Summary Table of Study Protocol

Title	General Use-Results Survey of IMDELLTRA in Patients with Small Cell Lung Cancer Progressed after Cancer Chemotherapy
Protocol version identifier	20230313, Ver 1.0
Date of last version of the protocol	24 March 2025
EU Post Authorization Study (PAS) Register No	NA
Active Substance	Tarlatamab
Medicinal Product	IMDELLTRA
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	In accordance with the conditions for approval of IMDELLTRA (Tarlatamab), the objectives are to describe the incidence of interstitial lung disease and CCI [redacted] in patients treated with tarlatamab in the post-marketing clinical setting in Japan.
Country of Study	Japan
Author	PPD (PMS Supervisor) Post Marketing Surveillance, Global Patient Safety – Japan, Amgen K.K.

Marketing Authorization Holder

Marketing authorization holder(s)	PPD, President Amgen K.K. Midtown Tower, 9-7-1 Akasaka, Minato-ku, Tokyo 107-6239, Japan PPD
MAH Contact	PPD Post Marketing Surveillance, Global Patient Safety – Japan, Amgen K.K.

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Proper Version Numbering and Dating

VERSIONING:

Original version (initial and resub-for-final-approval) – Version 1.0—dated when this document is finalized and ready for submission. For Version 1.0 ensure that the date of the document and the date on the page headers are the same. (Drafts of documents prior to Version 1.0 should be versioned as 0.x.)

Superseding Protocol Versions 1 – Version 1.0 (as it is replacing the original on file)—document is dated as the Original Version 1.0; however, the page headers are dated the date of the completed revision. Subsequent Superseding Protocol Versions follow the same dating procedure.

Protocol Amendment 1 becomes Version 2.0 dated when the previously approved protocol (or amendment) was approved, however the page headers are dated when the revisions are completed.

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1. Table of Contents

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List of Tables

List of Appendices

2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
ADR	Adverse Drug Reaction
AMQ	Amgen Medical Dictionary for Regulatory Activities Query
ASTCT	American Society for Transplantation and Cellular Therapy
CRF	Case Report Form
CCI [redacted]	
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	
EDC	Electronic Data Capture
EPPV	Early Post-Marketing Phase Vigilance
GPSP	Good Post-Marketing Study Practice
HCP	Health Care Professional
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
J-PSUR	Japan Periodic Safety Update Report
J-RMP	Japan Risk Management Plan
MedDRA	Medical Dictionary for Regulatory Activities
CCI [redacted]	
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post-Marketing Surveillance
CCI [redacted]	
Q	Quartile
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
CCI [redacted]	
SMQ	Standardized Medical Dictionary for Regulatory Activities Queries

3. Responsible Parties

3.1 Sponsor

Role	**Name**
Marketing authorization holder(s)	Amgen K.K. Midtown Tower, 9-7-1 Akasaka, Minato-ku, Tokyo, 107-6239, Japan

The organizational structure for the study shall be separately specified within Amgen KK.

3.2 Contract Research Organization

Contract Research Organization (CRO)	Scope of Work
EPS Corporation	Monitoring, data management, statistical analysis, medical writing and others (Project Management, self inspection)

The contract between EPS Corporation and Amgen is based on the good post-marketing study practice (GPSP) ordinance.

3.3 Physicians

Physicians at institutions with active contracts for this study in Japan

4. Abstract

- Study Title

General Use-Results Survey of IMDELLTRA in Patients with Small Cell Lung Cancer Progressed after Cancer Chemotherapy

- Study Background and Rationale

This study is one of the post-marketing commitments in Japan and as a part of post-marketing additional pharmacovigilance activities in Japan risk management plan (J-RMP). Regarding interstitial lung disease (ILD) that is safety specification in J-RMP, because there is limited information on the safety related to ILD, we will describe the incidence and CCI and explore effectiveness in the post-marketing clinical setting.

This study will be conducted in accordance with good post-marketing study practice (GPSP) ordinance.

- Study Feasibility and Futility Considerations

Target sample size is CCI patients. The number of patients who experienced 2 lines of therapy for small cell lung cancer (SCLC) and will be treated with tarlatamab is expected to be approximately CCI patients in 2025, CCI patients in 2026 and CCI patients in 2027. It is expected that the target sample size of CCI patients will be secured within CCI-year enrollment period of this study.

The follow-up period is CCI year. About ILD that is related to the primary objective, in the multi-regional clinical trial of tarlatamab (NCT05060016; Study 20200491), the median (min, max) time from first dose to first onset of ILD was 122.0 days (2, 252). Therefore, it

can be expected that almost all of ILD occurrences after the administration of tarlatamab can be ascertained during the CCI-year follow-up period.

- Research Question and Objective(s)

This study will be conducted to assess the risk of ILD associated with tarlatamab in the post-marketing clinical setting. The details are as shown in table below.

Objectives	Endpoints
Primary	
The following related to ILD in SCLC patients treated with tarlatamab. • To describe the incidence • To describe frequent time of onset • To describe management after occurrence of ILD	• Incidence of ILD • Summarize frequent time of onset for ILD • Summarize management after occurrence of ILD
Secondary	
• To describe the incidence of adverse events (AE) and adverse drug reactions (ADR) in SCLC patients treated with tarlatamab	• Incidence of ADRs • Incidence of serious ADRs • Incidence of AEs • Incidence of serious AEs
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  - Hypothesis(es)/Estimation
    There is no formal hypothesis to be tested. Instead, this study is expected to provide preliminary information on the safety profile of tarlatamab in SCLC patients in the post-marketing clinical setting in Japan.

- Study Design/Type

This is a prospective observational cohort study of SCLC patients treated with tarlatamab in the post-marketing clinical setting in Japan, and in Japan regulatory, this study is relevant to a general drug use-results survey to evaluate safety for treatment period.

