%])

Efficacy results

Response was assessed by BICR per RECIST v1.1.

Table 27. Overall summary of study 20200491 key efficacy results – Interim analysis (18 October 2024 data cutoff) (Safety analysis set)

	Part 1 1->10 mg (N = 99)	Part 2 1->100 mg (N = 87)	Part 1 and Part 2 Overall (N = 186)	Part 3 1->10 mg Modified Safety Monitoring (N = 34)
Best overall response[a] per BICR - n (%)				
Confirmed complete response	4 (4.0)	7 (8.0)	11 (5.9)	1 (2.9)
Confirmed partial response	36 (36.4)	21 (24.1)	57 (30.6)	11 (32.4)
Objective response rate per BICR – n (%) (95% CI[b])	40 (40.4) (30.7, 50.7)	28 (32.2) (22.6, 43.1)	68 (36.6) (29.6, 43.9)	12 (35.3) (19.7, 53.5)
Duration of response per BICR				
Median DOR in months (95% CI)[c]	9.7 (6.9, NE)	12.5 (5.6, NE)	12.5 (7.0, 23.5)	7.1 (4.2, NE)
Median follow-up time for DOR (KM) in months (95% CI)[c]	23.5 (20.7, 26.1)	20.7 (16.6, 26.0)	23.3 (20.6, 26.0)	13.6 (2.8, NE)
Disease control per BICR				
Disease control rate– n (%) (95% CI[b])	70 (70.7) (60.7, 79.4)	55 (63.2) (52.2, 73.3)	125 (67.2) (60.0, 73.9)	18 (52.9) (35.1, 70)
Median duration of disease control (KM) in months (95% CI)[c]	6.9 (5.4, 8.6)	6.7 (4.1, 8.4)	6.9 (5.4, 8.3)	7.8 (5.0, 8.5)
KM estimate at 6 months -- % (95% CI)[d]	54.2 (41.4, 65.3)	51.1 (36.7, 63.8)	52.8 (43.3, 61.4)	65.4 (35.1, 84.2)
KM estimate at 12 months -- % (95% CI)[d]	33.1 (21.9, 44.8)	30.6 (18.6, 43.6)	32.0 (23.7, 40.7)	24.5 (6.0, 49.5)
Progression-free survival per BICR				
Median PFS in months (95% CI)[c]	4.3 (3.0, 5.6)	3.2 (2.6, 4.2)	4.0 (2.9, 5.4)	3.9 (1.4, 6.4)
Median follow-up time for PFS (KM) in months (95% CI)[c]	24.7 (21.9, 25.1)	22.0 (17.9, 27.4)	24.6 (21.9, 24.9)	16.5 (4.0, NE)
KM estimate of PFS at 6 months -- % (95% CI)[d]	39.7 (29.6, 49.6)	33.9 (23.7, 44.5)	37.0 (29.7, 44.3)	35.8 (19.0, 53.0)
KM estimate of PFS at 12 months -- % (95% CI)[d]	24.3 (15.9, 33.6)	20.4 (12.2, 30.0)	22.5 (16.4, 29.1)	13.4 (3.5, 29.9)
Overall survival				
Median OS (KM) in months (95% CI)[c]	15.2 (10.8, 21.3)	14.1 (12.1, 21.2)	14.1 (12.3, 19.0)	6.4 (3.8, 9.1)
Median follow-up time for OS (KM) in months (95% CI)[c]	26.2 (24.2, 27.1)	25.9 (23.8, 27.4)	25.9 (24.8, 26.9)	17.6 (15.2, 19.1)
KM estimate of OS at 6 months -- % (95% CI)[d]	73.4 (63.2, 81.2)	71.4 (60.1, 80.0)	72.5 (65.2, 78.5)	54.8 (36.6, 69.8)
KM estimate of OS at 12 months -- % (95% CI)[d]	57.0 (46.2, 66.3)	61.8 (50.0, 71.6)	59.1 (51.3, 66.1)	30.5 (16.0, 46.3)

-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose)
BICR = blinded independent central review; DOR = duration of response; KM = Kaplan-Meier; NE = not estimable; OS = overall survival; PFS = progression-free survival
The safety analysis set for all parts included all subjects who received at least 1 dose of tarlatamab.
a Assessment of disease response was determined using RECIST 1.1 guidelines.
b Exact CI was calculated using the Clopper-Pearson method.
c Medians were estimated using Kaplan-Meier method, and 95% CI was estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method.
d 95% CIs were estimated using the Kalbfleisch and Prentice (1980) method.

20160323 - Study Title: A Phase 1 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Tarlatamab in Subjects With Small Cell Lung Cancer (DeLLphi-300)

Study 20160323 is an ongoing phase 1, FIH, open-label, ascending, multiple-dose study evaluating the safety, tolerability, and PK of tarlatamab in subjects > 18 years of age with previously treated SCLC who progressed or recurred following at least 1 platinum-based regimen.

As of the data cutoff date of 18 October 2024, a total of 269 subjects were enrolled in this study, and 266 subjects (98.9%) were treated with at least 1 dose of tarlatamab across various dose ranges; 88 subjects (32.7%) were treated at the 10 mg Q2W dose with one-step dosing. Subjects were treated

until disease progression, subject request, investigator decision, safety concern, death, lost to follow-up, or decision by sponsor.

Subjects must have had relapsed or refractory SCLC with measurable disease per modified RECIST v1.1, which applies aspects of the immune-related response criteria to RECIST v1.1; an ECOG performance status of ≤ 2; and adequate organ function.

Baseline Demographics

Sex: 150 men (56.4%), 116 women (43.6%)

Median age: 63.0 years (range: 32 to 80)

Race: White (211 subjects [79.3%]), Asian (26 subjects [9.8%]), other (20 subjects [7.5%]), Black or African American (9 subjects [3.4%])

Ethnicity: Not Hispanic/Latino (205 subjects [77.1%]), Hispanic/Latino (6 subjects [2.3%])

Efficacy results

Table 28. Overall summary of study 20160323 key efficacy results – Primary analysis (18 October 2024 data cutoff) (Safety analysis set)

	Tarlatamab 1->10 mg (N = 88)	Tarlatamab Overall[a] (N = 266)
Best overall response per investigator- n (%)		
Confirmed complete response	2 (2.3)	4 (1.5)
Confirmed partial response	24 (27.3)	62 (23.3)
Objective response rate per investigator – n (%) (95% CI[b])	26 (29.5) (20.3, 40.2)	66 (24.8) (19.7, 30.5)
Duration of response per investigator		
Median DOR in months (95% CI)[d]	14.8 (6.6, NE)	11.2 (7.6, 14.9)
Median follow-up time for DOR[c] (KM) in months (95% CI[d])	9.2 (5.6, 18.0)	24.8 (12.2, 32.8)
Disease control rate per investigator – n (%) (95% CI[b])	47 (53.4) (42.5, 64.1)	141 (53.0) (46.8, 59.1)
Progression-free survival (KM) per investigator		
Median PFS in months (95% CI[d])	3.4 (1.9, 4.4)	3.3 (2.1, 3.7)
Median follow-up time for PFS (KM) in months (95% CI[d])	11.1 (9.3, 19.8)	25.5 (13.6, 33.1)
KM estimate of PFS at 6 months – % (95% CI[e])	30.2 (20.9, 40.1	29.3 (23.7, 35.1)
KM estimate of PFS at 12 months – % (95% CI[e])	17.8 (9.9, 27.5)	16.4 (11.9, 21.6)
Overall survival (KM)		
Median OS in months (95% CI[d])	14.9 (9.7, 22.2)	13.2 (11.3, 17.8)
Median follow-up time for OS (KM) in months (95% CI[d])	12.0 (10.2, 12.8)	12.1 (12.0, 12.9)
KM estimate of OS at 6 months – % (95% CI[e])	70.6 (59.3, 79.2)	73.4 (67.4, 78.4)
KM estimate of OS at 12 months – % (95% CI[e])	55.2 (42.8, 65.9)	54.4 (47.7, 60.7)

-> = step dose to target dose (eg, 1 -> 10 mg = 1 mg step dose to 10 mg target dose

DOR = duration of response; NE = not estimable; OS = overall survival; PFS = progression-free survival
a Includes all subjects who received any dose of tarlatamab monotherapy or combination therapy.
b Exact 95% CI is calculated using the Clopper Pearson method.
c Follow-up time is measured by reversing the status indicator for censored and events.
d 95% CI using Brookmeyer and Crowley (1982) method.
e 95% CI using Kalbfleisch and Prentice (1980) method.
The safety analysis set includes all subjects who received at least 1 dose of tarlatamab.
Source: Modified from Study 20160323 Supplemental PA CSR, Table 14-4.1.1, Table 14-4.2.1, Table 14-4.3.1, and Table 14-4.4.1; eCTD 2.7.3

Summary of efficacy for tarlatamab 10 mg across the pivotal and supportive studies

Kaplan-Meier estimates for median OS (95% CI):

- 13.6 months (11.1, NE) in Study 20210004
- 15.2 months (10.8, 21.3) in Study 20200491
- 14.9 months (9.7, 22.2) in Study 20160323

Kaplan-Meier estimates of median PFS (95% CI):

- 4.2 months (3.0, 4.4) in Study 20210004
- 4.3 months (3.0, 5.6) in Study 20200491
- 3.4 months (1.9, 4.4) in Study 20160323

ORR (95% CI):

- 35.0% (29.2, 41.3) in Study 20210004
- 40.4% (30.7, 50.7) in Study 20200491
- 29.5% (20.3, 40.2) in Study 20160323

Kaplan-Meier estimates of median (95% CI) DOR:

- 6.9 (4.5, 12.4) months in Study 20210004
- 9.7 (6.9, NE) months in Study 20200491
- 14.8 (6.6, NE) months in Study 20160323

DCR (95% CI):

- 68.1% (62.0, 73.8) in Study 20210004
- 70.7% (60.7, 79.4) in Study 20200491
- 53.4% (42.5, 64.1) in Study 20160323

5.3.6. Patient experience data (PED)

PRO was a secondary endpoint in the pivotal study, and results are reported in the section *Outcomes and estimation*.

5.3.7. Overall discussion and conclusions on clinical efficacy

5.3.7.1. Discussion

The MAA for Imdylltra targets an indication in the second-line treatment of ES-SCLC. The application is based on data from the pivotal phase 3 study DeLLphi-304 and is supported by data from a phase 2 study (20200491) and a phase 1 FIH study (20160323), which included patients in at least third- and second-line treatment, respectively. The dose regimen for tarlatamab used in the pivotal study is based on findings from the phase 2 study and the FIH study. Overall, the clinical development plan includes adequate studies to evaluate Imdylltra for the proposed therapeutic indication.

Pivotal study - DeLLphi-304

The pivotal study is an ongoing, open-label, randomized, multi-centre, phase 3 study comparing tarlatamab with SOC therapy in patients with ES-SCLC who have progressed after one prior line of platinum-containing therapy, consistent with the current proposed indication. Subjects were randomized in a 1:1 allocation ratio to receive tarlatamab or SOC therapy (lurbinectedin or topotecan in the US, Canada, Australia, Singapore, and Korea; amrubicin in Japan; topotecan in all countries except Japan). Given that this is a globally conducted study, the chosen control-arm strategy is considered acceptable. Topotecan is the only drug licensed in the European Union for use as second-line therapy in SCLC. As outlined in the current ESMO guideline (ESMO Clinical Practice Guideline: Small Cell Lung Cancer | ESMO), amrubicin, which is not available in Western countries, has not demonstrated improved survival compared to topotecan in an RCT for second-line treatment of SCLC. According to the guideline, lurbinectedin is recommended as a treatment option for patients with platinum-resistant relapse but has failed to demonstrate superior OS compared to topotecan. Lurbinectedin is currently not approved in the EU for the treatment of SCLC.

Endpoints

OS is the primary endpoint of the pivotal study, as recommended for studies in patients with limited treatment options and short life-expectancy. The primary analysis of OS is based on a preplanned interim analysis and is presented as the primary analysis of OS because the interim efficacy boundary was crossed in accordance with the SAP. The primary analysis was not stratified for all stratification factors used in the randomization to avoid over-stratification. This was a change introduced with amendment 2 while the study was ongoing. As this is seen as a reasonable course of action and not expected to have a large impact on the outcome it will not be pursued further.

PFS is a key secondary endpoint, together with PRO. Radiological imaging was performed every 6 weeks and assessed according to RECIST v1.1 criteria. However, evaluations were conducted solely by investigators, despite blinded independent review being recommended by the CHMP scientific advice (EMA/SA/0000115184). Given that this is an open-label study and PFS is a key secondary endpoint, blinded independent review would have been preferable.

The choice of PRO as a key secondary endpoint is debatable. This is an open-label study with PRO assessments limited to the first 18 weeks. Thus, although the PRO data could be considered supportive, the PRO results are not included in the SmPC.

Study population

According to the study title, the DeLLphi-304 study should include subjects with relapsed ES-SCLC after platinum-based first-line chemotherapy. The definition of ES-SCLC included patients with LS-SCLC at diagnosis which had relapsed after initial platinum-based chemotherapy. In addition, the criteria allowed patients with relapse after adjuvant platinum-based chemotherapy, which is not

completely in line with the proposed indication, i.e. treatment with tarlatamab after platinum-based first-line chemotherapy. However, only one patient in the study belonged to this category, i.e. had only received adjuvant platinum-based chemotherapy and therefore had no influence on the outcome of the study.

No requirement regarding DLL3 expression has been specified for enrolment into DeLLphi-304. An exploratory endpoint focusing on biomarkers associated with clinical outcomes was removed in Amendment 2 to the protocol (06 Sept. 2023). Despite aiming for treatment of patients regardless of DLL3 expression, the applicant used a commercial test (Ventana SP347 immunohistochemistry (IHC) assay) to investigate the outcome in subgroups of patients according to DLL3 expression. Cut-offs of 25% and 75% tumour cell staining at 2+/3+ intensity were chosen for exploratory analysis based on available data and published literature at the time. Available data indicated that DLL3 expression was observed in at least 95% of SCLC patients (Paz-Ares et al, 2023).

Efficacy data and additional analyses

A total of 688 subjects were screened for enrolment into the pivotal study, of whom 509 were randomized. The treatment arms appear to be balanced overall with regard to baseline characteristics. Of the 509 subjects randomized, most were either White (57.2%) or Asian (40.1%), and 69% were men. The median age was 65 years (range: 20-86). The patients had an ECOG score of 1 (67%) or 0 (32%). The majority of the patients were either current smokers (21%) or former smokers (69%). Prior PD-1 or PD-L1 therapy was received by 71% of the patients. A total of 83 patients (39 randomized to tarlatamab, 44 randomized to SOC) had been treated with curative intent prior to enrolment and are considered to have had LS-SCLC at the initial diagnosis but recurred following platinum-based chemotherapy. In both treatment arms, 92% of the patients had stage IV disease at enrolment. Overall, the study population is representative of patients with ES-SCLC.

Protocol deviations

The protocol deviations listed by the applicant are not expected to have a major impact on the efficacy evaluation. These deviations predominantly involve the inclusion of patients who do not meet the eligibility criteria due to safety issues and off-schedule procedures (excluding tumour assessments). Overall, the deviations are balanced between the treatment arms. The most notable difference between the treatment arms is related to predose safety lab assessments, which concerns 12.5% of the tarlatamab treated patients and only 0.8% of those in the SOC arm.

Primary endpoint OS

The HR for the comparison of tarlatamab with SOC was 0.599 (95% CI: 0.468, 0.768). The difference was statistically significant (p-value <0.001), crossing the predefined interim p-value boundary of p<0.01. The data is sufficiently mature to conclude that tarlatamab is overall superior to the selected SOC. A 40% reduction in the risk of death compared to the active comparator arm is considered clinically relevant in this patient population. The OS in the SOC arm, i.e., 8.3 months, is slightly better than what has been reported for topotecan in clinical studies (~6 months). Additionally, there is a lack of information from RCTs regarding OS for lurbinectedin and amrubicin in the second-line treatment of SCLC.

In total, 44.4% (112/252) of the patients in the tarlatamab arm and 51.2% (125/244) of the patients in the SOC arm received subsequent anti-cancer therapy after progression, which could potentially impact the OS outcome. However, overall, no major deviations across treatment arms were observed. The most commonly used treatments included checkpoint inhibitors (SOC arm: 8.6%, tarlatamab arm: 7.5%), TKI (catequentinib) (SOC arm: 10.2%, tarlatamab arm: 2.8%) and single-agent chemotherapy (SOC arm: 38.9%, tarlatamab arm: 40.5%). Among single-agent chemotherapy, topotecan was

included (SOC arm: 3.3%, tarlatamab arm: 8.7%). In the SOC arm, 6.1% (15/244) of patients received tarlatamab after progression.