In this study, we will describe the incidence and frequent time of onset and CCI [redacted] for ILD, as well as the actual treatment for them. To detect ILD and obtain information for the details of treatment after the onset of the events, primary data collection is appropriate. Therefore, we selected “General Use Result Survey.”

- Study Population or Data Resource

SCLC patients who are treated with tarlatamab in Japan and meet the eligibility criteria will be included.

- Summary of Patient Eligibility Criteria
  - Inclusion criteria:
    - SCLC patients who are newly treated with marketed tarlatamab in accordance with the product label in Japan in the post-marketing clinical setting in Japan.
  - Exclusion criteria:
    - SCLC patients who had prior treatment with tarlatamab or other DLL3 targeted therapy
    - SCLC patients who currently enrolled in other interventional study (eg, a clinical study)
    - SCLC patients with a history of hypersensitivity to any of the ingredients of tarlatamab
- Follow-up

Patients will be followed for up to CCI year beginning the day after the first dose (step up dose) of tarlatamab. Follow-up will end at CCI year after the first dose of tarlatamab, discontinuation of tarlatamab, withdrawal of consent, death or lost to follow up whichever comes first.

Patients who discontinue tarlatamab before the end of CCI year will be followed up for CCI days from the last dose as supplementary safety follow-up. Supplementary safety follow-up may end prior to CCI days in the case of withdrawal of consent, death or lost to follow up.

- Variables
  - Outcome Variable(s)

    AEs (including AE name, date of onset, onset time from tarlatamab administration for CRS), expression site, presence or absence of imaging tests / bronchoalveolar lavage and findings for ILD, seriousness, grade, handling of tarlatamab for the AE, causal relations to tarlatamab reported by physician, outcomes and outcome date, risk factors for the AE other than tarlatamab, laboratory test values related to AE

(if applicable), prophylactic therapy, and specify therapy given reason for termination of tarlatamab and CCI [redacted]

– Exposure Variable(s)

Dosage, dates of tarlatamab administration within CCI year following the first dose, presence of drug Interruption and reason

– Covariate(s)

Patient demographics and medical history, therapeutic and medical history related to SCLC before tarlatamab administration, pregnancy and lactation during follow-up period, and CCI [redacted] with tarlatamab to SCLC

- Study Sample Size

Target sample size: CCI (as the safety analysis set)

In the multi-regional clinical trial (NCT05060016; Study 20200491), the incidence of AEs of ILD based on the standardized medical dictionary for regulatory activities queries (SMQ) narrow search was 2.3% (3/133 subjects). Assuming that the incidences of these events of safety specification observed in the clinical trial are the true incidences, if the target sample size is CCI patients, [redacted] patients can be expected to be identified with ILD with a probability of CCI %.

- Data Analysis

As primary analysis for safety, safety specifications (ie, ILD) related will be summarized such as incidence proportion, frequent time of onset or management after onset.

As secondary analysis for safety, the patient incidence proportion of all AEs/ADRs will be summarized.

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5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Not Applicable				

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Globally, lung cancer is the second most commonly diagnosed cancer and leading cause of cancer death, representing approximately 1 in 10 (11.4%) cancers diagnosed and 1 in 5 (18.0%) cancer deaths (Sung et al, 2021). small cell lung cancer (SCLC) accounts for approximately 15% of overall lung cancer cases with approximately 330 000 new cases worldwide each year based on an estimated 2.2 million cases of lung cancer in 2020 (National Cancer Institute, 2023; National Organization for Rare Disorders, 2021; Rudin et al, 2021; Sung et al, 2021). There are approximately 270 000 new deaths worldwide due to SCLC based on approximately 1.8 million lung cancer deaths in 2020 (Sung et al, 2021).

SCLC is a high-grade neuroendocrine tumor marked by an exceptionally high proliferative rate, strong predilection for early metastasis, and poor prognosis (Rudin et al, 2021). While 30% of patients present with disease that can be encompassed by 1 radiotherapy field (limited stage), the majority of cases have disease diagnosed as extensive stage. Although 20% to 30% of patients with limited stage can be cured with radio-chemotherapy, treatment is rarely curative in extensive stage, and SCLC is associated with poor long-term survival overall (5-year survival is $< 10\%$) (American Cancer Society, 2022).

A potential therapeutic target for SCLC is delta-like ligand 3 (DLL3), a non canonical ligand within the Notch signaling pathway, which plays a role in the development of pulmonary neuroendocrine cells. DLL3 is expressed almost exclusively in the intracellular compartment of a few normal tissues but is upregulated and abnormally expressed on the cell surface of SCLC and other high-grade neuroendocrine tumors (Giffin et al, 2021; Owen et al, 2019). Upregulation of DLL3 in SCLC leads to tumor growth and metastasis (Furata et al, 2019). In an international noninterventional study to evaluate DLL3 prevalence, positive DLL3 expression was identified in 85% of patients with SCLC using immunohistochemistry (Rojo et al, 2020). In the tarlatamab first in human (FIH) and phase 2 studies, 95.5% and 96.2% of evaluable tumor samples from

patients with SCLC showed DLL3 expression by immunohistochemistry, respectively. High cell surface expression of DLL3 on SCLC and low, mainly cytoplasmic expression on normal cells (Giffin et al, 2021) suggests DLL3 is a promising therapeutic target for SCLC.

Tarlatamab is a novel half-life extended bispecific T-cell engager (BiTE®) molecule. Tarlatamab consists of 2 single-chain variable fragment (scFv) binding domains that are specific for the tumor antigen DLL3 and for the T cell receptor associated complex cluster of differentiation 3 (CD3) on T cells. The scFv binding domains are fused to a single-chain fragment crystallizable half-life extension (scFc HLE) moiety.