The Applicant has presented analyses and KM plots of OS for subjects who did and did not receive subsequent therapy. These analyses indicate that the OS benefit for tarlatamab compared to SOC in the primary OS analysis is primarily driven by patients who did not receive subsequent therapy (HR 0.427), whereas patients who did receive subsequent therapy showed similar OS results for the two treatment groups (HR 0.973).

Key Secondary endpoint PFS

The median PFS was 4.2 months (95% CI: 3.0, 4.4) in the tarlatamab arm compared to 3.2 months (95% CI: 2.9, 4.2) in the SOC arm. The HR for PFS comparing tarlatamab to SOC was 0.716 (95% CI: 0.586, 0.875; p <0.001), which was concluded to be statistically significant. The Kaplan-Meier plot showed separation of the curves starting at approximately 2 months, with continued separation observed, although the difference between treatment arms remained limited. The PFS outcome is considered supportive of the primary endpoint of OS. However, the observed gain in terms of relative hazards and difference between medians appears to be greater for OS than for PFS, with HRs of 0.716 (95% CI: 0.586, 0.875) and 0.599 (95% CI: 0.468, 0.768), respectively.

Key Secondary endpoint PRO

The PRO data showed a statistically significant improvement in dyspnoea and cough from baseline through week 18, along with a non-significant trend towards improvement in chest pain. The null hypotheses for Physical Functioning and GHS/QOL were not subsequently tested, as the null hypothesis was not rejected for all three symptom endpoints. At 18 weeks from baseline, differences in LS mean change between treatment groups favoured tarlatamab for Physical Functioning and GHS/QOL. Despite these positive results for tarlatamab, criticism persists regarding the open-label design of the study and the limitations of PRO analyses to data from the first 18 weeks of treatment. The PRO data is therefore omitted from the SmPC.

Secondary endpoint ORR/DOR/DCR

The ORR was 35.0% (95% CI: 29.2, 41.3) in the tarlatamab arm compared to 20.4% (95% CI: 15.6, 25.9) in the SOC arm (odds ratio of 2.1; 95% CI: 1.4, 3.2). A higher proportion of patients were assessed to have stable disease in the SOC arm, contributing to a similar disease control rate between the treatment arms, i.e., 68.1% (95% CI: 62.0, 73.8) in the tarlatamab arm and 64.3% (95% CI: 58.1, 70.2) in the SOC chemotherapy arm. The median DOR was 6.9 months (95% CI: 4.5, 12.4) and 5.5 months (95% CI: 4.2, 5.7), respectively, in the two study arms. Notably, while the confidence intervals for median DOR overlap, with similar lower limits for both treatment arms, the confidence interval for the tarlatamab arm is wider, suggesting greater variability in patient response.

Subgroup analyses

Subgroup analyses of OS aligned with the overall OS result except for the following: black race, North America region, and DLL3 expression. For the two former subgroups, the observed outcome can be attributed to baseline characteristics and the small sample sizes.

In the subpopulation with DLL3 expression <25% (DLL3 staining intensity at 2+/3+), the median OS was 7.8 (95% CI: 5.6, 11.1) months in the tarlatamab arm and 7.9 (95% CI: 5.2, 9.2) months in the SOC chemotherapy arm, with a hazard ratio 0.954 (95% CI: 0.590, 1.541). In comparison, in the subpopulation with DLL3 expression ≥25%, the median OS was 17.1 (95% CI: 12.8, NE) months and 9.6 (95% CI: 6.9, 10.3) months, respectively, and the HR was 0.505 (95% CI: 0.365, 0.698). The PFS analysis of the subgroup with DLL3 expression <25% indicates inferior efficacy of tarlatamab compared to SOC (HR 1.50; 95% CI: 0.97, 2.30). The applicant has provided OS and PFS results

based on the 16 patients in the SOC arm and 10 patients in the tarlatamab arm who did not test positive for DLL3. The results appear to be largely consistent with those for the subgroup of patients with DLL3 expression <25%, indicating that patients may obtain OS efficacy similar to SOC even if they lack measurable expression of DLL3. Taking into consideration the negative trend for PFS, uncertainty remains whether the OS outcome in the DLL3 <25% subgroup could be partially driven by patients who received further lines of therapy after progression on tarlatamab. The effect of the DLL3 assay measurement error (misclassification) has not been characterized which further contributes to the uncertainty of the interpretation of subgroup results.

The applicant has provided an integrated summary of efficacy based on the 3 studies of tarlatamab in SCLC which does not bring further enlightenment to the issue on whether there is a limit to the lower level of DLL3 expression that is important for obtaining benefit from tarlatamab treatment compared to SOC. Further division into sublevels of DLL3 expression is not expected to provide additional clarification since the subgroups will likely be too small to draw any conclusions.

Since overall OS benefit has been indisputably shown compared to SOC treatment and no negative OS trend has been observed for patients with low DLL3 expression, further investigation of the available data is not expected to clarify whether any patient subset should be excluded from treatment with tarlatamab. Restriction of the indication based on DLL3 expression is not justified since tarlatamab demonstrates robust efficacy in terms of OS in the ITT population. Furthermore, DLL3 is not routinely tested in clinical practice.

Post hoc analyses of tarlatamab versus the individual SOCs in the overall population showed point estimates for HR below 1, favouring tarlatamab in terms of both OS and PFS. Post hoc analyses of OS and PFS of tarlatamab vs topotecan for patients with DLL3 expression <25% provided OS outcome similar to the subgroup which included all patients with DLL3 expression <25%.

The subgroup analyses yielded similar HRs for platinum-sensitive and platinum-resistant patients.

Supportive studies

While acknowledging differences in study design and patient populations, the supportive studies provide efficacy results for tarlatamab 10 mg that are overall consistent with those observed in the pivotal study.

Notably, the subgroup analyses of patients in the phase 2 study, both for ORR and PFS, indicate limited efficacy for patients with DLL3 expression below 25% 2+ and 3+ staining intensity.

5.3.7.2. Conclusions on the clinical efficacy

Overall, the outcomes of the pivotal study and the supportive studies demonstrate that tarlatamab, in the treatment of patients with ES-SCLC who have progressed on or after first-line treatment with platinum-based chemotherapy, led to statistically significant and clinically relevant improvements in OS compared to SOC, including topotecan. These findings are further supported by improvements in PFS and ORR. It cannot be excluded that tarlatamab may be inferior to SOC for patients with low DLL3 expression. However, the data provided does not allow exclusion of patient subgroups from treatment with tarlatamab.

5.4. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal

product is administered, and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

Tarlatamab's safety profile is primarily supported by data from study 20210004. In addition, pooling of safety data between studies 20210004, 20200491, and 20160323 for subjects treated with tarlatamab 10 mg is presented as supportive information, along with pooled safety data from studies 20210004, 20200491, and 20160323 across all doses and all subjects treated with tarlatamab monotherapy.

In studies 20210004, 20200491, and 20160323, adverse events and serious adverse events were collected on a continuous basis throughout the treatment period.

In studies 20210004 and 20200491, safety follow-up visits were conducted approximately 60 (+5) days and 42 (+5) days, respectively, after the last dose of study treatment, irrespective of whether subsequent anti-cancer therapy had been initiated during that period. In study 20160323, the safety follow-up period lasted up to approximately 42 (+5) days after the last dose of tarlatamab.

During the subsequent long-term follow-up phase of studies 20210004 and 20200491, serious adverse events suspected to be related to investigational product were reported to the Sponsor. In Study 20210004, long-term follow-up was to be conducted every 12 weeks (± 14 days) from the safety follow-up visit (or last imaging visit, whichever is later) for up to 3 years after the last subject was enrolled, or 1 year from the subject's last dose of study treatment, whichever was later. In study 20200491, long-term follow-up was to be conducted every 3 months (± 2 weeks) for 1 year after the last subject's last dose of tarlatamab or 5 years from the first subject enrolled, whichever occurred first.

The safety assessments for subjects from studies 20210004, 20200491, and 20160323 included the incidence of treatment-emergent adverse events (TEAEs) (AEs starting after first dose of any study treatment up to 65 days after the last dose of any treatment or the end of study, whichever comes first), treatment-related TEAEs (any TEAE that per investigator review has a reasonable possibility of being caused by the investigational product), serious adverse events (SAEs), adverse events of special interest (AESI), deaths, clinical laboratory evaluations, Hy's law, vital signs and physical measurements, and immunogenicity. For studies 20200491 and 20160323, statistical analyses of electrocardiogram (ECG) measurements were also performed.

For all studies, the presented safety data do not include AEs related to disease progression.

AEs were coded to PT and SOC using MedDRA v 27.1. For studies 20210004 and 20200491, CRS and ICANS severity was graded using ASTCT guidelines (Lee et al, 2019), and other AEs were graded using CTCAE v5.0. For the monotherapy cohorts of study 20160323, the severity of each AE, with the

exception of CRS, was graded using CTCAE v4.0 criteria and converted from CTCAE v4.0 to v5.0 where possible. CRS was graded according to criteria by Lee et al, 2014 and converted to reflect ASTCT guidelines (Lee et al, 2019) where possible.

5.4.2. Patient exposure

Table 29. Patient exposure (at data cutoff)

	Patients enrolled	***Patients exposed****	***Patients exposed to the proposed dose range***	***Patients with long term** safety data***
Blinded studies (placebo-controlled; Study 20230016)	171	NA	NA	NA
Blinded studies (active - controlled; Study 20200041)	323	NA	NA	NA
Open studies (studies 20210004, 20200491, and 20160323)	735	730	473	Treatment duration (10 mg) >6 months: 188 >9 months: 114 >12 months: 66
Open studies (Study 20230273)	32	31	31	Treatment duration (10 mg) >6 months: 2 >9 months: 0 >12 months: 0
Post marketing	-	919 PY	NA	NA
Compassionate use	126	NA	NA	NA

NA = Not available; PY = patient-years.
* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.
Data cutoff date: 29 January 2025 for study 20210004; 18 October 2024 for studies 20200491 and 20160323; 28 March 2025 for study 20230273; 24 March 2025 for studies 20230016 and 20200041; 15 May 2025 for post marketing patient exposure; 25 November 2025 for the compassionate use program.

To support safety of tarlatamab monotherapy for the proposed indication at the indicated dose (10 mg), the Applicant has provided results from:

- The randomized, open-label pivotal phase 3 study 20210004, which compared tarlatamab to SOC chemotherapy (amrubicin, lurbinectedin, topotecan) in subjects with SCLC who have had progression on or after platinum-based chemotherapy (tarlatamab **N=252**; SOC chemotherapy **N=244**); and
- a supportive primary integrated safety analysis, which pools data from subjects with SCLC treated with tarlatamab 10 mg across studies 20210004 (N=252), 20200491 (phase 2 trial in subjects with recurrent SCLC who have progressed or recurred after 1 platinum-based regimen with or without checkpoint inhibitor and at least 1 other line of therapy; N=133), and 20160323 (first-in-human phase 1 trial in subjects with SCLC who have progressed or recurred following at least 1 platinum-based regimen; N=88) (**N=473**)

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

Additional supportive integrated safety data across all doses (up to 100 mg) and all subjects treated with tarlatamab monotherapy have also been provided (**N=730**).

Key demographic characteristics and baseline disease characteristics are presented in the Clinical Efficacy section.

For study 20210004, the median duration of tarlatamab treatment was 18.21 (range 0.1-74.6) weeks, administered over 5.0 (range 1-19) cycles. At the time of data cutoff, 10.3% subjects had received tarlatamab treatment for ≥ 12 months in study 20210004, and 27.2% subjects were still undergoing tarlatamab treatment. The median number of tarlatamab doses administered per subject was 11.0 (range 1-39), and the median cumulative tarlatamab dose was 101.00 (range 1.0-381.0) mg. In the SOC chemotherapy group, the median duration of treatment was 10.86 (range 0.1-64.0) weeks, administered over 4.0 (range 1-21) cycles. The median number of investigational product doses received was 15.0 (range 1-105), and the median cumulative dose was 24.93 (range 1.4-2209.6) mg/m2.

Further details on exposure to tarlatamab in study 20210004 and across pooled datasets is presented in Table 30.

Data cutoff date: 29 January 2025 for study 20210004; 18 October 2024 for studies 20200491 and 20160323.

Table 30. Exposure to Tarlatamab - Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Number of doses per participant				
n	252	0	473	730
Mean	13.3	-	14.6	14.6
SD	9.6	-	13.3	15.4
Median	11.0	-	10.0	9.0
Q1, Q3	5.0, 20.0	-, -	5.0, 20.0	4.0, 19.0
Min, Max	1, 39	-, -	1, 88	1, 98
Cumulative dose (mg)				
n	252	0	473	730
Mean	123.542	-	135.007	478.497
SD	95.368	-	129.096	1164.824
Median	101.000	-	91.000	126.000
Q1, Q3	41.000, 191.000	-, -	41.000, 191.000	41.000, 311.000
Min, Max	1.000, 381.000	-, -	1.000, 671.000	0.036, 9701.000
Relative dose intensity (%)[a]				
n	252	0	473	730
Mean	92.77	-	91.70	89.54
SD	16.14	-	19.73	33.24
Median	100.00	-	100.00	100.00
Q1, Q3	92.91, 100.00	-, -	90.10, 100.00	87.65, 100.00

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Min, Max	4.8, 100.0	-, -	3.2, 225.5	0.3, 663.3
Treatment duration (weeks)				
n	252	0	473	730
Mean	23.74	-	26.55	27.06
SD	19.36	-	27.30	32.50
Median	18.21	-	18.00	16.14
Q1, Q3	6.14, 37.50	-, -	6.14, 37.57	4.43, 36.43
Min, Max	0.1, 74.6	-, -	0.1, 175.1	0.1, 204.1
Treatment duration (months) - n (%)				
≥ 3	149 (59.1)	0 (0.0)	275 (58.1)	396 (54.2)
≥ 6	104 (41.3)	0 (0.0)	188 (39.7)	266 (36.4)
≥ 9	58 (23.0)	0 (0.0)	114 (24.1)	169 (23.2)
≥ 12	26 (10.3)	0 (0.0)	66 (14.0)	110 (15.1)

N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.
a Relative dose intensity (%) is calculated as (actual cumulative dose/planned cumulative dose)*100, where cumulative actual dose is the total dose of tarlatamab given up to the data cutoff. For participants who did not take any drug the cumulative actual dose is 0 mg; Cumulative planned dose is the planned dose of tarlatamab accumulated over the actual duration on study treatment.

Safety monitoring period

To support the proposed safety monitoring period, additional data from the following studies has been provided (tarlatamab 10 mg):

- The phase 2a study 20230273 investigating tarlatamab in Chinese subjects with advanced SCLC after at least two prior treatments (only data on cytokine release syndrome (CRS); 6- to 8-hour monitoring)
- The randomized, double-blind, placebo-controlled phase 3 study 20230016 assessing tarlatamab in subjects with limited-stage SCLC who have not progressed following concurrent chemoradiation therapy (aggregate data on disposition, demographics and serious adverse events (not identifying the treatment); 1- to 2-hour monitoring)
- The randomized, blinded phase 3 study 20200041 comparing tarlatamab plus durvalumab to durvalumab alone in extensive-stage SCLC subjects with stable disease or ongoing response after first-line therapy with platinum chemotherapy, etoposide, and durvalumab (aggregate data on disposition, demographics and serious adverse events (not identifying the treatment); 1- to 2-hour monitoring)

Data cutoff date: 28 March 2025 for study 20230273; 24 March 2025 for studies 20230016 and 20200041.

5.4.3. Adverse events

Overview of adverse events

In study 20210004, nearly all subjects in the tarlatamab group (98.8%) and SOC chemotherapy group (99.6%) experienced TEAEs; 93.3% of subjects in the tarlatamab group and 91.4% of subjects in the SOC chemotherapy group had TEAEs that were considered treatment-related by the investigator.

The overall adverse events experience in study 20210004 as well as across pooled datasets is summarized in Table 31.