The activity of tarlatamab requires the simultaneous binding to both target cells and T cells. The pharmacological effect of tarlatamab is mediated by specific redirection of previously primed cytotoxic CD8+ or CD4+ T lymphocytes to kill DLL3 positive cells. Tarlatamab efficacy was evaluated in SCLC cell lines and in orthotopic and patient derived xenograft mouse SCLC models (Giffin et al, 2021). In vitro, tarlatamab showed specific killing of SCLC cell lines, even those with very low DLL3 expression (< 1000 molecules per cell). In vivo, tarlatamab engaged systemically administered human T cells, induced T-cell activation and tumor infiltration, and redirected T cells to promote significant tumor regression and complete responses in patient derived xenograft models and in orthotopic models of primary and metastatic SCLC (Giffin et al, 2021). Thus, DLL3 is a novel and promising target for the development of T cell targeted therapies for SCLC. Importantly, DLL3 expression is maintained at a high level in SCLC cells from patients at all stages of disease and lines of treatment (Rojo et al, 2020). Based on the differential expression of DLL3 in cancer cells, the high potency of tarlatamab observed in nonclinical models, and a distinct mechanism of action from available SCLC therapies, tarlatamab is hypothesized to provide patients with more durable responses compared with current standard of care and emerging therapies, even in patients who did not respond to PD-1 or PD-L1 inhibitors.

Tarlatamab 10 mg monotherapy demonstrated a clinically meaningful, rapid, and durable objective response among subjects with advanced SCLC in multi-regional clinical trial (NCT05060016; Study 20200491) (ORR of 41.4% [97.5% CI: 30.3, 53.2] and median DOR of NE [95% CI: 5.9, NE]). In addition, the median OS was 14.3 months (95% CI: 10.8, NE) and median PFS was 4.3 months (95% CI: 3.0, 5.6) from the pivotal, nonrandomized phase 2 clinical trial (NCT05060016; Study 20200491), 10 mg dose.

6.2 Rationale

This study is one of the post-marketing commitments in Japan and as a part of post-marketing pharmacovigilance activities in Japan risk management plan. Regarding interstitial lung disease (ILD) that is safety specification in Japan Risk Management Plan (J-RMP), because there is limited information on the safety related to ILD, we will describe the incidence and CCI in the post-marketing clinical setting in Japan.

This study will be conducted in accordance with good post-marketing study practice (GPSP) ordinance.

6.3 Feasibility and Futility Considerations

Target sample size is CCI patients. The number of patients who experienced 2 lines of therapy for SCLC and will be treated with tarlatamab is expected to be approximately CCI patients in 2025, CCI patients in 2026 and CCI patients in 2027. It is expected that the target sample size of CCI patients will be secured within CCI-year enrollment period of this study.

The follow-up period is CCI year. About ILD that is related to the primary objective, in the multi-regional clinical trial of tarlatamab (NCT05060016; Study 20200491), the median (min, max) time from first dose to first onset of ILD was 122.0 days (2, 252). Therefore, it can be expected that almost all of ILD occurrences after the administration of tarlatamab can be ascertained during CCI-year follow-up period.

6.4 Statistical Inference (Estimation or Hypothesis)

There is no formal hypothesis to be tested. Instead, the study is expected to provide preliminary information on the safety profile of tarlatamab in patients in the post-marketing clinical setting in Japan.

7. Research Question and Objectives

Safety specification of J-RMP in this study is ILD. This study will be conducted to assess the risk of ILD associated with tarlatamab in the post-marketing clinical setting.

7.1 Primary

The following related to ILD in SCLC patients treated with tarlatamab

- To describe the incidence
- To describe frequent time of onset
- To describe management after occurrence of ILD

7.2 Secondary

To describe the incidence of adverse events (AEs) and adverse drug reactions (ADRs) in SCLC patients treated with tarlatamab.

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8. Research Methods

8.1 Study Design

This is a prospective observational cohort study of SCLC patients treated with tarlatamab in the post-marketing clinical setting in Japan, and in Japan regulatory, this study is relevant to a general drug use-results survey to evaluate safety for treatment period.

In this study, we will describe the incidence, frequent time of onset and CCI [redacted] for ILD, as well as the actual treatment for them. To detect ILD and obtain information for the details of treatment after the onset of the events, primary data collection is appropriate. Therefore, we selected “General Use Result Survey.”

8.1.1 Study method

This study is a prospective observational cohort study in the post-marketing clinical setting in Japan. The summary of study method is below:

1. We will contract with the medical institutions that tarlatamab is available across Japan.
2. After obtaining patient's consent, patients will be enrolled* into the study before or on the day of the first dosing of tarlatamab.

   *We will recommend the physicians to enroll in a row as much as possible.

3. Physicians will enter case report form (CRF)** about the enrolled patients after each study follow-up period.

   ** Collected in 2 CRFs (vol.1 and vol.2) per a patient. Vol. 1 will be used to collect data at baseline and from the beginning of administration to the end of CCI [redacted] months; vol. 2 will be used to collect data from the beginning of CCI [redacted] months to the end of CCI year.

8.2 Setting and Study Population

8.2.1 Study Period

- Planned study period: CCI years
  - From the completion of CCI-month early post-marketing phase vigilance (EPPV)

- Expected from CCI 2025 to CCI 2029
- This period includes time for preparation for the study such as contract with medical institution, CRF data collection and data cleaning

– Planned enrollment period: CCI years

- From the start of the study period to the enrollment of CCI patients
- Expected from CCI 2025 to CCI 2027

8.2.2 Selection and Number of Institutions

About 60 nation-wide institutions that tarlatamab is available equipped with department of oncology, respiratory or others and medical experts of committing participation and co-operation of the study.

8.2.3 Patient/Healthcare Professional Eligibility

8.2.3.1 Inclusion Criteria

- SCLC patients who are newly treated with marketed tarlatamab in accordance with the product label in Japan in the post-marketing clinical setting in Japan.