Table 31. Summary of Treatment-Emergent Adverse Events – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
All treatment-emergent adverse events	249 (98.8)	243 (99.6)	470 (99.4)	726 (99.5)
Grade ≥ 2	228 (90.5)	237 (97.1)	434 (91.8)	675 (92.5)
Grade ≥ 3	136 (54.0)	195 (79.9)	281 (59.4)	449 (61.5)
Grade ≥ 4	41 (16.3)	91 (37.3)	86 (18.2)	128 (17.5)
Serious adverse events	129 (51.2)	125 (51.2)	256 (54.1)	416 (57.0)
Leading to dose interruption and/or reduction of tarlatamab	94 (37.3)	0 (0.0)	165 (34.9)	261 (35.8)
Leading to discontinuation of tarlatamab	13 (5.2)	0 (0.0)	29 (6.1)	49 (6.7)
Serious	11 (4.4)	0 (0.0)	21 (4.4)	37 (5.1)
Nonserious	2 (0.8)	0 (0.0)	8 (1.7)	17 (2.3)
Fatal adverse events	20 (7.9)	21 (8.6)	30 (6.3)	41 (5.6)
Treatment-related treatment-emergent adverse events	235 (93.3)	223 (91.4)	446 (94.3)	689 (94.4)
Grade ≥ 2	170 (67.5)	206 (84.4)	337 (71.2)	538 (73.7)
Grade ≥ 3	67 (26.6)	152 (62.3)	141 (29.8)	249 (34.1)
Grade ≥ 4	12 (4.8)	60 (24.6)	26 (5.5)	46 (6.3)
Serious adverse events	70 (27.8)	75 (30.7)	140 (29.6)	259 (35.5)
Leading to dose interruption and/or reduction of tarlatamab	48 (19.0)	0 (0.0)	77 (16.3)	138 (18.9)
Leading to discontinuation of tarlatamab	7 (2.8)	0 (0.0)	15 (3.2)	30 (4.1)
Serious	5 (2.0)	0 (0.0)	10 (2.1)	22 (3.0)
Nonserious	2 (0.8)	0 (0.0)	5 (1.1)	12 (1.6)
Fatal adverse events	1 (0.4)	4 (1.6)	2 (0.4)	3 (0.4)

N = Number of participants in analysis set; n = Number of participants with observed data; CRS = Cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; SOC = Standard of care.

Common adverse events

Treatment-emergent adverse events

Subject incidence of TEAEs (any grade) that occurred in ≥5% of subjects in the tarlatamab all doses safety analysis set are provided for Study 20210004 as well as for the pooled datasets Table 32.

Table 32. Treatment-emergent Adverse Events by Preferred Term (occurring in ≥5% of Subjects Across Tarlatamab All Doses) – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting treatment-emergent adverse events	249 (98.8)	243 (99.6)	470 (99.4)	726 (99.5)
Cytokine release syndrome	142 (56.3)	3 (1.2)	268 (56.7)	426 (58.4)
Decreased appetite	89 (35.3)	54 (22.1)	172 (36.4)	279 (38.2)
Pyrexia	69 (27.4)	27 (11.1)	151 (31.9)	256 (35.1)
Constipation	72 (28.6)	54 (22.1)	144 (30.4)	242 (33.2)
Dysgeusia	61 (24.2)	4 (1.6)	148 (31.3)	226 (31.0)
Fatigue	72 (28.6)	74 (30.3)	141 (29.8)	218 (29.9)
Anaemia	78 (31.0)	156 (63.9)	142 (30.0)	213 (29.2)
Nausea	61 (24.2)	78 (32.0)	118 (24.9)	188 (25.8)
Asthenia	28 (11.1)	36 (14.8)	90 (19.0)	147 (20.1)
Headache	38 (15.1)	21 (8.6)	77 (16.3)	129 (17.7)
Weight decreased	31 (12.3)	16 (6.6)	70 (14.8)	121 (16.6)
Hyponatraemia	43 (17.1)	24 (9.8)	79 (16.7)	120 (16.4)
Cough	31 (12.3)	34 (13.9)	70 (14.8)	106 (14.5)
Dyspnoea	18 (7.1)	28 (11.5)	52 (11.0)	100 (13.7)
Vomiting	35 (13.9)	28 (11.5)	67 (14.2)	99 (13.6)
Back pain	22 (8.7)	17 (7.0)	54 (11.4)	91 (12.5)
Pruritus	22 (8.7)	9 (3.7)	49 (10.4)	88 (12.1)
Diarrhoea	28 (11.1)	37 (15.2)	54 (11.4)	83 (11.4)
Hypokalaemia	24 (9.5)	19 (7.8)	49 (10.4)	82 (11.2)
Alanine aminotransferase increased	19 (7.5)	14 (5.7)	49 (10.4)	79 (10.8)
Aspartate aminotransferase increased	19 (7.5)	8 (3.3)	47 (9.9)	77 (10.5)
Arthralgia	19 (7.5)	17 (7.0)	39 (8.2)	75 (10.3)
Hypomagnesaemia	17 (6.7)	8 (3.3)	46 (9.7)	75 (10.3)
Neutropenia	27 (10.7)	76 (31.1)	49 (10.4)	72 (9.9)
Insomnia	18 (7.1)	21 (8.6)	36 (7.6)	69 (9.5)
Hypotension	11 (4.4)	6 (2.5)	34 (7.2)	68 (9.3)
Lymphopenia	23 (9.1)	10 (4.1)	45 (9.5)	67 (9.2)
COVID-19	8 (3.2)	2 (0.8)	27 (5.7)	65 (8.9)
Dizziness	24 (9.5)	25 (10.2)	39 (8.2)	60 (8.2)
Pneumonia	23 (9.1)	32 (13.1)	38 (8.0)	60 (8.2)
Abdominal pain	19 (7.5)	10 (4.1)	38 (8.0)	54 (7.4)
Hypertension	14 (5.6)	4 (1.6)	33 (7.0)	54 (7.4)
Hypoalbuminaemia	22 (8.7)	14 (5.7)	39 (8.2)	54 (7.4)
Rash	21 (8.3)	12 (4.9)	34 (7.2)	53 (7.3)
Neutrophil count decreased	20 (7.9)	42 (17.2)	31 (6.6)	52 (7.1)
Hyperglycaemia	12 (4.8)	4 (1.6)	31 (6.6)	49 (6.7)
Lymphocyte count decreased	15 (6.0)	12 (4.9)	31 (6.6)	49 (6.7)
Urinary tract infection	16 (6.3)	8 (3.3)	38 (8.0)	49 (6.7)
Myalgia	16 (6.3)	6 (2.5)	33 (7.0)	47 (6.4)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Thrombocytopenia	14 (5.6)	62 (25.4)	33 (7.0)	47 (6.4)
White blood cell count decreased	24 (9.5)	32 (13.1)	32 (6.8)	47 (6.4)
Chills	7 (2.8)	2 (0.8)	26 (5.5)	46 (6.3)
Hypophosphataemia	5 (2.0)	2 (0.8)	17 (3.6)	46 (6.3)
Productive cough	11 (4.4)	15 (6.1)	24 (5.1)	44 (6.0)
Confusional state	1 (0.4)	3 (1.2)	15 (3.2)	39 (5.3)

N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.

Treatment-related Treatment-emergent adverse events based on investigator assessment

Subject incidence of treatment-related TEAEs (any grade) that occurred in ≥ 5% of subjects in the tarlatamab all doses safety analysis set are provided for study 20210004 as well as for the pooled datasets in Table 33.

Table 33. Treatment-related Treatment-emergent Adverse Events by Preferred Term (occurring in ≥5% of Subjects in Tarlatamab All Doses) – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		**Integrated Analysis (Studies 20210004, 20200491, and 20160323)**	
Preferred Term	**Tarlatamab 10 mg (N = 252) n (%)**	**SOC Chemotherapy (N = 244) n (%)**	**Tarlatamab 10 mg (N = 473) n (%)**	**Tarlatamab All Doses (N = 730) n (%)**
Number of participants reporting treatment-related treatment-emergent adverse events	235 (93.3)	223 (91.4)	446 (94.3)	689 (94.4)
Cytokine release syndrome	142 (56.3)	1 (0.4)	266 (56.2)	424 (58.1)
Pyrexia	52 (20.6)	14 (5.7)	122 (25.8)	213 (29.2)
Dysgeusia	58 (23.0)	3 (1.2)	135 (28.5)	199 (27.3)
Decreased appetite	66 (26.2)	46 (18.9)	123 (26.0)	186 (25.5)
Fatigue	50 (19.8)	65 (26.6)	98 (20.7)	153 (21.0)
Nausea	42 (16.7)	70 (28.7)	81 (17.1)	126 (17.3)
Anaemia	50 (19.8)	150 (61.5)	82 (17.3)	117 (16.0)
Asthenia	21 (8.3)	32 (13.1)	61 (12.9)	105 (14.4)
Constipation	34 (13.5)	32 (13.1)	58 (12.3)	80 (11.0)
Headache	28 (11.1)	5 (2.0)	44 (9.3)	67 (9.2)
Pruritus	17 (6.7)	6 (2.5)	40 (8.5)	66 (9.0)
Vomiting	26 (10.3)	23 (9.4)	45 (9.5)	64 (8.8)
Neutropenia	19 (7.5)	72 (29.5)	38 (8.0)	59 (8.1)
Weight decreased	17 (6.7)	11 (4.5)	35 (7.4)	59 (8.1)
Lymphopenia	16 (6.3)	10 (4.1)	33 (7.0)	52 (7.1)
Alanine aminotransferase increased	15 (6.0)	8 (3.3)	37 (7.8)	51 (7.0)
Aspartate aminotransferase increased	12 (4.8)	5 (2.0)	31 (6.6)	45 (6.2)
Hyponatraemia	22 (8.7)	2 (0.8)	29 (6.1)	44 (6.0)
Lymphocyte count decreased	14 (5.6)	10 (4.1)	28 (5.9)	41 (5.6)
Neutrophil count decreased	15 (6.0)	40 (16.4)	23 (4.9)	41 (5.6)
Chills	5 (2.0)	2 (0.8)	22 (4.7)	40 (5.5)

Preferred Term	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
White blood cell count decreased	19 (7.5)	29 (11.9)	26 (5.5)	40 (5.5)
Myalgia	13 (5.2)	4 (1.6)	27 (5.7)	37 (5.1)
Rash	16 (6.3)	5 (2.0)	24 (5.1)	35 (4.8)
Hypomagnesaemia	7 (2.8)	3 (1.2)	21 (4.4)	34 (4.7)
Immune effector cell-associated neurotoxicity syndrome	15 (6.0)	0 (0.0)	22 (4.7)	33 (4.5)
Hypotension	5 (2.0)	1 (0.4)	13 (2.7)	30 (4.1)
Diarrhoea	12 (4.8)	25 (10.2)	19 (4.0)	28 (3.8)
Dizziness	12 (4.8)	11 (4.5)	15 (3.2)	25 (3.4)
Thrombocytopenia	8 (3.2)	58 (23.8)	19 (4.0)	25 (3.4)

N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.

Grade ≥ 3 adverse events

In study 20210004, grade ≥ 3 adverse events were reported for 54.0% of the subjects in the tarlatamab group (treatment-related for 26.6% of subjects) and for 79.9% of the subjects in the SOC chemotherapy group (treatment related for 62.3% of subjects).

Subject incidence of grade ≥ 3 adverse events and treatment-related grade ≥ 3 adverse events that occurred in ≥ 1% of subjects in the tarlatamab all doses safety analysis set are provided for study 20210004 as well as for the pooled datasets in Table 34 and Table 35, respectively.

Table 34. Grade 3 or Higher Treatment-emergent Adverse Events by Preferred Term (occurring in ≥ 1% of Subjects Across Tarlatamab All Doses) – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analyses Set)

Preferred Term	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting grade 3 or higher treatment-emergent adverse events	136 (54.0)	195 (79.9)	281 (59.4)	449 (61.5)
Hyponatraemia[a]	12 (4.8)	13 (5.3)	28 (5.9)	46 (6.3)
Anaemia	11 (4.4)	70 (28.7)	22 (4.7)	40 (5.5)
Lymphopenia[a]	10 (4.0)	3 (1.2)	29 (6.1)	40 (5.5)
Neutropenia	15 (6.0)	57 (23.4)	22 (4.7)	38 (5.2)
Pneumonia[a]	14 (5.6)	20 (8.2)	23 (4.9)	38 (5.2)
Fatigue	9 (3.6)	17 (7.0)	20 (4.2)	36 (4.9)
Lymphocyte count decreased	7 (2.8)	9 (3.7)	21 (4.4)	34 (4.7)
Hypertension[a]	8 (3.2)	3 (1.2)	17 (3.6)	28 (3.8)
Neutrophil count decreased	10 (4.0)	28 (11.5)	17 (3.6)	27 (3.7)
Asthenia[a]	4 (1.6)	7 (2.9)	14 (3.0)	24 (3.3)
Cytokine release syndrome	3 (1.2)	0 (0.0)	9 (1.9)	22 (3.0)
Decreased appetite	5 (2.0)	4 (1.6)	9 (1.9)	19 (2.6)

Preferred Term	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Dyspnoea	7 (2.8)	6 (2.5)	10 (2.1)	18 (2.5)
White blood cell count decreased[a]	5 (2.0)	11 (4.5)	6 (1.3)	14 (1.9)
Alanine aminotransferase increased[a]	3 (1.2)	0 (0.0)	8 (1.7)	13 (1.8)
Hypokalaemia	4 (1.6)	6 (2.5)	8 (1.7)	12 (1.6)
Aspartate aminotransferase increased[a]	2 (0.8)	0 (0.0)	8 (1.7)	11 (1.5)
Confusional state	1 (0.4)	0 (0.0)	3 (0.6)	11 (1.5)
Febrile neutropenia	5 (2.0)	28 (11.5)	7 (1.5)	10 (1.4)
Pyrexia	3 (1.2)	3 (1.2)	3 (0.6)	10 (1.4)
Hypoxia[a]	2 (0.8)	1 (0.4)	8 (1.7)	9 (1.2)
Syncope[a]	2 (0.8)	3 (1.2)	6 (1.3)	9 (1.2)
Urinary tract infection[a]	5 (2.0)	0 (0.0)	8 (1.7)	9 (1.2)
Weight decreased	1 (0.4)	1 (0.4)	5 (1.1)	9 (1.2)
Acute kidney injury[a]	6 (2.4)	0 (0.0)	7 (1.5)	8 (1.1)
Sepsis[a]	6 (2.4)	6 (2.5)	8 (1.7)	8 (1.1)
Leukopenia[a]	4 (1.6)	34 (13.9)	4 (0.8)	7 (1.0)
Respiratory failure[a]	2 (0.8)	3 (1.2)	5 (1.1)	7 (1.0)
Superior vena cava syndrome	0 (0.0)	4 (1.6)	5 (1.1)	7 (1.0)
Thrombocytopenia[a]	2 (0.8)	28 (11.5)	4 (0.8)	7 (1.0)

N = Number of participants in analysis set; n = Number of participants with observed data; CRS = Cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; SOC = Standard of care.
[a] Indicates that cytokine release syndrome/adverse events retain their originally assigned Lee et al. 2014/CTCAE version 4.0 grade.

Table 35. Grade 3 or Higher Treatment-related Treatment-emergent Adverse Events by Preferred Term (in ≥ 1% of Subjects Across Tarlatamab All Doses) – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analyses Set)

Preferred Term	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting grade 3 or higher treatment-related treatment-emergent adverse events	67 (26.6)	152 (62.3)	141 (29.8)	249 (34.1)
Lymphopenia[a]	9 (3.6)	3 (1.2)	23 (4.9)	33 (4.5)
Lymphocyte count decreased	7 (2.8)	7 (2.9)	18 (3.8)	28 (3.8)
Neutropenia	11 (4.4)	54 (22.1)	16 (3.4)	27 (3.7)
Fatigue	6 (2.4)	16 (6.6)	11 (2.3)	24 (3.3)

Preferred Term	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Cytokine release syndrome	3 (1.2)	0 (0.0)	7 (1.5)	20 (2.7)
Neutrophil count decreased	6 (2.4)	27 (11.1)	9 (1.9)	18 (2.5)
Asthenia[a]	3 (1.2)	5 (2.0)	7 (1.5)	15 (2.1)
Anaemia	5 (2.0)	68 (27.9)	9 (1.9)	14 (1.9)
Hyponatraemia[a]	6 (2.4)	1 (0.4)	7 (1.5)	13 (1.8)
White blood cell count decreased[a]	2 (0.8)	10 (4.1)	3 (0.6)	11 (1.5)
Confusional state	0 (0.0)	0 (0.0)	2 (0.4)	9 (1.2)
Hypertension[a]	3 (1.2)	0 (0.0)	7 (1.5)	9 (1.2)
Decreased appetite	2 (0.8)	3 (1.2)	5 (1.1)	8 (1.1)
Pyrexia	1 (0.4)	3 (1.2)	1 (0.2)	8 (1.1)
Alanine aminotransferase increased[a]	2 (0.8)	0 (0.0)	5 (1.1)	7 (1.0)
Weight decreased	1 (0.4)	0 (0.0)	4 (0.8)	6 (0.8)
Aspartate aminotransferase increased[a]	1 (0.4)	0 (0.0)	5 (1.1)	5 (0.7)
Encephalopathy	0 (0.0)	0 (0.0)	1 (0.2)	5 (0.7)

N = Number of participants in analysis set; n = Number of participants with observed data; CRS = Cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; SOC = Standard of care.
[a] Indicates that cytokine release syndrome/adverse events retain their originally assigned Lee et al. 2014/CTCAE version 4.0 grade.

5.4.3.1. Adverse drug reactions

A summary of ADRs proposed for inclusion by the applicant in the SmPC is presented in Table 36.

Table 36. Summary of ADRs proposed for inclusion by the applicant in the SmPC

System Organ Class Preferred Term	*All Grades (%)*	*Grades ≥3 (%)*
Blood and lymphatic system disorders		
Anaemia	30.0	4.7
Neutropenia[a]	16.9	8.2
Lymphopenia[a,b]	15.6	10.6
Thrombocytopenia[b]	7.0	0.8
Leukopenia[b]	5.9	0.8
Gastrointestinal disorders		
Constipation	30.4	0.4
Nausea	24.9	0.8
Vomiting	14.2	0.2
Diarrhoea	11.4	0.6
General disorders and administration site conditions		
Pyrexia	31.9	0.6
Fatigue	29.8	4.2

Asthenia[b]	19.0	3.0
Chills	5.5	0.0
Immune system disorders		
Cytokine release syndrome	56.7	1.9
Investigations		
Weight decreased	14.8	1.1
Alanine aminotransferase increased[b]	10.4	1.7
Aspartate aminotransferase increased[b]	9.9	1.7
White blood cell count decreased[b]	6.8	1.3
Metabolism and nutrition disorders		
Decreased appetite	36.4	1.9
Hyponatraemia[b]	16.7	5.9
Hypokalaemia	10.4	1.7
Hypomagnesaemia	9.7	0.4
Musculoskeletal and connective tissue disorders		
Myalgia	7.0	0.0
Nervous system disorders		
Dysgeusia	31.3	0.8
Headache	16.3	0.0
Dizziness	8.2	0.0
Immune effector cell-associated neurotoxicity syndrome	4.7	0.2
Tremor	1.9	0.0
Neurotoxicity	0.8	0.0
Ataxia	0.4	0.2
Seizure	0.4	0.2
Encephalopathy	0.2	0.2
Psychiatric disorders		
Confusional state	3.2	0.6
Delirium	1.3	0.2
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	11	2.1
Skin and subcutaneous tissue disorders		
Pruritus	10.4	0.2
Rash[b]	7.2	0.2
Vascular disorders		
Hypotension	7.2	1.3
Hypertension[a]	7.0	3.6

[a] "Lymphopenia" is combined preferred term of "Lymphopenia" and "Lymphocyte count decreased," whereas "Neutropenia" is combined preferred term of "Neutropenia" and "Neutrophil count decreased."
[b] Indicates that cytokine release syndrome/adverse events retain their originally assigned Lee et al. 2014/CTCAE version 4.0 grade.

Adverse drug reactions (ADRs) were determined based on adverse events reported in subjects with SCLC treated with tarlatamab at a dose of 10 mg Q2W from pooled studies 20210004, 20200491, and 20160323. A medical review focused on common, grade ≥ 3, and serious adverse events was conducted by the Applicant. Frequently occurring adverse events were assessed, considering expected incidence in patients with underlying diseases to establish an initial threshold. Additional factors, including temporal association, biological plausibility, and medical judgment, were considered to confirm the final adverse drug reactions.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Adverse events of special interest

Events of interest (EOIs) were determined for tarlatamab based on review of the safety data of the ongoing tarlatamab clinical studies.

The EOIs included the important identified risks of **cytokine release syndrome (CRS**), **neutropenia, immune-effector cell-associated neurotoxicity syndrome (ICANS**) and associated neurological events, and **neurological events** (nervous system disorders [system organ class/psychiatric disorder system organ class], and the potential risk (not important) of **hypersensitivity**. All except Hypersensitivity are listed as ADRs in section 4.8 of the SmPC.

The identified events of interest are presented below.

- **Cytokine Release Syndrome**

Assessment of Cytokine Release Syndrome Events Regardless of the Safety Monitoring Period

  - *Summary of CRS events in studies 20210004, 20200491 and 20160323*

An overview of treatment-emergent CRS events is presented in Table 37.

Table 37. Summary of Treatment-emergent Adverse Events of Cytokine Release Syndrome (AMQ Narrow) - Study 20210004 and Integrated Analysis (Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323) (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Event of Interest	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Cytokine Release Syndrome (AMQ Narrow)				
All treatment-emergent adverse events of interest	142 (56.3)	3 (1.2)	268 (56.7)	426 (58.4)
Grade ≥ 2	35 (13.9)	1 (0.4)	82 (17.3)	150 (20.5)
Grade ≥ 3	3 (1.2)	0 (0.0)	9 (1.9)	22 (3.0)
Grade ≥ 4	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Serious adverse events	43 (17.1)	1 (0.4)	93 (19.7)	170 (23.3)
Leading to dose interruption and/or reduction of tarlatamab	4 (1.6)	0 (0.0)	10 (2.1)	30 (4.1)
Leading to discontinuation of tarlatamab	1 (0.4)	0 (0.0)	3 (0.6)	5 (0.7)
Serious	1 (0.4)	0 (0.0)	3 (0.6)	5 (0.7)
Nonserious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of participants in analysis set; n = Number of participants with observed data; AMQ = Amgen MedDRA query; CRS = Cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; SOC = Standard of care.

In study 20210004, CRS events were considered related to the investigational product in 56.3% of subjects in the tarlatamab group and 0.4% in the SOC chemotherapy group. On cycle 1 day 1, grade ≥ 2 CRS events required hospitalization in 2.4% of tarlatamab subjects, with interventions including low-flow oxygen/IV hydration (9.1%), tocilizumab (1.6%), and vasopressor/high-flow oxygen (0.4%). On cycle 1 day 8, hospitalization for grade ≥ 2 CRS events occurred in 1.2% of tarlatamab subjects, with interventions including low-flow oxygen/IV hydration (4.0%) and tocilizumab (0.4%). In the integrated safety analysis, slightly higher incidence of CRS events, including severity, discontinuations and dose interruptions/reductions were observed. One grade 4 CRS event in the tarlatamab 10 mg group led to death, with advanced SCLC identified as the primary cause and CRS as a contributing factor.

An overview of time to onset and time to resolution of CRS events in the integrated safety analysis is provided in Table 38 below.

Table 38. Summary of Time to Onset and Resolution of Adverse Events of Cytokine Release Syndrome (AMQ Narrow) – Tarlatamab Arm of Study 20210004, Study 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20160323	Studies 20210004, 20200491, and 20160323	Studies 20200491 and 20160323	Studies 20210004, 20200491, and 20160323
Event of Interest Safety Analysis Set	Tarlatamab < 10 mg (N = 35) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab > 10 mg (N = 222) n (%)	Tarlatamab All Doses (N = 730) n (%)
Adverse Events n (%)	12 (34.3)	268 (56.7)	146 (65.8)	426 (58.4)
Serious Adverse Events n (%)	4 (11.4)	93 (19.7)	73 (32.9)	170 (23.3)
Fatal Adverse Events n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade ≥ 3 Adverse Events n (%)	1 (2.9)	9 (1.9)	12 (5.4)	22 (3.0)
Median (Q1, Q3) Time to First Onset of Any Grade Adverse Event From First Dose (hours)	8.3 (6.8, 13.1)	15.2 (8.1, 165.8)	24.6 (10.9, 177.1)	17.6 (8.6, 174.2)
Median (Q1, Q3) Time to First Onset of Any Grade Adverse Event From Last Dose After Each Dose (hours)	8.1 (7.4, 13.5)	15.9 (9.0, 26.5)	11.7 (6.9, 23.9)	13.8 (8.0, 25.7)
Median (95% CI) Time to Resolution Any Grade (days)[b]	3.0 (2.0, 4.0)	3.0 (2.0, 3.0)	4.0 (3.0, 4.0)	3.0 (NE, NE)

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eIV = extended intravenous; ICANS = Immune effector cell-associated neurotoxicity syndrome; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the safety analysis set; n = number of subjects with observed data; NE = not evaluable; Q3W = every 3 weeks
b Median/percentiles were estimated using the Kaplan-Meier method and their 95% confidence intervals were estimated using log-log transformation of KM survival estimate.

- *Summary of Cytokine Release Syndrome Interventions During First Two Tarlatamab Doses in Studies 20210004 and 20200491*

To further characterize CRS events with tarlatamab, the profiles of interventions are provided here. Updated eCRF data collection for CRS began with study 20200491, excluding data from study 20160323.

In studies 20210004 and 20200491, 55.1% of subjects receiving tarlatamab 10 mg experienced CRS. On cycle 1 day 1, 13.2% had grade ≥2 CRS events, with interventions including low-flow oxygen/IV fluids (9.9%), high-flow oxygen (0.5%), and vasopressors (0.3%). Median time to onset of first CRS event was 8.8 h (Q1, Q3: 5.9, 13.2). Median time to onset of first grade 2+ CRS event without a preceding lower grade CRS event was 10.0 h (Q1, Q3: 5.9, 18.5).

On cycle 1 day 8, 4.2% had grade ≥2 CRS events, with interventions including low-flow oxygen/IV fluids (2.9%) and vasopressors (0.3%). Median time to onset of first CRS event was 20.8 h (Q1, Q3: 12.2, 25.4). Median time to onset of first grade 2+ CRS event without a preceding lower grade CRS event was 20.6 h (Q1, Q3: 13.7, 24.4).

By cycle 1 day 15, grade ≥2 CRS events decreased to 1.7%, and from cycle 2 onward, to 0.8%.

Assessment of CRS Events with Modified Safety Monitoring Periods

The tarlatamab development program has undertaken a stepwise, data-informed process to evaluate the appropriate monitoring period for the initial tarlatamab treatments as shown in the table below.

Table 39. Monitoring Period of Select Studies in Tarlatamab Development Program

Study	Cohorts	Protocol Mandated Safety Monitoring Period
First-in-human, Phase 1 Study 20160323	Parts A, C, D, G	72 hours of inpatient monitoring for first 3 tarlatamab doses initially, monitoring period later changed to 48 hours per protocol amendment 4
Study 20160323	Part E	24-hour monitoring period for cycle 1 doses
Study 20160323	Part F	6- to 8-hour outpatient monitoring for cycle 1 doses
Phase 2 Study 20200491	Parts 1 and 2	48 hours of inpatient monitoring for first 2 tarlatamab doses
Study 20200491	Part 3	24-hour monitoring period
Phase 3 Study 20210004	-	48-hour monitoring required initially, subsequently modified to 6- to 8-hour monitoring postinfusion for first two tarlatamab doses as the trial progressed
Phase 2 China Study 202300273	-	6- to 8-hour monitoring post-infusion for first two doses
Phase 3 Study 20200041	-	1- to 2-hour monitoring post-infusion for first two doses
Phase 3 Study 20230016	-	1- to 2-hour monitoring post-infusion for first two doses

A CRS analysis of all subjects who received tarlatamab 10 mg under modified monitoring criteria for the following studies are provided:

- 6- to 8-hour versus 24- to 48-hour monitoring cohorts of study 20160323

- 6- to 8-hour versus 48-hour monitoring cohorts of study 20210004
- 6- to 8-hour monitoring cohorts from the integrated analysis of studies 20210004 and 20160323 compared side by side with 24- to 48-hour monitoring cohorts from the integrated analysis of studies 20210004, 20200491, and 20160323. Data from study 20200491 are not included in the 6- to 8-hour cohort of pooled studies as this monitoring period was not evaluated per protocol.
- Six- to 8-hour monitoring from China study 20230273

Additional safety data of 1- to 2-hour safety monitoring from ongoing blinded phase 3 Studies 20200041 and 20230016 is also provided.

  - *Summary of Cytokine Release Syndrome Adverse Events Under 6- to 8-hour Monitoring Versus 24- to 48-hour Monitoring in Studies 20210004, 20200491, and 20160323*

An overall summary of CRS AEs during the first two tarlatamab doses is provided in the table below.

Table 40. Summary of Treatment-emergent CRS Events (AMQ Narrow) During First Two Tarlatamab Doses Among Participants With and More Than 6 to 8 Hours Monitoring – Tarlatamab Arm of Study 20210004, Study 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Studies 20210004, 20200491, and 20160323, **More Than 6 to 8 Hours** Monitoring Criteria	Studies 20210004 and 20160323, With 6 to 8 Hours Monitoring Criteria	Study 20160323, With 6 to 8 Hours Monitoring Criteria	Study 20160323, **More Than 6 to 8 Hours** Monitoring Criteria	Study 20210004, With 6 to 8 Hours Monitoring Criteria	Study 20210004, **More Than 6 to 8 Hours** Monitoring Criteria	Overall
	Tarlatamab 10 mg (N = 400) n (%)	Tarlatamab 10 mg (N = 73) n (%)	Tarlatamab 10 mg (N = 30) n (%)	Tarlatamab 10 mg (N = 58) n (%)	Tarlatamab 10 mg (N = 43) n (%)	Tarlatamab 10 mg (N = 209) n (%)	Tarlatamab 10 mg (N = 473) n (%)
All treatment-emergent adverse events	229 (57.3)	34 (46.6)	18 (60.0)	36 (62.1)	16 (37.2)	125 (59.8)	263 (55.6)
Grade ≥ 2	71 (17.8)	7 (9.6)	3 (10.0)	14 (24.1)	4 (9.3)	31 (14.8)	78 (16.5)
Grade ≥ 3	7 (1.8)	0 (0.0)	0 (0.0)	3 (5.2)	0 (0.0)	3 (1.4)	7 (1.5)
Grade ≥ 4	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.2)
Serious adverse events	79 (19.8)	8 (11.0)	5 (16.7)	13 (22.4)	3 (7.0)	39 (18.7)	87 (18.4)
Leading to dose interruption and/or reduction of tarlatamab	9 (2.3)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	4 (1.9)	9 (1.9)
Leading to discontinuation of tarlatamab	3 (0.8)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	1 (0.5)	3 (0.6)
Serious	3 (0.8)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	1 (0.5)	3 (0.6)
Nonserious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of participants in analysis set; n = Number of participants with observed data; AMQ = Amgen MedDRA query; C1D1 = Cycle 1 day 1; C1D8 = Cycle 1 day 8; CRS = Cytokine release syndrome.

- *Overall Summary of CRS Adverse Events by Cycle 1 Day 1 and Cycle 1 Day 8 During First Two Tarlatamab Doses:*

CRS events occurred primarily after the first or second dose of tarlatamab in cycle 1 during studies 20160323 and 20210004. In study 20210004, CRS incidence on cycle 1 day 1 was 25.6% with 6–8-hour monitoring and 42.1% with 48-hour monitoring. Grade ≥2 CRS events were reported in 9.3% vs. 12.0%, and grade ≥3 events in 0.0% vs. 1.0% for 6–8-hour vs. 48-hour monitoring, respectively. No subject reported grade 4 or 5 events with either monitoring criteria during cycle 1 day 1. Serious adverse events occurred in 4.7% vs. 11.0% of subjects in cycle 1 day 1 with 6- to 8-hour versus 48-hour monitoring criteria, respectively.

On cycle 1 day 8, CRS incidence in study 20210004 was 23.3% vs. 37.3% for 6–8-hour vs. 48-hour monitoring. Grade ≥2 CRS events were reported in 2.3% vs. 5.3%, and grade ≥3 events in 0.0% vs. 0.5%. with 6-8-hour versus 48-hour monitoring criteria, respectively. No subject reported grades 4 or 5 events during cycle 1 day 8. Serious adverse events occurred in 4.7% vs. 12.0%.

No CRS-related dose interruption, reduction, or discontinuation occurred with 6–8-hour monitoring. With 48-hour monitoring, CRS-related dose adjustments were reported in 1.0% of subjects on cycle 1 day 1 and day 8, and discontinuation occurred in 0.5% on cycle 1 day 1. Integrated safety analysis results aligned with these findings (data not shown).

- *Summary of CRS Interventions During First Two Tarlatamab Doses*

A summary of CRS interventions during the first two tarlatamab doses is provided in the table below.