8.2.3.2 Exclusion Criteria

- SCLC patients who have had prior treatment with tarlatamab or other DLL3 targeted therapy
- SCLC patients who currently enrolled in other interventional study (eg, a clinical study)
- SCLC patients with a history of hypersensitivity to any of the ingredients of tarlatamab

The former is for avoiding bias and the latter is for avoiding administration to contraindications of Japanese package insert.

8.2.4 Matching

Not applicable

8.2.5 Baseline Period

Patient background all historical data physicians know at the start of administration, such as demographics, medical history, prior treatments, will be collected as baseline data.

8.2.6 Study Follow-up

Patients will be followed for up to CCI year beginning the day after the first dose (step up dose) of tarlatamab. Follow-up will end at CCI year after the first dose of tarlatamab, discontinuation of tarlatamab, withdrawal of consent, death or lost to follow up whichever comes first.

Patients who discontinue tarlatamab before the end of CCI year will be followed up for CCI days from the last dose as supplementary safety follow-up. Supplementary safety

follow-up may end prior to CCI days in the case of withdrawal of consent, death or lost to follow up.

Rationale of follow-up period:
In the multi-regional clinical trial of tarlatamab (NCT05060016; Study 20200491), the median (min, max) time from first dose to first onset of ILD was 122.0 days (2, 252). Therefore, it can be expected that almost all of ILD occurrences after the administration of tarlatamab can be ascertained during the CCI-year follow-up period.

8.3 Variables

Information described in this section will be collected in CRFs or patient enrollment form per a patient.

Table 8-1 List of variables

Variables	Form for collecting		Data collection points		Type of variable				Remarks
	Enrollment form	CRF	Baseline	During follow-up period	Exposure Assessment	Outcome Assessment	Covariate Assessment	Other	
Exposure related									
Dosage		●		●	●				
Dates of tarlatamab administration	●	●		●	●				· The planned date of first administration of tarlatamab will be collected by patient enrollment form. · All dates of tarlatamab administration within [redacted] year following the first dose
Reason for dose selection		●		●				●	Only when the dosage differs from that specified in the package insert
Reason for termination of tarlatamab among patients who discontinue tarlatamab		●		●		●			Only patients with discontinued tarlatamab
Presence of drug Interruption and reason		●		●	●				
AE related									
AE name		●		●		●			
Date of onset		●		●		●			
Onset time from tarlatamab administration		●		●		●			For CRS
Expression site		●		●		●			For ILD
Presence or absence of imaging tests / bronchoalveolar lavage and findings		●		●		●			For ILD
Seriousness		●		●		●			

Variables	Form for collecting		Data collection points		Type of variable				Remarks
	Enrollment form	CRF	Baseline	During follow-up period	Exposure Assessment	Outcome Assessment	Covariate Assessment	Other	
Grade		•		•		•			· American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading 2019 (Lee et al, 2019; see **Appendix G**) for CRS and neurological events (including immune effector cell-associated neurotoxicity syndrome (ICANS)) · Common Terminology Criteria for Adverse Events (CTCAE) grade (see **Appendix D**) for other AE
Handling of tarlatamab for the AE (eg, interruption or discontinuation)		•		•		•			
Causal relations to tarlatamab reported by physician		•		•		•			
Outcome and outcome date		•		•		•			
Risk factors for the AE other than tarlatamab		•		•		•			
Laboratory test values related to AE		•		•		•			If applicable
Prophylactic therapy		•		•		•			For CRS
Specify therapy given		•		•		•			
Other safety findings (Medication errors, overdose, underdose, misuse, abuse, addiction, transmission of an infectious agent through a contaminated Amgen product, accidental exposure, occupational exposure, lack or loss of		•		•				•	

Variables	Form for collecting		Data collection points		Type of variable				Remarks
	Enrollment form	CRF	Baseline	During follow-up period	Exposure Assessment	Outcome Assessment	Covariate Assessment	Other	
therapeutic efficacy, missed dose, unexpected therapeutic benefit, reports of patient "death" after exposure to Amgen's product where no other details are provided, off-label use with or without AE)									
Patient demographics and medical history									
Sex	●		●				●		
Birth year/month	●		●				●		If the birth information cannot be provided, the age at the start of tarlatamab
Reason for tarlatamab usage	●		●				●		
Patient experience of tarlatamab or other DLL3-targeted therapy	●		●					●	
Applicable/not applicable to contraindications of tarlatamab	●		●					●	
Date of initial diagnosis of SCLC		●	●				●		If the date of initial diagnosis is unknown, disease duration
Limited disease (LD) / extensive disease (ED) category at initial diagnosis of SCLC		●	●				●		
CCI [redacted]									

Variables	Form for collecting		Data collection points		Type of variable				Remarks
	Enrollment form	CRF	Baseline	During follow-up period	Exposure Assessment	Outcome Assessment	Covariate Assessment	Other	
CCI [redacted]									
Pregnancy and lactation at baseline and during follow-up period, pregnancy with partners									
Pregnancy/lactation or not		●	●	●			●		
Birth (planned) year/month		●	●	●				●	
CCI [redacted]									
Administrative items for this study									
Information that can identify the patient at the institution	●		●					●	Not a medical record number
Current enrolled in other interventional study or not	●		●					●	
Lot Number		●		●				●	Only at the time of AE occurrence
Date of last follow-up		●		●				●	

Medical institution name, physician's name and name of department will be collected as administrative items.

8.3.1 Exposure Assessment

See **Table 8-1**.

8.3.2 Outcome Assessment

See **Table 8-1**.

8.3.3 Covariate Assessment

See **Table 8-1**.

8.3.4 Validity and Reliability

This is a prospective, observational cohort study. Therefore, variables which are measured at medical institutions in post-marketing clinical setting in Japan, are selected for this study in reference to clinical trials and guidelines for diagnosis and treatment of the lung cancer.