Table 41. Participant Incidence of Intervention Utilization in Relation to Treatment-emergent CRS Events (AMQ Narrow) During First Two Tarlatamab Doses Among Participants With and More Than 6 to 8 Hours Monitoring – Tarlatamab Arm of Study 20210004, Study 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Studies 20210004, 20200491, and 20160323, **More Than 6 to 8 Hours** Monitoring Criteria	Studies 20210004 and 20160323, With 6 to 8 Hours Monitoring Criteria	Study 20160323, With 6 to 8 Hours Monitoring Criteria	Study 20160323, **More Than 6 to 8 Hours** Monitoring Criteria	Study 20210004, With 6 to 8 Hours Monitoring Criteria	Study 20210004, **More Than 6 to 8 Hours** Monitoring Criteria	Overall
	Tarlatamab 10 mg (N = 400) n (%)	Tarlatamab 10 mg (N = 73) n (%)	Tarlatamab 10 mg (N = 30) n (%)	Tarlatamab 10 mg (N = 58) n (%)	Tarlatamab 10 mg (N = 43) n (%)	Tarlatamab 10 mg (N = 209) n (%)	Tarlatamab 10 mg (N = 473) n (%)
Number of participants with at least 1 CRS event	229 (57.3)	34 (46.6)	18 (60.0)	36 (62.1)	16 (37.2)	125 (59.8)	263 (55.6)
Tocilizumab use	23 (5.8)	1 (1.4)	0 (0.0)	7 (12.1)	1 (2.3)	8 (3.8)	24 (5.1)
Corticosteroids use	65 (16.3)	15 (20.5)	6 (20.0)	11 (19.0)	9 (20.9)	32 (15.3)	80 (16.9)
Vasopressor use	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.4)

	Studies 20210004, 20200491, and 20160323, **More Than 6 to 8 Hours** Monitoring Criteria	Studies 20210004 and 20160323, With 6 to 8 Hours Monitoring Criteria	Study 20160323, With 6 to 8 Hours Monitoring Criteria	Study 20160323, **More Than 6 to 8 Hours** Monitoring Criteria	Study 20210004, With 6 to 8 Hours Monitoring Criteria	Study 20210004, **More Than 6 to 8 Hours** Monitoring Criteria	Overall
Single vasopressor (excluding vasopressin)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.4)
Multiple vasopressor (excluding vasopressin)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IV fluid use	28 (7.0)	3 (4.1)	0 (0.0)	8 (13.8)	3 (7.0)	12 (5.7)	31 (6.6)
IV fluid bolus	28 (7.0)	3 (4.1)	0 (0.0)	8 (13.8)	3 (7.0)	12 (5.7)	31 (6.6)

N = Number of participants in analysis set; n = Number of participants with observed data; AMQ = Amgen MedDRA query; C1D1 = Cycle 1 day 1; C1D8 = Cycle 1 day 8; CRS = Cytokine release syndrome; IV = Intravenous. The safety analysis set is defined as all participants who receive at least 1 dose of tarlatamab.

In study 20210004, hospitalization rates due to any-grade CRS during the first two doses of tarlatamab were similar between 6–8-hour (7.0%) and 48-hour (7.7%) monitoring criteria.

Median time to intervention from last prior tarlatamab administration to first CRS intervention after each dose was 16.6 hours in subjects under the tarlatamab 6- to 8-hour monitoring criteria and 27.3 hours in subjects under the 48-hour monitoring criteria.

- *Duration and Resolution of CRS Events During First Two Tarlatamab Doses:*

In study 20210004, the median (Q1, Q3) duration of resolved CRS events was shorter with 6–8-hour monitoring compared to 48-hour monitoring: 2.0 (2.0, 2.0) days versus 2.5 (2.0, 4.0) days for any grade CRS and 2.0 (2.0, 3.0) versus 3.0 (2.0, 5.0) days for grade ³ 2 CRS, respectively. Kaplan-Meier median time to resolution followed a similar trend: 2.0 vs. 3.0 days for any-grade CRS and grade ≥2 CRS. Integrated safety analysis results were consistent (data not shown).

- *Cytokine Release Syndrome Data from Study 20230273 (China Cohorts; Using 6- to 8-hours Monitoring Period)*

In the phase 2 China study 20230273, 87.1% of 31 subjects receiving tarlatamab 10 mg reported CRS events. Grade 1 CRS was reported by 61.3%, with fever as the only symptom in 53%. Grade ≥2 CRS occurred in 25.8%, with no grade 3, 4, or fatal events. Serious CRS events were reported in 16.1%, and 3.2% experienced dose interruption/reduction, with no discontinuations. Fever (87.1%) and tachycardia (19.4%) were the most common symptoms.

CRS interventions were reported by 38.7%, primarily corticosteroids (35.5%), followed by supplemental oxygen (12.9%), tocilizumab (6.5%), and IV fluids (6.5%). Median (Q1, Q3) time to intervention from last prior tarlatamab administration to first CRS intervention after each dose during first 2 tarlatamab doses was 16.8 (7.9, 19.9).

The median (Q1, Q3) duration of resolved CRS adverse events was 2.0 (1.0, 3.0) days for any grade CRS and 3.0 (2.5, 3.5) days for grade ≥ 2 CRS events. The Kaplan-Meier median (95% CI) time to resolution was 2.0 (2.0, 3.0) days for any grade CRS and 3.0 (1.0, NE) days for grade ≥ 2 CRS events.

On cycle 1 day 1, 71.0% reported CRS, with grade 2 events in 22.6% and serious events in 16.1%. No grade 3, 4, or fatal events occurred, and no dose adjustments or discontinuations were reported. Grade ≥2 CRS requiring interventions occurred in 19.4% (low-flow oxygen/IV hydration) and 6.5% (tocilizumab). No subject required vasopressor or supplemental high-flow oxygen use.

On cycle 1 day 8, 67.7% reported CRS, with grade 2 events in 3.2% and serious events in 3.2%. One subject (3.2%) reported dose interruption/reduction, with no discontinuations. Grade ≥2 CRS did not require interventions. Hospitalization due to any grade of CRS events was reported in 5 subjects (16.1%) after the cycle 1 day 1 and cycle 1 day 8 doses.

- *Safety from Ongoing Studies 20200041 and 20230016 (Using 1- to 2-Hours Monitoring Period)*

As agreed with multiple health authorities based on reported safety profiles and provision of Data Monitoring Committee (DMC) reports, ongoing phase 3 tarlatamab Studies 20200041 and 20230016 utilize a 1- to 2-hour safety monitoring period following the first 2 doses of tarlatamab. An independent external DMC reviews interim safety and efficacy data from these studies, and providing recommendations related to continuing, modifying, or stopping the studies. This review is performed every 6 months, in addition to when 20, 60, 120, and 180 subjects have been randomized and have had the opportunity to receive 2 cycles of treatment and in the event of grade 4 or higher CRS.

As of April 2025, DMC reviews for both studies have not recommended changes to the studies or monitoring periods.

Additional high-level aggregate (ie, tarlatamab group + comparator group pooled together in one group) safety results from these 2 blinded studies were provided in the context for the MAA procedure.

- **Immune Effector Cell-associated Neurotoxicity Syndrome and Associated Neurological Events**

Immune effector cell-associated neurotoxicity syndrome (ICANS) and associated neurological EOIs are presented using the AMQ broad search strategies which consist of 65 preferred terms that include ICANS and terms that are potentially suggestive of ICANS.

An overview of treatment-emergent ICANS and associated neurological events is presented in the table below.

Table 42. Summary of Treatment-emergent Adverse Immune Effector Cell-associated Neurotoxicity Syndrome and Associated Neurological Events (AMQ Broad Search) – Study 20210004 and Integrated Analysis (Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323) (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Event of Interest	n (%)	n (%)	n (%)	n (%)
ICANS and associated neurological events (AMQ Broad)				
All treatment-emergent adverse events of interest	21 (8.3)	14 (5.7)	53 (11.2)	113 (15.5)
Grade ≥ 2	10 (4.0)	9 (3.7)	24 (5.1)	64 (8.8)
Grade ≥ 3	1 (0.4)	4 (1.6)	4 (0.8)	20 (2.7)
Grade ≥ 4	1 (0.4)	0 (0.0)	2 (0.4)	4 (0.5)
Serious adverse events	11 (4.4)	4 (1.6)	17 (3.6)	40 (5.5)
Leading to dose interruption and/or reduction of tarlatamab	3 (1.2)	0 (0.0)	4 (0.8)	15 (2.1)
Leading to discontinuation of tarlatamab	1 (0.4)	0 (0.0)	2 (0.4)	6 (0.8)
Serious	1 (0.4)	0 (0.0)	1 (0.2)	5 (0.7)
Nonserious	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Fatal adverse events	1 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)

N = Number of participants in analysis set; n = Number of participants with observed data; AMQ = Amgen MedDRA query; CRS = Cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; SOC = Standard of care.

In study 20210004, the most frequently reported (≥ 4% of subjects) ICANS and associated neurological adverse events in the tarlatamab group was ICANS (6.0%, all events treatment-related) and in the SOC chemotherapy group was muscular weakness (4.1%). ICANS was reported for 0.8% of subjects in the SOC chemotherapy group. In the tarlatamab group, one fatal event was reported (0.4%) and no other grade ≥ 3 or grade ≥ 4 ICANS events were reported in this group.

In the integrated analysis, slightly higher incidence of ICANS and associated neurological adverse events were reported. ICANS was reported for 4.7% of subjects at the 10 mg tarlatamab dose (all events treatment-related). Fatal events were reported for 2 subjects, and the preferred terms were ICANS and seizure (1 subject each). The event of seizure was considered confounded and not associated with ICANS.

An overview of time to onset and time to resolution of ICANS and associated neurological events are provided in Table 43 below.

Table 43. Summary of Adverse Events of Immune Effector Cell-associated Neurotoxicity Syndrome and Associated Neurological Adverse Events (AMQ Broad Search) of Interest – Tarlatamab Arm of Study 20210004, Study 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20160323	Studies 20210004, 20200491, and 20160323	Studies 20200491 and 20160323	Studies 20210004, 20200491, and 20160323
Event of Interest Safety Analysis Set	**Tarlatamab < 10 mg (N = 35) n (%)**	**Tarlatamab 10 mg (N = 473) n (%)**	**Tarlatamab > 10 mg (N = 222) n (%)**	**Tarlatamab All Doses (N = 730) n (%)**
Adverse Events n (%)	6 (17.1)	53 (11.2)	54 (24.3)	113 (15.5)
Serious Adverse Events n (%)	2 (5.7)	17 (3.6)	21 (9.5)	40 (5.5)
Fatal Adverse Events n (%)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Grade ³ 3 Adverse Events n (%)	1 (2.9)	4 (0.8)	15 (6.8)	20 (2.7)
Median (Q1, Q3) Time to First Onset of Any Grade Adverse Event From First Dose (days)	26.5 (8.0, 158.0)	15.0 (8.5, 92.5)	13.0 (9.0, 85.0)	14.0 (8.5, 92.5)
Median (Q1, Q3) Time to First Onset of Any Grade Adverse Event From Last Dose After Each Dose (days)	7.0 (1.0, 10.0)	3.0 (2.0, 7.0)	4.0 (2.0, 8.0)	4.0 (2.0, 8.0)
Median (95% CI) Time to Resolution Any Grade (days)[b]	2.0 (1.0, 5.0)	19.0 (6.0, 45.0)	8.0 (5.0, 19.0)	8.0 (5.0, 19.0)

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eIV = extended intravenous; ICANS = Immune effector cell-associated neurotoxicity syndrome; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the safety analysis set; n = number of subjects with observed data; NE = not evaluable; Q3W = every 3 weeks

- **Neurological Events**

An overview of treatment-emergent neurological events is presented in the table below.

Table 44. Summary of Treatment-emergent Neurological Adverse Events – Study 20210004 and Integrated Analysis (Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323) (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Event of Interest	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Neurological events [Nervous system disorders (System Organ Class) / Psychiatric disorders (System Organ Class)]				
All treatment-emergent adverse events of interest	140 (55.6)	86 (35.2)	304 (64.3)	502 (68.8)
Grade ≥ 2	66 (26.2)	46 (18.9)	148 (31.3)	262 (35.9)
Grade ≥ 3	9 (3.6)	14 (5.7)	31 (6.6)	62 (8.5)
Grade ≥ 4	2 (0.8)	0 (0.0)	6 (1.3)	8 (1.1)
Serious adverse events	16 (6.3)	10 (4.1)	38 (8.0)	81 (11.1)
Leading to dose interruption and/or reduction of tarlatamab	11 (4.4)	0 (0.0)	19 (4.0)	41 (5.6)
Leading to discontinuation of tarlatamab	3 (1.2)	0 (0.0)	6 (1.3)	12 (1.6)
Serious	3 (1.2)	0 (0.0)	5 (1.1)	11 (1.5)
Nonserious	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)
Fatal adverse events	1 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)

N = Number of participants in analysis set; n = Number of participants with observed data; AMQ = Amgen MedDRA query; CRS = Cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; SOC = Standard of care.

In study 20210004, neurological events were considered by the investigator as related to investigational product for 113 subjects (44.8%) in the tarlatamab group and 35 subjects (14.3%) in the SOC chemotherapy group. The most frequently reported (≥ 5% of subjects) neurological events in the tarlatamab group were dysgeusia (24.2%), headache (15.1%), dizziness (9.5%), insomnia (7.1%), and ICANS (6.0%). Neurological events reported were predominantly low grade.

For the integrated safety analysis, events were reported at a slightly higher frequency, as shown in the table above. The most frequently reported (≥ 2% of subjects) neurological adverse events were dysgeusia (31.3%), headache (16.3%), insomnia (7.6%), dizziness (8.2%), confusional state (3.2%), ICANS (4.7%), anxiety (2.3%), somnolence and depression (2.1%), neuropathy peripheral (2.5%), paraesthesia and taste disorder (2.7% each).

- **Neutropenia**

An overview of treatment-emergent neutropenia events is presented in Table 45.

Table 45. Summary of Treatment-emergent Adverse Events of Neutropenia (AMQ Narrow Search) – Study 20210004 and Integrated Analysis (Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323) (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Event of Interest				
Neutropenia (AMQ Narrow)				
All treatment-emergent adverse events of interest	52 (20.6)	124 (50.8)	87 (18.4)	128 (17.5)
Grade ≥ 2	45 (17.9)	116 (47.5)	72 (15.2)	109 (14.9)
Grade ≥ 3	30 (11.9)	96 (39.3)	46 (9.7)	72 (9.9)
Grade ≥ 4	11 (4.4)	46 (18.9)	16 (3.4)	25 (3.4)
Serious adverse events	7 (2.8)	32 (13.1)	11 (2.3)	19 (2.6)
Leading to dose interruption and/or reduction of tarlatamab	13 (5.2)	0 (0.0)	15 (3.2)	31 (4.2)
Leading to discontinuation of tarlatamab	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Serious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nonserious	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Fatal adverse events	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of participants in analysis set; n = Number of participants with observed data; AMQ = Amgen MedDRA query; CRS = Cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; SOC = Standard of care.

In study 20210004, the most frequently reported (≥ 5% of subjects) neutropenia events (AMQ narrow search) in the tarlatamab group were neutropenia (10.7%, 7.5% treatment-related) and neutrophil count decreased (7.9%), and in the SOC chemotherapy group were neutropenia (31.1%, 29.5% treatment-related), neutrophil count decreased (17.2%), and febrile neutropenia (11.5%). Neutropenia events were considered by the investigator as related to investigational product for 34 subjects (13.5%) in the tarlatamab group and 119 subjects (48.8%) in the SOC chemotherapy group.

In the integrated safety analysis tarlatamab 10 mg group, neutropenia events were considered treatment related for 62 subjects (13.1%). The most frequently reported (≥ 2% of subjects) neutropenia events in the tarlatamab 10 mg group were neutropenia (10.4%, 8.0% treatment-related) and decreased neutrophil count (6.6%).

- **Hypersensitivity**

An overview of treatment-emergent hypersensitivity events is presented in Table 46.

Table 46. Summary of Treatment-emergent Adverse Events of Hypersensitivity (SMQ Narrow) – Study 20210004 and Integrated Analysis (Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323) (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Event of Interest	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hypersensitivity narrow events [Hypersensitivity (SMQ Narrow) / Anaphylactic reactions (SMQ Narrow)]				
All treatment-emergent adverse events of interest	36 (14.3)	28 (11.5)	65 (13.7)	121 (16.6)
Grade ³ 2	16 (6.3)	10 (4.1)	24 (5.1)	49 (6.7)
Grade ³ 3	1 (0.4)	0 (0.0)	4 (0.8)	7 (1.0)
Grade ³ 4	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Serious adverse events	2 (0.8)	0 (0.0)	3 (0.6)	4 (0.5)
Leading to dose interruption and/or reduction of tarlatamab	2 (0.8)	0 (0.0)	3 (0.6)	4 (0.5)
Leading to discontinuation of tarlatamab	2 (0.8)	0 (0.0)	2 (0.4)	3 (0.4)
Serious	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Nonserious	1 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Fatal adverse events	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)

N = Number of participants in analysis set; n = Number of participants with observed data; AMQ = Amgen MedDRA query; CRS = Cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; SOC = Standard of care.

In study 20210004, one subject (0.4%) in the tarlatamab group had a fatal event of "circulatory collapse" which was captured under hypersensitivity MedDRA term, and no other subject had grade 3 or higher events in this group; the investigator considered the event unrelated to the investigational product and considered the death event more likely to be a cardiovascular event (eg, stroke).