Exposures, outcomes, and all other variables observed and measured by each institution will be collected through electronic data capture (EDC) system. Standardized error check program is installed in EDC system and generates error messages automatically before physicians send. If logical inconsistencies or discrepancies are found in CRF, a query form will be prepared and delivered to the institutional physicians for clarification and correction. Institutional physicians and staff are requested to check the data against medical records, and accuracy and completeness of data consistent with information in medical records is confirmed and attested by signature of physicians.

8.4 Data Sources

The original source of the data used in the study is patient medical records. Data are collected through CRF, which are populated by the physicians.

Laboratory test values will be measured by each institution with their own method.

8.5 Study Size

Target sample size: CCI (as the safety analysis set)

In the multi-regional clinical trial (NCT05060016; Study 20200491), the incidence of AEs of ILD based on the standardized medical dictionary for regulatory activities queries (SMQ) narrow search was 2.3% (3/133 subjects). Assuming that the incidences of these events of safety specification observed in the clinical trial are the true incidences, if the target sample size is CCI patients, [redacted] patients can be expected to be identified with ILD with a probability of CCI%.

8.6 Data Management

Physician will enter enrollment fomes before the first dose of tarlatamab, and CRFs after the completion of each study follow-up period.

Data collection is conducted by using a validated EDC system, developed by an external service provider, Fujitsu Japan, Tokyo, Japan. Data management is conducted by EPS Corporation under its own standard operating procedure with oversight by the Amgen K.K.

8.6.1 Obtaining Data Files

Not applicable

8.6.2 Linking Data Files

Not applicable

8.6.3 Review and Verification of Data Quality

Quality and completeness will be periodic confirmed by self-inspection per the GPSP ordinance.

8.7 Data Analysis

Statistical analysis will be conducted by EPS Corporation in accordance with the statistical analysis plan (SAP), developed with Amgen K.K. Definition detail of data exclusion (e.g. patient exclusion from the safety analysis set) will be specified in the SAP.

8.7.1 Planned Analyses

For the timely sharing of the collected data with Pharmaceuticals and Medical Devices Agency (PMDA), analysis of interim data will be performed at the time of Japan periodic safety update report (J-PSUR). After the last patient completes the study follow-up, a data analysis will be performed and a final report summarizing the results of the study will be completed.

8.7.1.1 Primary Analysis

As primary analysis for safety, safety specifications (ie, ILD) related will be summarized such as incidence proportion, frequent time of onset or management after onset.

The details will be specified in the SAP.

8.7.1.2 Secondary Analysis

As secondary analysis for safety, the patient incidence proportion of all AEs/ADRs will be summarized.

The details will be specified in the SAP.

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8.7.1.4 Other

Patient disposition, demographics and baseline characteristics will be summarized and safety-related analyzes other than objectives related will also be performed if necessary.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

In general, a descriptive analysis will be conducted. Categorical variables will be summarized with frequencies and percentage. Continuous variables will be summarized with mean, standard deviation, median, minimum, maximum, 1st Quartile (Q), and 3rd Q. When statistical testing and inference are applied (ie, exploratory analysis in this study), two-sided p-value of <0.05 will be considered significant and the 95% CI will be estimated. The details of analysis methods will be specified in the SAP.

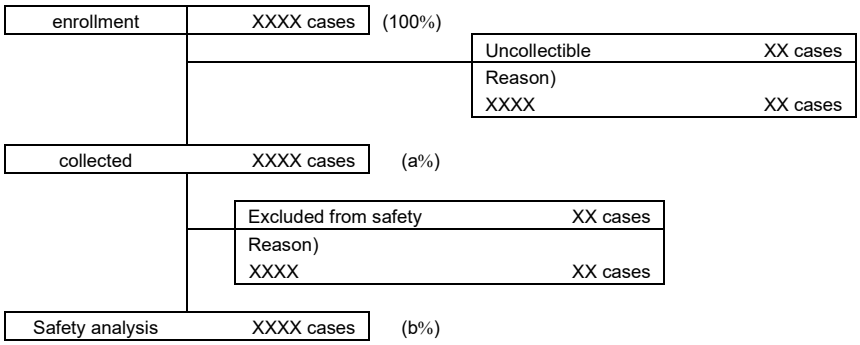
8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

In general, it is expected that tarlatamab will be prescribed in institutions with oncology expertise. Therefore, the rate of lost to follow-up is expected to be very low. If missing data still occur, no imputation will be performed.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

All enrolled patients will be summarized in the tree of patient disposition, as described below:



Percentage of a% and b% (corresponding to enrollment) will be calculated.

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[redacted]

8.7.2.3.3 Description of Exposure Variables

Description of exposure variable will be summarized for the overall cohort and stratified by presence of ILD event.

The details will be specified in the SAP.

8.7.2.4 Analysis of the Primary, Secondary, and CCI [redacted] Endpoint(s)

– Primary Endpoint:

- The incidence proportions of AEs/ADRs for ILD will be summarized.
- The frequent time of onset for ILD will be summarized.
- The management after occurrence of ILD will be summarized.

– Secondary Endpoints: The incidence proportions of all AEs/ADRs will be summarized.

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[redacted]

The most current version of the medical dictionary for regulatory activities (MedDRA) at the time of analysis will be used.

Safety and effectiveness in the post-marketing clinical setting related analysis other than those listed above will also be performed if necessary.

The details will be specified in the SAP.

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

Not applicable

8.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

All objective of this study are for safety, see Section 8.7.1 and 8.7.2.

8.8 Quality Control

Quality control will be conducted by checking whether data management operations are conducted based on the standard operation procedures of data management, and all results of quality control, including deviations and their measurements, will be documented/reported and corrected deviations appropriately if they are found.

8.9 Limitations of the Research Methods

This is a prospective, observational cohort study. It has a limitation of internal validity and strength of external validity in comparison with an interventional clinical trial. Limitations common to this type of study, along with how to reduce errors, are summarized below.