The most frequently reported hypersensitivity adverse events were rash. Hypersensitivity events were considered by the investigator as related to investigational product for 10.7% of subjects in the tarlatamab group and 5.3% in the SOC chemotherapy group.

Hypersensitivity events observed in study 20210004 were consistent with those reported in the integrated analysis. Hypersensitivity events were considered by the investigator as related to investigational product for 9.1% (43 subjects) in the tarlatamab 10 mg group. The PTs were as follows: Rash (n=24), Rash maculo-papular (n=6), Infusion related reaction (n=5), Rash macular (n=2), Injection site rash (n=2), and Hypersensitivity, Urticaria, Bronchospasm, Dermatitis, Rash erythematous, Rash pustular, and Type I hypersensitivity (n=1 each). These events were predominantly low grade and infrequently led to treatment discontinuation.

Safety With Long-term Exposure

Analysis of adverse events for different periods, severity, and outcome of the known serious risks of EOIs were further characterized based on the integrated safety analysis of data from subjects with extensive stage SCLC.

The periods analysed were:

Period 1: From cycle 1 day 1 to 90 days after cycle 1 day 1 or end of treatment, whichever occurs earlier

Period 2: From 90 days after cycle 1 day 1 to end of treatment

Period 3: From end of treatment to end of safety follow up

Period 4: From end of safety follow up to end of long term follow up or end of study, whichever occurs later.

CRS: During period 1, all CRS adverse events (AMQ narrow search) of any grade were reported for 56.0% of subjects treated with 10 mg of tarlatamab. Grade ≥ 2 CRS events were reported for 16.5% and Grade ≥ 3 CRS events were reported for 1.3% of subjects. No grade ≥ 4 CRS events were reported. Two subjects (0.4%) had a CRS event that led to tarlatamab treatment discontinuation. No CRS events were fatal. Serious CRS (AMQ narrow) events during period 1 were reported by 19.0% of subjects. Grade ≥ 2 and ≥ 3 serious CRS events were reported in 7.6% and 0.2% of subjects , respectively. No grade 4 or fatal serious CRS events were reported. Two subjects (0.4%) had a serious CRS event that led to tarlatamab treatment discontinuation. During period 2 there were a total of 3 CRS events (0.6%). During periods 3 and 4, there were a total of 0 (0.0%) and 2 events (0.4%).

ICANS: During period 1, all ICANS and associated neurological adverse events (AMQ broad search) of any grade were reported for 38 subjects (8.0%) of 473 subjects treated with 10 mg of tarlatamab. Grade ≥ 2 ICANS and associated neurological events were reported for 17 subjects (3.6%). Grade ≥ 3 ICANS and associated neurological events were reported for 2 subjects (0.4%). One (0.2%) grade ≥ 4 ICANS and associated neurological events were reported. One subject (0.2%) had ICANS and associated neurological events that led to tarlatamab treatment discontinuation. One (0.2%) ICANS and associated neurological events were fatal. Serious ICANS and associated neurological (AMQ broad) events during period 1 were reported by 16 subjects (3.4%). Grade ≥ 2 and ≥ 3 serious ICANS and associated neurological events were reported in 12 subjects (2.5%) and 2 subjects (0.4%), respectively. One (0.2%) grade ≥ 4 events and 1 (0.1%) fatal serious ICANS and associated neurological events were reported. One subject (0.2%) had a serious ICANS and associated neurological event that led to tarlatamab treatment discontinuation. During period 2, there were a total of 16 ICANS events (3.4%). During periods 3 and 4, there were a total of 0 (0.0%) and 1 event (0.2%).

Serious adverse events

Treatment-emergent serious adverse events are shown in Table 47 below.

In study 20210004, the most common serious adverse events (≥ 5 subjects) for tarlatamab were: CRS (43 subjects, 17.1%), pyrexia (14 subjects, 5.6%), pneumonia (10 subjects, 4.0%), ICANS (9 subjects, 3.6%), dyspnoea (6 subjects, 2.4%), and febrile neutropenia, hyponatremia, and sepsis (5 subjects, 2.0% each). In the SOC chemotherapy group, these included: febrile neutropenia (24 subjects, 9.8%), pneumonia (21 subjects, 8.6%), thrombocytopenia (11 subjects, 4.5%), anaemia (10 subjects, 4.1%), neutropenia and platelet count decreased (6 subjects, 2.5% each), and pancytopenia (5 subjects, 2.0%).

Table 47. Treatment-emergent Serious Adverse Events by Preferred Term (Occurring in at Least 1% of Subjects Across Tarlatamab All Doses) - Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting treatment-emergent serious adverse events	129 (51.2)	125 (51.2)	256 (54.1)	416 (57.0)
Cytokine release syndrome	43 (17.1)	1 (0.4)	93 (19.7)	170 (23.3)
Pyrexia	14 (5.6)	0 (0.0)	22 (4.7)	34 (4.7)
Pneumonia	10 (4.0)	21 (8.6)	18 (3.8)	32 (4.4)
Hyponatraemia	5 (2.0)	4 (1.6)	12 (2.5)	22 (3.0)
Immune effector cell-associated neurotoxicity syndrome	9 (3.6)	0 (0.0)	13 (2.7)	22 (3.0)
Dyspnoea	6 (2.4)	2 (0.8)	7 (1.5)	13 (1.8)
Fatigue	4 (1.6)	1 (0.4)	7 (1.5)	12 (1.6)
Confusional state	1 (0.4)	0 (0.0)	1 (0.2)	9 (1.2)
Encephalopathy	0 (0.0)	0 (0.0)	1 (0.2)	9 (1.2)
Febrile neutropenia	5 (2.0)	24 (9.8)	7 (1.5)	9 (1.2)
COVID-19	2 (0.8)	0 (0.0)	3 (0.6)	8 (1.1)
Respiratory failure	2 (0.8)	3 (1.2)	5 (1.1)	7 (1.0)
Superior vena cava syndrome	0 (0.0)	4 (1.6)	5 (1.1)	7 (1.0)

N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.
The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.

Treatment-related serious adverse events are shown in the table below.

Table 48. Treatment-related Treatment-emergent Serious Adverse Events by Preferred Term (Occurring in at Least 1% of Subjects Across Tarlatamab All Doses) - Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 – (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting treatment-related treatment-emergent serious adverse events	70 (27.8)	75 (30.7)	140 (29.6)	259 (35.5)
Cytokine release syndrome	43 (17.1)	1 (0.4)	92 (19.5)	169 (23.2)
Pyrexia	11 (4.4)	0 (0.0)	17 (3.6)	28 (3.8)
Immune effector cell-associated neurotoxicity syndrome	9 (3.6)	0 (0.0)	13 (2.7)	22 (3.0)
Encephalopathy	0 (0.0)	0 (0.0)	1 (0.2)	8 (1.1)
Fatigue	3 (1.2)	1 (0.4)	4 (0.8)	8 (1.1)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.0)

N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.

As shown in the tables above, no differences were observed in the incidence of serious adverse events between the tarlatamab arm in study 20210004 and the integrated safety analysis. The most frequently reported treatment-related serious adverse events in the pivotal study 20210004 and in the tarlatamab 10 mg group of the integrated safety analyses (≥3% of subjects) were cytokine release syndrome, pyrexia and ICANS. These are included in the ADRs table in section 4.8 of the SmPC.

Deaths

An overview of treatment-emergent fatal adverse events is presented in Table 49 below.

Table 49. Treatment-emergent Fatal Adverse Events by Preferred Term - Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting treatment-emergent fatal adverse events	20 (7.9)	21 (8.6)	30 (6.3)	41 (5.6)
Pneumonia	4 (1.6)	6 (2.5)	6 (1.3)	7 (1.0)
Cardio-respiratory arrest	3 (1.2)	1 (0.4)	3 (0.6)	5 (0.7)
Respiratory failure	1 (0.4)	2 (0.8)	3 (0.6)	4 (0.5)
Aspiration	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)
Cardiac arrest	1 (0.4)	3 (1.2)	1 (0.2)	2 (0.3)
Euthanasia	1 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Sepsis	2 (0.8)	0 (0.0)	2 (0.4)	2 (0.3)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiopulmonary failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Chronic obstructive pulmonary disease	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Circulatory collapse	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Coronavirus infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Death	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Dyspnoea	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Gastric haemorrhage	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Haemoptysis	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Hepatic failure	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Immune effector cell-associated neurotoxicity syndrome	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Myocardial infarction	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pulmonary oedema	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Respiratory acidosis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Seizure	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Arteriovenous fistula site haemorrhage	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Febrile neutropenia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
General physical health deterioration	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Hepatotoxicity	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Pneumonia aspiration	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Pneumonitis	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory tract infection	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Sudden death	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Tumour lysis syndrome	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care. The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.

In study 20210004, the most frequently reported fatal adverse events (> 1% subject in either group) for tarlatamab were: pneumonia (4 subjects, 1.6%), and cardio-respiratory arrest (3 subjects, 1.2%); for SOC chemotherapy these included: pneumonia (6 subjects, 2.5%), and cardiac arrest (3 subjects, 1.2%).

In the integrated safety analysis in subjects receiving any dose of tarlatamab, fatal adverse events were reported for 41 subjects (5.6%). Overall, the most frequently reported fatal adverse event by preferred term (occurring in ≥ 1% of the subjects) was pneumonia (7 subjects, 1.0%).

Fatal adverse events were reported for 30 subjects (6.3%) treated with tarlatamab 10 mg. The most frequently reported fatal adverse event by preferred term (occurring in ≥ 1% of the subjects) was pneumonia (6 subjects, 1.3%).

Across all doses, treatment-related fatal adverse events were reported for 3 subjects (0.4%) treated with tarlatamab monotherapy, including 2 subjects (0.4%) treated with tarlatamab monotherapy at 10 mg, one of whom experienced a fatal event of respiratory failure and the other a fatal event of ICANS. The third subject, in the tarlatamab < 10 mg group, experienced a fatal event of respiratory failure.

Narratives were provided for all deaths. The two treatment-related fatal events for tarlatamab 10 mg dose were:

- ICANS event: The final cause of death was reported as ICANS, secondary to tarlatamab. Upon sponsor's medical review, it was determined that the subject's clinical deterioration and death were likely attributable to severe pneumonia in the context of metastatic SCLC with bronchial obstruction. Due to the presence of significant confounding factors—including 2 episodes of grade 3 pneumonia, it was concluded that pneumonia, rather than CRS or ICANS, was the likely cause of fever, hypotension, subsequent encephalopathy, and death.
- Respiratory failure event: The final cause of death was assessed as grade 5 respiratory failure, considered multifactorial, due to both pneumonitis and severe underlying disease.

Infections and infestations

The overall subject incidence of adverse events in the Infections and Infestations organ system were similar across the groups (tarlatamab [36.1%] and SOC chemotherapy [38.9%]) in study 20210004. The incidence was comparable to that in the integrated analysis (41.2% with tarlatamab 10 mg).

According to the applicant, the majority of the serious adverse events in this organ system did not suggest a causal association with tarlatamab.

5.4.5. Discontinuation due to adverse events

Adverse events leading to dose reduction and/or interruptions

The protocol for study 20210004 does not allow dose reduction for tarlatamab and only provides guidance for dose interruption. Adverse events that led to dose interruption and/or reduction of investigational product were reported for 94 subjects, 37.3%, in the tarlatamab group and 159 subjects, 65.2%, in the SOC chemotherapy group. Treatment-related TEAEs that occurred in at least 1% of subjects across tarlatamab all doses safety analysis set and that led to dose interruptions in study 20210004 and interruptions/dose reductions for the integrated safety analysis are presented in the table below.

Table 50. Treatment-related Treatment-emergent Adverse Events Leading to Dose Interruption and/or Reduction of Tarlatamab and SOC Chemotherapy by Preferred Term (Occurring in at Least 2 Subjects Across Tarlatamab All Doses) – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting treatment-related treatment-emergent adverse events leading to dose interruption and/or reduction of tarlatamab and SOC chemotherapy	48 (19.0)	134 (54.9)	77 (16.3)	138 (18.9)
Cytokine release syndrome	4 (1.6)	1 (0.4)	10 (2.1)	30 (4.1)
Neutropenia	8 (3.2)	35 (14.3)	10 (2.1)	19 (2.6)
Fatigue	6 (2.4)	17 (7.0)	11 (2.3)	14 (1.9)
Decreased appetite	6 (2.4)	3 (1.2)	9 (1.9)	12 (1.6)
Neutrophil count decreased	5 (2.0)	17 (7.0)	5 (1.1)	9 (1.2)
Asthenia	1 (0.4)	11 (4.5)	3 (0.6)	7 (1.0)

N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.

Adverse events leading to discontinuations

In study 20210004, adverse events that led to discontinuation of investigational product were reported for 13 subjects, 5.2%, in the tarlatamab group and 30 subjects, 12.3%, in the SOC chemotherapy group. Treatment-related TEAEs occurring in at least 2 subjects across tarlatamab all doses leading to discontinuation in study 20210004 and the integrated safety analysis are presented in the table below.

Table 51. Treatment-related Treatment-emergent Adverse Events Leading to Discontinuation of Tarlatamab and SOC Chemotherapy by Preferred Term (Occurring in at Least 2 Subjects Across Tarlatamab All Doses) – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting treatment-related treatment-emergent adverse events leading to discontinuation of tarlatamab and SOC chemotherapy	7 (2.8)	15 (6.1)	15 (3.2)	30 (4.1)
Cytokine release syndrome	1 (0.4)	0 (0.0)	3 (0.6)	5 (0.7)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)
Pneumonitis	1 (0.4)	0 (0.0)	1 (0.2)	3 (0.4)
Acute kidney injury	1 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Immune effector cell-associated neurotoxicity syndrome	1 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Neutrophil count decreased	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.3)
Tumour lysis syndrome	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)

N = Number of participants in analysis set; n = Number of participants with observed data; SOC = standard of care.

5.4.6. Safety in special populations

Adverse events reported for subjects receiving tarlatamab monotherapy were analysed based on intrinsic factors (race, age, and sex) and the extrinsic factor of geographic region. Small sample sizes in certain subgroups limit the ability to draw definitive conclusions.

Intrinsic Factors

- **Race**: No meaningful differences were observed in the types of adverse events reported across race subgroups.
- **Age**: Adverse events were analysed for subjects aged <65 years and ⩾65 years. No meaningful differences were observed between these age groups.
- **Sex**: Adverse events were analysed for male and female subjects. No meaningful differences were observed between sex groups.

Extrinsic Factors

- **Geographic Region**: Adverse events were analysed by region (Asia, Europe, North America, and Rest of the World). No meaningful differences were observed across regions.

5.4.7. Immunological events

Please refer to the Clinical pharmacology section.

5.4.8. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with tarlatamab. Initiation of tarlatamab treatment causes transient release of cytokines that may suppress cytochrome P450 (CYP450) enzymes and may result in increased exposures of concomitant CYP450 substrates. In patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring is recommended for known adverse events. Adjustment of the dose of the concomitant drug required as needed.

5.4.9. Vital signs and laboratory findings

Laboratory parameters

In the tarlatamab group of Study 20210004, the most frequently reported (> 5% of subjects) shifts of worst laboratory toxicity changes ⩾3 grades from baseline were decreases in lymphocytes (26.4%), total neutrophils (10.1%), sodium (8.4%), and white blood cells (6.5%). In the SOC chemotherapy group, the most frequently reported (> 5% of subjects) shifts of ⩾ 3 grades from baseline were decreases in total neutrophils (35.5%), haemoglobin and white blood cells (28.3% each), lymphocytes (27%), platelets (19.9%), and sodium (5.8%).

Hepatotoxicity

Potential hepatotoxicity was evaluated by reviewing subject incidence of chemistry laboratory criteria consistent with potential Hy's law cases (ALT or AST > 3 x ULN and total bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN); to identify all potential cases, subjects with any of the laboratory components occurring within 30 days of each other were included.

Table 52. Participant Incidence of Potential Hy's Law Cases - Study 20210004, Study 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Category Time Point	Tarlatamab 10 mg (N = 252) n / N1 (%)	SOC Chemotherapy (N = 244) n / N1 (%)	Tarlatamab 10 mg (N = 473) n / N1 (%)	Tarlatamab All Doses (N = 730) n / N1 (%)
ALT or AST ≥ 3 x ULN				
Baseline	8 / 252 (3.2)	12 / 244 (4.9)	12 / 473 (2.5)	14 / 730 (1.9)
On study	31 / 250 (12.4)	23 / 224 (10.3)	73 / 471 (15.5)	114 / 728 (15.7)
Total bilirubin ≥ 2 x ULN				
Baseline	1 / 251 (0.4)	0 / 244 (0.0)	1 / 472 (0.2)	1 / 729 (0.1)
On study	5 / 249 (2.0)	9 / 224 (4.0)	20 / 470 (4.3)	32 / 727 (4.4)
ALT or AST ≥ 3 x ULN and Total bilirubin ≥ 2 x ULN and ALP < 2 x ULN				
Baseline	0 / 251 (0.0)	0 / 241 (0.0)	0 / 472 (0.0)	0 / 729 (0.0)
On study within 30 days	1 / 249 (0.4)	2 / 220 (0.9)	2 / 470 (0.4)	7 / 727 (1.0)

N = Number of participants in analysis set; N1 = Number of participants with nonmissing values for specified Hy's Law parameter(s) at each time point; n = Number of participants meeting criterion; ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; SOC = Standard of care; ULN = Upper Limit of Normal.
Baseline was the last nonmissing assessment taken prior to the first administration of tarlatamab.