Limitations	How to reduce errors
Missing and incomplete data are unavoidable, because there are some cases that data could not collected at all evaluation time points, and some patients could be lost to follow-up.	Efforts will be made to collect as complete data as possible through EDC system and instructions to physicians. Analysis results will be interpreted with caution, acknowledging the limitations
Information bias and confounding cannot be excluded.	Analysis results will be interpreted with caution, acknowledging the limitations, whether or not appropriate statistical methods could be applied to address the bias.

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error(s)/Misclassification(s)

As with any Japanese post-marketing surveillance (PMS) that relies on data entry from multiple institutions, there is the potential for misclassifying AEs and ADRs.

Misclassifications can impact the validity of outcomes as well as affect overall conclusions. To reduce misclassifications, we will set appropriate error check program or documents for manual check.

8.9.1.2 Information Bias

Missing or incomplete data is a potential risk for information bias and efforts will be made to collect complete data through the use of clear instructions to physicians regarding the completion of CRFs.

There is no systematic review or systematic method of AE collection. AEs are collected as part of a regular interaction with the patients as would be in normal practice. Therefore, there is a possibility of reporting bias in the collected AEs, but such effect is inherent in post-marketing clinical setting.

8.9.1.3 Selection Bias

Patients will be enrolled within the contract number of patients at the contract institutions. As with all PMS in Japan, selection bias may occur because which patients to enroll will depend on the physician. Selection bias affects the validity of the results and may affect the overall conclusions. To reduce selection bias, we will recommend the physicians to register in a row as much as possible.

8.9.1.4 Confounding

This study will enroll patients treated with tarlatamab under Japanese regulations. Therefore, unmeasured confounding may be present in the CCI [redacted] and as such these results will be interpreted with caution.

8.9.2 External Validity of Study Design

This study is expected to be enrolled patients from medical institutions across Japan and will set an upper limit of number of contracted patients per institution in operation rule, so it is considered that the results will not be regionally biased. Also, the setting of enrollment period that is before or on the day of the first dosing of tarlatamab is useful for avoiding bias (especially selection bias), and the exclusion criteria are bare minimum. Therefore, the selected population is expected to represent the patient population intended to be treated with tarlatamab.

8.9.3 Analysis Limitations

This study is observational study in post-marketing clinical setting, missing or incomplete data may be collected, so there is a possibility of underestimate of the incidence of AEs and ADRs. However, in general, it is expected that tarlatamab will be prescribed in

institutions with oncology expertise, therefore, the rate of lost to follow-up is expected to be very low.

Also, the effectiveness in the post-marketing clinical setting will not be directly compared with the efficacy for tarlatamab obtained in the multi-regional clinical trial, because missing or incomplete data may be collected, and the judgment of the effectiveness in the post-marketing clinical setting will depend on individual physicians in the post-marketing clinical setting, and there is a risk of underestimation of the effectiveness.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

This study is observational study in post-marketing clinical setting, and some patients may discontinue the study, creating missing or incomplete data for the study endpoint assessments. Such discontinuations may be related or informative to the outcomes. Consequently, there is a risk for bias due to missing completed data and lack of robust data to analyze results.

8.10 Other Aspects

All written information and other material to be used by patients and health care professionals (HCPs) must use vocabulary and language that are clearly understood.

9. Protection of Human Patients

9.1 Informed Consent

Before a patient's participation in this study, the physician will explain to the patient, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and obtain written informed consent for participation if this study etc.

An initial sample informed consent form will be provided to the physician by Amgen K.K., who will modify the informed consent form as necessary before using at the institution.

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

9.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

This study protocol will be reviewed and approved by the local regulatory agency, PMDA as well as external ethics committee. The study and data collection are conducted in accordance with the Pharmaceutical and Medical Device Act, GPSP and Helsinki Declaration. Local Medical Act provides HCPs 'Confidentiality Obligation' of patients that is set forth in the study agreement between the representatives of institution and Amgen K.K.

9.3 Patient Confidentiality

Before enrollment of the patient to this study, physician will inform the patient about the objective, method, and potential risk of the study and utilization of the patient's data in keeping individual patient's information unidentified.

The physician must ensure that the patients' confidentiality is maintained for documents submitted to Amgen.

Patient will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

For AEs reported to Amgen, patients are to be identified by their unique patient identification number and age (in accordance with Japanese laws and regulations).

Documents that are not submitted to Amgen.K.K. are to be kept in confidence by the physician.

9.4 Patients Decision to Withdraw

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the patient does not wish to or is unable to continue further study participation. Patient data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. As per Japanese regulations, upon withdrawal of consent, the patient has the right to request removal of their data that was collected and not have it further processed. The physician is to discuss with the patient appropriate steps for withdrawal of their consent from the study.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

10.1 Definition of Reportable Events

10.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an AE includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the physician's responsibility to evaluate whether an AE is related to an Amgen product prior to reporting the AE to Amgen K.K.

- An AE for which a causal relationship to tarlatamab cannot be ruled out is regarded as an ADR.

10.1.2 Serious Adverse Events

A serious AE is any AE as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other medically important serious event" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other medically important serious events" refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

10.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an AE) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction, or abuse involving an Amgen product
- Use of an Amgen product while pregnant and/or breast feeding
- Transmission of infectious agents
- Reports of uses outside the terms for authorized use of the product including off-label use
- Accidental or Occupational exposure

- Any lack or loss of intended effect of the product(s)
- Unexpected benefit when used as per prescribing information

10.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) or combination product(s) includes investigational product.

Product complaints are collected separately from this study in accordance with standard operating procedures of product complaints of Amgen K.K.

10.2 Safety Collection, Recording and Submission to Amgen Requirements

This study will be collecting information from physicians prospectively. All reportable events (AEs, product complaints, and other safety findings) considered to have occurred following patient exposure to tarlatamab will be collected from patient start of administration to final study contact. The physician is responsible for ensuring that all reportable events they become aware of during study period, are recorded in the patient's appropriate study documentation. It is the physician's responsibility to evaluate whether an AE is related to an Amgen product prior to reporting the AE to Amgen. If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the patient's records after the patient ends the study. All reportable events must be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within the timelines stated in **Table 10-1** below.

Table 10-1. Types of Safety Data to be Collected and Reported in primary data collection studies collecting all reportable events

Reportable Events/Event Type	* Reporting Timeframe
• Serious AEs (related and non-related) • Product Complaints (serious and non-serious) • Other Safety Findings (serious and non-serious) • Pregnancy and/or Lactation Exposure	• Within 1 business day from when vendor first becomes aware of the event
• Non-serious AEs (related and non-related)	• Within 15 calendar days from when vendor first becomes aware of the event

Reportable events that are suspected to be related to any Amgen medicinal product, combination product or device where there is no exposure to tarlatamab should be spontaneously reported to Amgen within 1 business day of vendor awareness. A list of all Amgen medicinal products can be found in the following link: https://wwwext.amgen.com/amgen-worldwide

To spontaneously report a reportable event to Amgen, refer to the following link to locate your Local Amgen contact information by country: https://wwwext.amgen.com/contact-us/product-inquiries

Additional details on what to collect and report to Amgen for the reportable event can be found in the following link: https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting

If the EDC system is unavailable to the institution staff, the reportable events listed in the table above must still be reported to Amgen K.K. within the specified reporting timeframes stated. For studies using Amgen's EDC system where the first notification of an AE is reported to Amgen K.K. via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See **Appendix C** for sample Safety Report Form(s), **Appendix D** for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and **Appendix E** for sample Pregnancy and Lactation Notification Forms. The physician may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

10.2.1 Collection of Pregnancy and Lactation Information

Female Patients Who Become Pregnant

Physician will collect pregnancy information on any female patient who becomes pregnant following exposure to tarlatamab through treatment period.

Information will be recorded on the Pregnancy Notification Form (see **Appendix E**). The worksheet must be submitted to Amgen Safety within 1 business day of when vendor first becomes aware of the patient's pregnancy (Note: physician is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide physician with a consent form and questionnaire to collect additional information. After obtaining the female patient's signed consent for release of pregnancy and infant health information, the physician will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female patient who becomes pregnant following exposure to tarlatamab through treatment period of the tarlatamab. This information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to CCI months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is considered another safety finding, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an AE or serious AE. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an AE, but still must be reported to Amgen as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious AE (eg, female patient experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the physician will report the event as a serious AE.

Male Patients with Partners who Become Pregnant [or Were Pregnant at the Time of Enrollment]

In the event a male patient fathers a child following exposure to tarlatamab, and for an additional CCI days after discontinuing tarlatamab, the information will be recorded on the

Pregnancy Notification Form. The form (see **Appendix E**) must be submitted to Amgen Safety within 1 business day of when the vendor first becomes aware of the pregnancy. (Note: physician is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide physician with a consent form and questionnaire to collect additional information. The physician will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information, the physician will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety.

Generally, infant follow-up will be conducted up to [redacted] months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

Physician will collect lactation information on any female patient who breastfeeds while taking tarlatamab through the treatment period.

Information will be recorded on the Lactation Notification Form (see **Appendix E**) and submitted to Amgen Safety within 1 business day of when the vendor's first becomes aware of the lactation exposure.

With the female patient s signed consent for release of mother and infant health information, the physician will collect mother and infant health information and complete the lactation questionnaire on any female patient who breastfeeds while taking tarlatamab through [redacted] days after discontinuing tarlatamab.

10.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, physicians/institutions, institutional review boards/independent ethics committees (IRBs/IECs), or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The

physician is to notify the appropriate IRB/IEC or other relevant ethical review board of reportable events in accordance with local procedures and statutes.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen K.K. may amend the protocol at any time. When Amgen K.K. amends the protocol, physicians have to follow amendments.

Amgen reserves the right to terminate the study at any time.

12. Plans for Disseminating and Communicating Study Results

Communication material will be developed for HCPs updating safety information and for the enlightenment of usage of tarlatamab in a right way at the point of J-PSUR.

12.1 Publication Policy

The results of final report will be submitted for publication consideration as conference abstracts and/or medical journal articles.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor

agreement will detail the procedures for, and timing of, Amgen K.K.'s review of publications if necessary.

13. Compensation

Participating institutions will receive payments for completing CRF and associated study-related activities. The amount of compensation will follow the standards set by Amgen K.K. based on a fair market value assessment and local industry guideline.
Compensation to the enrolled patients and their families in relation to health damage caused by ADRs in spite of proper use of drugs will be paid from the Japanese public relief system for sufferers from ADRs of any post marketed products, which is managed by the PMDA.

14. Additional measures that may be taken based on the result of this study and the decision criteria for initiation

J-RMP including the following contents will be reviewed at milestones.

- When new information on the safety of tarlatamab is obtained, the necessity of changing the risk minimization activities will be examined.
- When further investigation is considered necessary based on the obtained results, the necessity of implementing new pharmacovigilance activities will be examined.

15. Milestones and rationale related to the implementation and the result assessment, and reporting to the PMDA for this study

- At the time of J-PSUR:
  To comprehensively examine safety information.
- At the time of preparation of the final report:
  In order to examine the safety specifications of this study, the final report will be prepared and submitted when all data of patients subject to this study are fixed.