No clinically relevant changes were observed in the vital signs.

5.4.10. Post-marketing experience

As of 15 November 2024, tarlatamab was commercially available in 2 countries – the US and Canada. As of 29 May 2025, tarlatamab is commercially available in 10 countries. Cumulatively, since the International Birth Date (16 May 2024) of tarlatamab up to the end of the Periodic Benefit-Risk Evaluation Report No. 01 reporting period, there was an estimated 289 patient-years of exposure to tarlatamab in the marketed setting.

As of 15 November 2024, Amgen received and reported a total of 489 adverse drug reactions cumulatively from medically confirmed and unconfirmed spontaneous sources, 284 of 489 were serious and 205 were nonserious. Additionally, a total of 53 serious adverse drug reactions were reported cumulatively from noninterventional post marketing sources and other solicited sources. Cytokine release syndrome, ICANS, and neutropenia were important identified risks for tarlatamab. Cumulatively, 170 cases with 240 (156 serious, 84 nonserious) events of CRS were reported from post marketing sources. Of these 170 cases, 154 cases were medically confirmed. Five events had fatal outcome. During the reporting period and cumulatively, 64 cases with 65 events of ICANS (64 serious, 1 nonserious) were received from post marketing sources. Of these 64 cases, 57 cases were medically confirmed. Of these 64 cases, 1 case had a fatal event outcome.

For neutropenia, during the reporting period and cumulatively, 3 cases with 3 serious events were received from post marketing sources. All of these 3 cases were medically confirmed, and no events with fatal outcomes were reported.

During the reporting period of PBRER No. 01 the evaluation of safety data did not result in the detection of any new risks for tarlatamab. As of 14 October 2025, among approximately 3,750 patients treated with tarlatamab, 13 CRS cases and 4 ICANS cases with reported fatal outcome have been identified in the post marketing setting.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

The safety profile of tarlatamab is primarily supported by data from the pivotal phase 3 study 20210004, which compared tarlatamab at the indicated dose of 10 mg (administered as a step dosing regimen: 1 mg on cycle 1 day 1, followed by 10 mg on cycle 1 day 8, 10 mg on cycle 1 day 15, and subsequently 10 mg every two weeks) to SOC chemotherapy (amrubicin, lurbinectedin, topotecan) in patients with SCLC who had experienced disease progression on or after platinum-based chemotherapy (tarlatamab N=252; SOC chemotherapy N=244). In addition, an integrated safety analysis has been conducted, pooling data from studies 20210004, 20200491, and 20160323. This analysis includes all subjects treated with tarlatamab at the indicated dose of 10 mg (N=473), as well as data across all dose levels and all subjects receiving tarlatamab monotherapy (N=730). The ADRs reflected in the product information are based on data from subjects treated at the indicated dose of 10 mg (N=473). The pooling strategy is endorsed, and the size of the safety database and collection of safety data is considered acceptable.

Key demographic and baseline characteristics are comparable between treatment groups in study 20210004 and align with the overall population receiving tarlatamab across studies. Median relative tarlatamab dose intensity was consistently high across datasets (100%), indicating treatment adherence. However, exposure time is short, with a median treatment duration of 18.2 weeks and with only 10.3% of subjects treated for ≥12 months in study 20210004 as of the data cutoff date. At that time, 27.2% of the subjects in the study were still undergoing tarlatamab treatment. Updated data from the ongoing studies are expected in the final CSRs. Long-term safety has been included as missing information in the RMP and data will be provided in a PASS category 3 study, Q3 2030.

Adverse Events

Nearly all subjects experienced treatment-emergent adverse events (TEAEs) and treatment-related TEAEs. In study 20210004, the incidence of TEAEs (98.8% vs 99.6%), treatment-related TEAEs (93.3% vs 91.4%), serious adverse events (SAEs) (51.2% vs 51.2%), and treatment-related SAEs (27.8% vs 30.7%) was similar between the tarlatamab and SOC chemotherapy groups, but the tarlatamab group demonstrated lower rates of grade ≥3 AEs (54.0% vs 79.9%), treatment-related grade ≥3 AEs (26.6% vs 62.3%), grade ≥4 AEs (16.3% vs 37.3%), and treatment-related grade ≥4 AEs (4.8% vs 24.6%) compared to the SOC chemotherapy group.

In study 20210004, the common treatment-related TEAEs generally mirrors common TEAEs, albeit occurring at lower frequencies. In the tarlatamab group, the most frequently reported treatment-related TEAEs (>15% of subjects), were CRS (56.3%), decreased appetite (26.2%), dysgeusia (23.0%), pyrexia (20.6%), anaemia and fatigue (19.8% each), and nausea (16.7%). Overall, common TEAEs were consistent between study 20210004 and the integrated analysis.

Neutropenia (4.4%) and lymphopenia (3.6%) were the most frequently reported treatment-related grade ≥3 TEAEs in study 20210004. Grade ≥ 3 TEAEs reported in subjects treated with tarlatamab 10 mg in the integrated safety analysis were generally consistent with those observed in the tarlatamab arm of study 20210004.

Deaths

Fatal adverse events were reported for 7.9% (0.4% treatment-related) of subjects in the tarlatamab group and 8.6% (1.6% treatment related) in the SOC chemotherapy group in study 20210004. Pneumonia was the most frequent fatal AE for tarlatamab (1.6%, not considered treatment-related). A treatment-related fatal event due to ICANS was observed in one subject. This has been reflected in section 4.4 of the SmPC.

Serious Adverse Events (SAEs)

Serious adverse events were reported for 51.2% of subjects in both treatment groups in study 20210004. Treatment-related SAEs were comparable between tarlatamab (27.8%) and SOC chemotherapy (30.7%). CRS, pyrexia, and ICANS were the most frequent treatment-related SAEs for tarlatamab. A high SAE incidence highlights the need for close monitoring including dose modification and management as described in section 4.2 of the SmPC.

Adverse Events of Special Interest (AESIs)

CRS, ICANS, neutropenia, neurological events, and hypersensitivity are defined as AESIs. All except hypersensitivity are listed as ADRs in the SmPC. The most frequently reported hypersensitivity PT Rash (5.1%) is included as an ADR in Section 4.8 of the SmPC. A warning in SmPC Section 4.4 addresses hypersensitivity, which will continue to be monitored as an AESI as part of routine pharmacovigilance activities.

CRS was the most frequently reported adverse event for tarlatamab in study 20210004 (56.3%), with all events assessed as treatment-related. Grade ≥2 and grade ≥3 CRS events were reported in 13.9% and 1.2% of subjects, respectively, while no grade ≥4 events were observed. Serious CRS events occurred in 17.1% of subjects, and one subject (0.4%) discontinued treatment due to CRS. In the integrated analysis, slightly higher CRS incidence and severity were noted, with a dose-related trend observed (more frequent events at doses >10 mg).

Data indicate that most CRS events occur after the first two doses. Among subjects receiving tarlatamab 10 mg in studies 20210004 and 20200491, 55.1% had at least one CRS event, with grade ≥2 CRS events declining from 13.2% on cycle 1 day 1 to 4.2% on cycle 1 day 8, and further to 1.7% by cycle 1 day 15. By cycle 2 and beyond, grade ≥2 CRS events decreased to 0.8%.

A stepwise reduction in CRS monitoring requirements was applied during clinical development. Data from subjects under 6–8-hour monitoring criteria in studies 20210004 (N = 43), 20160323 (N = 30), and 20230273 (N = 31), as well as subjects under 1–2-hour monitoring in studies 20200041 (N = 317, incl. control) and 20230016 (N = 167, incl. control), were provided.

In study 20210004, CRS incidence was lower with 6–8-hour monitoring (25.6%) vs. 48-hour monitoring (42.1%) on cycle 1 day 1. Grades ≥ 2 and ≥ 3 CRS occurred in 9.3% and 0% (6–8-hour) vs. 12.0% and 2% (48-hour). SAEs were reported in 4.7% (6-8-hour) vs. 11.0% (48-hour). On cycle 1 day 8, CRS incidence was 23.3% (6–8-hour) vs. 37.3% (48-hour), with grades ≥ 2 and ≥ 3 CRS in 2.3% and 0% vs. 5.3% and 0.5%, respectively. SAEs were 4.7% (6–8-hour) vs. 12.0% (48-hour). Similar trends were observed across other studies.

The higher CRS incidence in the 48-hour group may reflect longer monitoring, capturing more events. However, the 6–8-hour regimen showed comparable safety, with shorter median time to intervention (16.6 vs. 27.3 hours). CRS events were most frequent after the first two doses, decreasing in severity/incidence over time. Despite fewer events captured, the 6–8-hour monitoring demonstrated similar safety outcomes to the 48-hour regimen.

Recommendations in section 4.2 of the SmPC specifies a monitoring time of 6–8 hours for the first two doses.

While the majority of CRS events were of low grade and resolved with appropriate management, serious CRS events were reported, which underscores the need for careful monitoring and patient education. As outlined in section 4.2 and 4.4 of the SmPC, both patients and caregivers should be informed about the signs and symptoms of CRS prior to discharge. Additional risk minimisations measures have also been put in place, as the MAH will have to ensure that all patients/carers receive a patient card before taking imdylltra.

In study 20210004, ICANS was reported in 6.0% of subjects in the tarlatamab group (all events considered treatment-related) and 0.8% of subjects in the SOC chemotherapy group. In the tarlatamab group, one fatal ICANS event was reported (0.4%) while no other grade ≥ 3 or grade ≥4 ICANS events were reported. ICANS occurred in 4.7% of subjects receiving the 10mg tarlatamab dose in the integrated analysis (all events considered treatment-related). A warning regarding the risk of ICANS has been included in section 4.4 of the SmPC, and patients and/or caregivers will receive a patient card to raise awareness about the risk.

In study 20210004, neutropenia (PT) was reported in 10.7% of subjects in the tarlatamab group (7.5% considered treatment-related). In comparison, 31.3% of subjects in the SOC chemotherapy group experienced neutropenia (29.5% considered treatment-related). Similarly, in the integrated safety analysis for the tarlatamab 10 mg group, neutropenia (PT) was reported in 10.4% of subjects.

For 8.0% of subjects in this group, neutropenia was considered treatment related. A warning regarding the risk of neutropenia has been included in section 4.4 of the SmPC.

Infections and infestations

The overall incidence of adverse events in the Infections and Infestations SOC was 36.1% in the tarlatamab group in study 20210004, comparable to that in the integrated analysis (41.2% with tarlatamab 10 mg). Pneumonia was reported in 8.0% of the tarlatamab 10 mg group, with 4 cases (0.8%) assessed as treatment-related. The incidence of sepsis was 1.7% in the tarlatamab 10 mg group, with all events considered unrelated to treatment. It is acknowledged that lung cancer increases the risk of both pneumonia and sepsis. Based on the current data, it is accepted not to include "pneumonia" and "sepsis" as ADRs at present. However, a warning regarding the risk of infections (including serious and fatal cases) in section 4.4 of the SmPC has been included to mitigate and manage the risk.

Dose Interruptions and Discontinuations

In study 20210004, treatment-related dose interruptions occurred in 19% of subjects in the tarlatamab group, compared to 54.9% in the SOC chemotherapy group. Neutropenia (3.2%), fatigue and decreased appetite (2.4% each) and neutrophil count decreased (2.0%) were the most common reasons for interruptions, all included as ADRs in section 4.8 of the SmPC. Similar rates were observed in the integrated analysis, with a median relative dose intensity of 100% across datasets, indicating treatment tolerance.

Discontinuations due to adverse events were reported for 5.2% of patients in the tarlatamab group and 12.3% in the SOC chemotherapy group in study 20210004. Pneumonia was the most common AE leading to discontinuation in the tarlatamab group (1.2%). Overall, discontinuations due to treatment-related AEs were low, further supporting the tolerability of tarlatamab.

Subgroup Analysis

No clinically meaningful differences in the safety profile were observed across subgroups (age, sex, race, region). However, small and uneven subgroup sizes may limit interpretability.

Hepatotoxicity

ALT/AST elevations (≥3x ULN) were reported in 12.4% of subjects in the tarlatamab group of study 20210004 (10.3% in the SOC group), and 15.5% of subjects at the 10 mg tarlatamab dose in the integrated analysis. Elevations in ALT and AST have been included as ADRs in Section 4.8, and a warning on hepatotoxicity has been included in Section 4.4 of the SmPC. Laboratory values meeting Hy's law criteria were observed in 0.4% (n=2) of subjects at the 10 mg dose and in 1.0% (n=7) overall. However, these cases were determined not to meet the criteria for true Hy´s law cases.

Post-Marketing Data

Post-marketing data include reports of fatal cases of CRS and ICANS. Information about these fatal events have been included in sections 4.4 and 4.8 of the SmPC. No specific patient characteristics (including, but not limited to, tumour load, relapse within <>90 days, etc.) that might increase susceptibility to CRS, ICANS, or their fatal outcomes have been identified as this time.

SmPC

Specific precautions for use, such as close patient monitoring during treatment initiation and detailed management recommendations, are included in the SmPC. As requested, an updated monitoring period of 6-8 hours for the first two doses is listed in section 4.2. Section 4.3 is supported by the provided data. Section 4.4 includes proposed warnings on the AESIs CRS, ICANS, neutropenia, and

hypersensitivity, which are agreed upon. Additionally, warnings regarding infections, hepatotoxicity, and fatal CRS and ICANS cases have been added to section 4.4. The provided data support the proposed wording in section 4.7, which appropriately highlights the potential impact of ICANS and other neurological events on driving and operating machinery.

5.4.11.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs included in section 4.8 of the SmPC are described in section 5.4.3.1 above.

Section 4.8 is based on data from 473 subjects receiving tarlatamab 10 mg, this is considered appropriate.

5.4.11.2. Conclusions on clinical safety

The safety profile of tarlatamab for the claimed indication in adult patients with SCLC appears overall manageable based on the provided data. CRS and ICANS are included as important identified risks in the RMP, and fatal cases of CRS and ICANS have been reported, highlighting the need for careful patient management and monitoring. The risk of CRS and ICANS will also be mitigated by additional risk minimisation measures as a patient card will be distributed to patients/carer prior treatment.

The limited follow-up time and short exposure duration impose uncertainties regarding the characterization of long-term safety (included in the RMP as Missing Information) but updated data will be provided in a PASS category 3 study, Q3 2030.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

Table 53: Summary of safety concerns in the RMP

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

6.1.2. Discussion on proposed safety specification

CRS and ICANS are agreed to be important identified risks based on clinical trial data and their potential severity. CRS was reported in 56.7% of subjects receiving the proposed 10 mg dose of tarlatamab in clinical trials. Furthermore, CRS can be serious, and fatal cases have been reported post-marketing, underscoring its clinical significance. Similarly, ICANS has been identified as an important risk based on clinical study data, where it occurred in 4.7% of subjects treated with the 10 mg dose of tarlatamab. Like CRS, ICANS has the potential to be serious and/or life-threatening with fatal cases reported, warranting its inclusion as an identified risk.

Across studies 20210004, 20200491, and 20160323, 14% of subjects treated with tarlatamab at a

10 mg dose had received tarlatamab treatment for ≥ 12 months. The median duration of tarlatamab treatment within this pooled dataset was 18.00 weeks. Long-term safety is included as Missing information in the RMP.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

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 54. 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

Table 55. (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.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

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

6.2.2.2. Additional pharmacovigilance activities

Long-term-safety

Long-term safety is included as Missing Information in the RMP. The Applicant has proposed to address this missing information by conducting an Integrated Safety Analysis (ISA) pooling data from several clinical studies, which is considered acceptable.

Based on the average follow-up time after the last dose across the 3 studies (20160323, 20200491, and 20210004) included in integrated summary of safety (ISS) submitted with the marketing authorisation application and applying extrapolation to all studies listed in RMP Annex 3, the total expected follow-up amounts to approximately 1500 person-years. The anticipated proportion of exposed subjects expected to reach 12, 24 and 36 months after the last dose are 15%, 5%, and 0% respectively.