16. References

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17. Appendices

Appendix A. List of Stand-alone Documents

Not applicable

Appendix B. ENCePP Checklist for Study Protocols

Study title:
General Use-Results Survey of Tarlatamab in Patients with Small Cell Lung Cancer Progressed after Cancer Chemotherapy

EU PAS Register® number:TBD
Study reference number (if applicable): 20230313

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8.2.1
1.1.2 End of data collection[2]	☒	☐	☐	8.2.1
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	8.7.1, 15
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	8.7.1

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.6
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.7.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.7.1
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10.2

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.2.1
	4.2.2 Age and sex	☒	☐	☐	8.2.3
	4.2.3 Country of origin	☒	☐	☐	8.2.3
	4.2.4 Disease/indication	☒	☐	☐	8.2.3
	4.2.5 Duration of follow-up	☒	☐	☐	8.2.6
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.3.4
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.7.2.4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.3.4
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.9.1.3
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9.1.2

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.7.1.3 8.7.2.4

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.7.2.4
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7.2
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	6.3
10.3 Are descriptive analyses included?	☒	☐	☐	8.7.2.1
10.4 Are stratified analyses included?	☒	☐	☐	8.7.2.4
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.9.3
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6.3

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9.1.3
12.1.2 Information bias?	☒	☐	☐	8.9.1.2
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	6.3

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9.2
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	11.1

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	15
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1

Comments:

Name of the main author of the protocol: PPD

Date: 26/August/2024

Signature: _____

Appendix C. Sample Safety Reporting Form(s)

Project ID:	A	**Observational Research Safety Reporting Form**	Date of Reporter Awareness:
			Date Reported to Amgen:
	Fax reports to: Amgen Local Office	*<<populate LAO fax here or delete language>>*	

1. Initial: ☐ Follow-up: ☐

2. Site Number: Subject Number:

3. Indicate event type: *(Please tick all that apply)* ☐ AE/Other Safety Finding ☐ Product Complaint (PC) ☐ Adverse Device Effect (ADE)

4. Contact Details (Vendor/Investigator)

Name	Phone	Fax
Address		
City	State/Province	
Postal Code	Country	

5. Reporter ID

Name or ID	Phone	Fax
Address		
City	State/Province	
Postal Code	Country	

6. HCP Contact Details (if other than reporter)

Name		
Country		
Address		
City	State/Province	Postal Code
Phone	Fax	

7. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No

Weight	Height	Race	Is patient also reporter?
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

8. Medical History (include primary diagnosis)

9. Suspect Product Information (include dosing details)

Product/Device: _____

Indication: _____

Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (day month year) (If patient died, list date of death) Cause of Death: (provide autopsy report)	Hospitalization: Hospitalized? ☐ Yes ☐ No Prolonged Hospitalization? ☐ Yes ☐ No Admitting dx _____ Date Admitted (day month year)	Hospitalization: Date Discharged (day month year)	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/Prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly/birth defect; 06 Other significant medical hazard; 07 Non serious	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (state outcome)	Outcome: 01 Recovered/ Resolved; 02 Recovering/ Resolving; 03 Not recovered/not resolved; 04 Recovered/ resolved with sequelae; 05 Fatal; 06 Unknown	Severity: 1=mild 2=moderate 3=severe	Relationship to Product/Device: Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N

Reporter Signature: _____ Page 3 of ____

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	Co-suspect Yes	Continuing No	Continuing Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year											
	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Appendix D. Additional Safety Reporting Information

The physician will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 which is available at the following location:http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

CRS and neurological events (including immune effector cell-associated neurotoxicity syndrome (ICANS)) are excluded, because their severities are assessed by American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).

Appendix E. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____) _____ **Fax** (____) _____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

CCI

Appendix G. ASTCT Consensus Grading (2019)

Table 17-2. American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019) for CRS

CRS Grade	Symptoms
1	Require symptomatic treatment only · Fever: ≥ 38℃ · Hypotension: none · Hypoxia: none
2	Require moderate intervention · Fever: ≥ 38℃ WITH · Hypotension: not requiring vasopressors AND/OR · Hypoxia: requiring low-flow nasal cannula or blow-by
3	Severe symptoms · Fever: ≥ 38℃ · Hypotension: requiring a single vasopressor (with or without vasopressin) OR · Hypoxia or dyspnea: requiring high-flow nasal cannula (> 6L/min) or facemask
4	Life-threatening symptoms · Fever: ≥ 38℃ WITH · Hypotension: requiring multiple vasopressors (excluding vasopressin) AND/OR · Hypoxia or dyspnea: requiring positive pressure, the condition worsens despite supplemental oxygen

Table 17-3. ASTCT 2019 Consensus Grading for neurological events (including immune effector cell-associated neurotoxicity syndrome (ICANS))

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable and unable to perform ICE)
Depression level of consciousness**	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings***	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging****	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

Neurological events grade is determined by the most severe event (eg, ICE score, depressed level of consciousness, seizure, motor findings, raised intracranial pressure [ICP]/cerebral edema) not attributable to any other cause.

* A patient with an ICE score of 0 may be classified as grade 3 neurological events if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 neurological events if unarousable.

** Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

*** Tremor and clonic muscle cramps associated with immune effector cell therapies may be graded per CTCAE v5.0, but they do not influence neurological events grade.

**** Intracranial haemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from neurological events grading It may be graded according to CTCAE v5.0.

Table 17-4. Immune-effector Cell-associated Encephalopathy (ICE) Assessment Tool

Neurotoxicity Domain	Score
Orientation: Orientation to year, month, city, hospital	4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following commands: ability to follow simple commands (eg, “Show me two fingers” or “Close your eyes and stick out your tongue”)	1 point
Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle”)	1 point
Attention: ability to count backwards from 100 by 10	1 point

ICE scoring

- 7-9: grade 1
- 3-6: grade 2
- 0-2: grade 3
- 0 due to patient unarousable and unable to perform ICE: Assessment, grade 4

CCI

[redacted]

Approval Signatures

Document Name: Protocol Original tarlatamab 20230313

Document Description:

Document Number: CLIN-000348662

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Type of Study Protocol: Original

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Document Approvals	
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