To increase the number of subjects with the potential to reach 36 months of follow-up, the MAH has added Study 20240178, a Phase 3 study in first-line SCLC evaluating tarlatamab in combination with durvalumab and chemotherapy. This approach is acceptable.

The final analysis will be conducted by Q3 2030, and interim analyses will be provided annually within the PSURs.

6.3. Risk minimisation measures

6.3.1. Proposed risk minimisation measures

V.1 Routine Risk Minimization Measures

Table 56. (Table Part V.1) Description of Routine Risk Minimisation 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.

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

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

V.2 Additional Risk Minimization Measures

Table 57. 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

6.3.2. Discussion on the risk minimisation measures

6.3.2.1. Routine risk minimisation measures

Routine risk minimisation measures haven been adequately presented.

6.3.2.2. Additional risk minimisation measures

Patients and/or caregivers will receive the Patient Card from their HCP prescribing IMDYLLTRA to alert then on the risks of ICANS and CRS and when to seek urgent medical attention.

6.4. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 0.3, dated 27.02.2026, is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the Product information. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 16.05.2024.

8. Product information

8.1. Summary of product characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The proposed indication at the time of submission is considered appropriate and supported by the data provided in the dossier.

8.2. Labelling

8.2.1. User consultation

8.2.1.1. Conclusion from the checklist for the review of user consultation

A well designed and thorough user consultation has been done. The consultation has been done in accordance with the requirement of the Guideline on the readability of the label and package leaflet of medicinal products for human use prior to placing the product on the market. The user consultation is acceptable.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Imdylltra (tarlatamab) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that

this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

The final indication is:

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.

9.1.1. Disease or condition

SCLC is an aggressive, poorly differentiated, high-grade neuroendocrine carcinoma of the lungs. If left untreated, the disease progresses rapidly, leading to significant morbidity and mortality. ES-SCLC refers to disease that has spread beyond one hemithorax, including distant metastases. While the initial response to chemotherapy is often robust, relapse is common. Mortality remains high, with a 5-year survival rate of less than 5% for extensive stage disease (Cittolin-Santos et al 2024).

SCLC predominantly affects older adults, with peak incidence between ages 60 and 70. It is strongly associated with tobacco smoking, with over 95% of cases linked to smoking history (Wéber et al 2023).

Common disease symptoms include cough, dyspnoea, chest pain, weight loss, and fatigue. Symptoms vary depending on disease stage and severity, with advanced stages often causing systemic manifestations such as bone pain, neurological deficits, or liver dysfunction. Patients frequently report anxiety and depression related to the poor prognosis and treatment side effects. Patients with ES-SCLC often have significantly impaired quality of life, a consequence of the physical limitations, psychological distress, and social challenges imposed by the disease and its treatment (Bebb et al 2023, Bennett et al 2017).

9.1.2. Available therapies and unmet medical need

Therapies for relapsed ES-SCLC patients in the EU

Treatment options for relapsed ES-SCLC in the EU are limited, with platinum rechallenge considered for platinum-sensitive patients (<90 days after completing first-line therapy) and other recommended regimens including topotecan, CAV (cyclophosphamide/doxorubicin/vincristine) or single agent chemotherapy (e.g., docetaxel, etoposide, gemcitabine, temozolomide) (ESMO Clinical Practice Guideline: Small Cell Lung Cancer). Topotecan is the only chemotherapeutic agent specifically approved in the EU for second-line treatment of relapsed SCLC. However, its efficacy is modest, with response rates of approximately 20% in platinum-sensitive patients and even lower rates in platinum-resistant cases. Median OS typically ranges from 6 to 7 months, and treatment is associated with significant toxicity, including myelosuppression, fatigue, and gastrointestinal side effects. Immunotherapy agents and other novel approaches have not yet demonstrated improved outcomes in this setting.

SCLC remains a serious, life-threatening condition with poor prognosis and limited survival outcomes.

The unmet medical need in this patient population underscores the importance of developing new therapies with improved efficacy and tolerability.

9.2. Main clinical studies

The MAA for Imdylltra is supported by one pivotal study, DeLLphi-304. This is an ongoing, randomised, open-label, multicentre phase 3 study comparing tarlatamab to a comparator arm consisting of three different SOC therapies, adapted to the regions where the study is conducted. The ITT population includes 509 patients, randomized in a 1:1 allocation ratio to receive tarlatamab 10 mg IV Q2W (n=254) or SOC therapy (n=255). Among patients treated with SOC therapies, 185 received topotecan, 23 received amrubicin, and 47 received lurbinectedin.

OS is the primary endpoint of the study. The analysis of OS is based on a preplanned interim analysis, which serves as the final analysis. For the key secondary endpoint PFS, contrast-enhanced CT/MRI imaging was performed every six weeks and assessed according to RECIST v1.1 criteria by the investigator, without confirmation by BICR.

9.3. Favourable effects

Pivotal study 20210004 (DeLLphi-304)

Primary endpoint: OS

The median OS was 13.6 months in the tarlatamab arm compared to 8.3 months in the SOC arm (HR=0.599; 95% CI: 0.468, 0.768; p-value <0.001).

Subgroup analysis of OS yielded similar HRs for platinum-sensitive patients with a chemotherapy-free interval of <90 days and platinum-resistant patients with a chemotherapy-free interval of ≥90 days, i.e. HR=0.601 (95% CI: 0.430, 0.840) and HR=0.649 (95% CI: 0.453, 0.931), respectively.

Key secondary endpoint: PFS

The median PFS was 4.2 months in the tarlatamab arm compared to 3.2 months in the SOC arm (HR= 0.716; 95% CI: 0.586, 0.875; p-value <0.001).

9.3.1. Uncertainties and limitations about favourable effects

The relevance of DLL3 tumour expression for predicting response to tarlatamab treatment has not been thoroughly investigated for the patients with low DLL3 tumour expression, specifically DLL3 expression <25%. For the subgroup of patients with DLL3 expression <25% in the pivotal study, the HR for OS is 0.954 (95% CI: 0.590, 1.541), indicating that tarlatamab may have similar efficacy to SOC. Of note, subgroup analyses of PFS for patients with DLL3 expression <25% (DLL3 staining intensity at 2+/3+), resulted in point estimates above 1It cannot be excluded that the OS outcome in this subgroup may be partially driven by patients who received further lines of therapy after progression on tarlatamab. Post hoc analyses of OS and PFS for tarlatamab versus topotecan in the subgroup of patients with DLL3 expression <25% provided results that were largely consistent with the HR for the comparison of tarlatamab and SOC in the overall subgroup of patients with DLL3 expression <25%.

The effect of the DLL3 assay measurement error (misclassification) has not been characterized which further contributes to the uncertainty of the interpretation of subgroup results.

9.4. Unfavourable effects

The pivotal phase 3 study 20210004 included 252 subjects who received 10 mg dose of tarlatamab and 244 subjects who received SOC chemotherapy. The supportive primary integrated safety analysis included 473 subjects who received 10 mg dose of tarlatamab and 730 subjects who received any dose of tarlatamab (up to 100 mg) across studies 20210004, 202000491, and 20160323. Data listed below represents data from the pivotal study.

- Median tarlatamab treatment duration was 18.21 weeks with 41.3% of subjects having a treatment duration of at least 6 months and 10.3% of subjects having a treatment duration of at least 12 months. At data cutoff, 27.2% were still receiving tarlatamab treatment.

- Overall, 98.8% of subjects receiving tarlatamab experienced TEAEs of any grade. The most common (>15%) TEAEs of any grade in the tarlatamab group included CRS (56.3%), decreased appetite (35.3%), anaemia (31.0%), fatigue and constipation (28.6% each), pyrexia (27.4%), nausea and dysgeusia (24.2% each), hyponatremia (17.1%), and headache (15.1%).

- Overall, 93.3% of subjects receiving tarlatamab experienced TEAEs that were considered treatment-related by the investigator. Treatment-related TEAEs reported in >15% of subjects in the tarlatamab group included CRS (56.3%), decreased appetite (26.2%), dysgeusia (23.0%), pyrexia (20.6%), anaemia and fatigue (19.8% each), and nausea (16.7%).

- Grade 3 or higher TEAEs were reported in 54.0% of subjects in the tarlatamab group and 79.9% of subjects in the SOC chemotherapy group. Treatment-related grade 3 or higher TEAEs were reported in 26.6% of subjects in the tarlatamab group versus 62.3% of subjects in the SOC chemotherapy group. The most common (≥3%) treatment-related grade 3 or higher TEAEs in the tarlatamab group were neutropenia (4.4%) and lymphopenia (3.6%).

- SAEs were observed in 51.2% of subjects in both treatment groups. Treatment-related SAEs were observed in 27.8% of subjects in the tarlatamab group versus 30.7% of subjects in the SOC chemotherapy group. The most common treatment-related SAEs (≥5 subjects) in the tarlatamab group were CRS (17.1%), pyrexia (4.4%), and ICANS (3.6%).

- Fatal TEAEs were reported for 7.9% of subjects in the tarlatamab group and 8.6% in the SOC chemotherapy group. One treatment-related fatal event due to ICANS was observed.

- Discontinuations due to adverse events were reported for 5.2% of patients in the tarlatamab group and 12.3% in the SOC chemotherapy group.

- AESIs were defined, including but not limited to CRS and ICANS;
    - CRS was experienced by 56.3% of subjects in the tarlatamab group. Grade ⩾2 and grade ⩾3 CRS events were reported in 13.9% and 1.2% of subjects, respectively, while no grade ⩾4 events were observed. Serious CRS events occurred in 17.1% of subjects, and one subject (0.4%) discontinued tarlatamab treatment due to CRS. Most CRS events occurred after the first two doses. Additionally, five cases of fatal CRS events have been reported in the post-marketing setting, further highlighting the need for careful monitoring during treatment.
    - ICANS and associated neurological events occurred in 8.3% of subjects in the tarlatamab group. Grade ⩾2 ICANS events were reported in 4.0% of subjects. A fatal

event due to ICANS was reported for one subject (0.4%) and no other grade ⩾3 and grade ⩾4 ICANS event were reported in the tarlatamab group. Serious ICANS events occurred in 4.4% of subjects, and one subject (0.4%) discontinued tarlatamab treatment due to ICANS.

9.4.1. Uncertainties and limitations about unfavourable effects

The short exposure time imposes uncertainties regarding the characterization of long-term safety. The MAH has committed to conduct an integrated safety analysis (PASS category 3 study) to evaluate the long-term safety of tarlatamab for 3 years. The final analysis is expected in Q3 2030.

9.5. Effects table

Table 58: Effects Table for IMDYLLTRA - Pivotal study 20210004 (DeLLphi-304)

	Treatment	*Control*		*Uncertainties/ Strength of evidence*	*Ref*
Favourable effects					
	Tarlatamab 10 mg IV Q2W N=254	SOC chemotherapy N=255			
Overall survival (median months, 95% CI)	13.6 (11.1, NE)	8.3 (7.0, 10.2)		**SoE:** randomized, controlled, phase 3 study **Unc:** Efficacy in subgroup of patients with low DLL3 expression.	Study 20210004
Hazard ratio (95% CI)	0.599 (0.468, 0.768), p<0.001				
Progression-free survival (median months, 95% CI)	4.2 (3.0, 4.4)	3.2 (2.9, 4.2)		**SoE:** randomized, controlled, phase 3 study **Unc:** open-label, no BICR. Efficacy in subgroup of patients with low DLL3 expression.	
Hazard ratio (95% CI)	0.716 (0.586, 0.875), p<0.001				
Unfavourable effects					
	Tarlatamab 10 mg integrated safety analysis	Tarlatamab 10 mg pivotal study	SOC chemotherapy		
TR grade ⩾3 TEAEs - no./total no. (%)	141/473 (29.8)	67/252 (26.6)	152/244 (62.3)	**SoE**: randomized, controlled, phase 3 study **Unc**: open-label study design	Study 20210004; Integrated safety analysis
TR serious TEAEs - no./total no. (%)	140/473 (29.6)	70/252 (27.8)	75/244 (30.7)		Study 20210004; Integrated safety analysis
TR Fatal TEAEs - no./total no. (%)	2/473 (0.4)	1/252 (0.4)	4/244 (1.6)		Study 20210004; Integrated safety analysis
TR TEAEs leading to discontinuation - no./total no. (%)	15/473 (3.2)	7/252 (2.8)	15/244 (6.1)		Study 20210004; Integrated safety analysis
CRS, all grades - no./total no. (%)	268/473 (56.7)	142/252 (56.3)	3/244 (1.2)		Study 20210004; Integrated safety analysis;
CRS, grade ≥ 3 - no./total no. (%)	9/473 (1.9)	3/252 (1.2)	0/244 (0.0)		Study 20210004; Integrated safety analysis;

	Treatment	Control		Uncertainties/ Strength of evidence	Ref
ICANS	22/473	15/252	2/244		Study 20210004; Integrated safety analysis
- no./total no. (%)	(4.7)	(6.0)	(0.8)		

Abbreviations: CRS = cytokine release syndrome; ICANS = immune effector cells-associated neurotoxicity syndrome; Ref: reference; SOC = standard of care; SoE: strength of evidence; TEAE, treatment-emergent adverse event; TR = treatment-related; Unc: uncertainties

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The applicant has provided a well-designed phase 3 study to compare tarlatamab to a comparator arm consisting of three SOC therapies adapted to regional practices.

The study population is relevant for the proposed indication, consisting of patients with ES-SCLC who have progressed following first-line platinum-based chemotherapy. OS is the primary endpoint, which is appropriate for this patient population with limited treatment options after progression on first-line therapy and short life-expectancy. PFS by Investigator is key secondary endpoint.

The primary analysis of OS is based on a preplanned interim analysis, as the interim efficacy boundary was crossed. The data is sufficiently mature to conclude that a statistically significant improvement in OS for tarlatamab compared to SOC has been demonstrated in the overall study population (HR=0.599; 95% CI: 0.468, 0.768; p-value <0.001). A 40% reduction in the risk of death compared to the active comparator arm is considered clinically relevant.

Post hoc subgroup analyses of patients randomized to either tarlatamab or topotecan showed comparable results to those observed in the overall population (HR=0.564; 95% CI: 0.425, 0.749; p-value <0.001). Furthermore, while a clear difference in prognosis is observed between patients with platinum-sensitive and platinum-resistant disease, both subgroups benefit similarly from tarlatamab treatment compared to SOC, as reflected by comparable HRs.

PFS and ORR, while showing modest improvements for tarlatamab compared to SOC, provide additional support for the primary endpoint with statistically significant results.

As tarlatamab targets DLL3 expressed on the surface of tumour cells, the level of DLL3 expression is expected to influence its efficacy. This is confirmed by the observed decline in tarlatamab efficacy in the subgroup of patients with DLL3 expression <25% (DLL3 staining intensity at 2+/3+) with the point estimate for OS just below 1 (HR 0.954, 95% CI 0.590, 1.541), indicating similar efficacy as SOC treatment. Taking into consideration that DLL3 expression has been found to be present in ca 85% of patients with SCLC (Rojo et al, 2020), and that expression of DLL3 is not routinely tested for in clinical practice, tarlatamab is justified as a treatment option for 2L+ patients regardless of DLL3 expression.

The safety profile of tarlatamab includes several clinically significant adverse reactions, with CRS being the most frequent treatment-related AE (56.3%). Serious CRS cases were reported in 17.1% of subjects, and fatal cases have been reported post-marketing, highlighting the importance of appropriate safety precautions. ICANS, while less frequent (6.0%), remains highly relevant due to its risk of serious neurological complications, including fatal cases. Careful evaluation of long-term safety is essential and will be collected through an integrated safety analysis of all tarlatamab studies (PASS cat. 3).

9.6.2. Balance of benefits and risks

The pivotal phase 3 study has provided sufficient evidence to conclude that treatment with tarlatamab in patients with ES-SCLC who have progressed on first-line platinum-based therapy provides statistically significant and clinically relevant improvement in OS compared to SOC. The observed efficacy of tarlatamab is clinically meaningful for the proposed patient population with limited treatment options and short life-expectancy. The overall benefit of treatment with tarlatamab outweighs concerns related to decline in efficacy for patients with low DLL3 expression and tarlatamab is expected to provide clinically relevant OS improvement for the majority of the patients in this setting.

From a safety perspective, the risks associated with tarlatamab, including CRS and ICANS, are clinically significant but overall manageable with appropriate interventions such as monitoring, education of patients (patient card) and healthcare professionals, and SmPC warnings. Long-term safety will be collected through an integrated safety analysis of all tarlatamab studies (PASS, cat. 3 study).

9.7. Benefit-risk conclusions

9.7.1. CHMP conclusions

The overall benefit-risk (B/R) balance of Imdylltra for the proposed therapeutic indication is positive.