Statistical Analysis Plan

Protocol Title:	Phase 2a Study Evaluating the Efficacy, Safety, Tolerability and Pharmacokinetics of Tarlatamab in Chinese Subjects with Advanced Small Cell Lung Cancer after Two or More Prior Lines of Treatment (DeLLphi-307)
Short Protocol Title:	Phase 2a Study Evaluating Tarlatamab in Chinese Subjects with Advanced Small Cell Lung Cancer after Two or More Prior Lines of Treatment (DeLLphi-307)
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NCT Number:	**NCT06502977**
Authors:	[redacted], IQVIA [redacted], AMGEN
Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320 Phone: +1 805-447-1000
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Version Number	**Date (DDMMMYYYY)**	**Summary of Changes, including rationale for changes**
Original (v1.0)	08JUL2024	Not applicable
Amendment 1 (v2.0)	**16Jan2025**	**1. Updated the Sample size justification** **2. Added the Last Know Alive date definition** **3. Updated the planned primary analysis time point** **4. Updated the Laboratory test results section for Hy's law** **5. Updated PFS, OS and DoDC definition**

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List of Abbreviations

Abbreviation	Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BICR	blinded independent central review
BMI	body mass index
BOR	best overall response
C1D1	cycle 1 day 1
CI	confidence interval
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	disease control
DCO	data cut-off
DCR	disease control rate
DoDC	duration of disease control
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
GSO-DM	Global Study Operations-Data Management
ICANS	immune-effector cell associated neurotoxicity syndrome
IP	investigational product
IPD	Important protocol deviations
KM	Kaplan-Meier
LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MG	milligram
MRI	magnetic resonance imaging
NCT	National Clinical Trials
NE	not evaluable
OR	objective response
ORR	objective response rate

OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
QTc	corrected QT interval
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SFU	Safety follow-up
SOC	standard of care
T1	timepoint 1
T2	timepoint 2
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TRAE	treatment-related adverse event
ULN	upper limit of normal
WHO	World Health Organization

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol **amendment 2.0** for study 20230273, Tarlatamab (AMG 757) dated **06Sep2024**. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. Pharmacokinetic/Pharmacodynamic analyses will be provided by the Department of Clinical Pharmacology, Modeling and Simulation (CPMS).

2. Objectives, Endpoints/Estimands and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• Evaluate efficacy of tarlatamab as assessed by objective response rate (ORR) based on blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)	• ORR BICR, defined as proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR)
Secondary	
• Evaluate efficacy of Tarlatamab as assessed by duration of response (DOR), disease control (DC) and progression-free survival (PFS) based on BICR per RECIST 1.1	• DOR, defined as time from the first documentation of objective response (OR) until the first documentation of disease progression or death due to any cause, whichever occurs first. Only subjects who have achieved OR will be evaluated for DOR • DC, defined as a BOR of CR or PR or stable disease (SD) • Duration of DC, defined as time from the first documentation of CR or PR or SD until the first documentation of disease progression or death due to any cause, whichever occurs first. Only subjects who have achieved CR or PR or SD will be evaluated for duration of DC • PFS, defined as time from enrolment until disease progression or death from any cause, whichever occurs first. Progression will be based on RECIST 1.1.

• Evaluate efficacy of Tarlatamab as assessed by ORR, DOR, DC and PFS based on investigator assessment per RECIST 1.1	• ORR (Investigator) • DOR (Investigator) • DC (Investigator) • Duration of DC (Investigator) • PFS (Investigator)
• Evaluate efficacy of Tarlatamab as assessed by overall survival (OS)	• OS, defined as time from enrolment until death from any cause
• Evaluate safety and tolerability	• Incidence of treatment-emergent • adverse events
• Characterize the pharmacokinetics of tarlatamab	• Serum concentration of tarlatamab
• Evaluate the immunogenicity of • tarlatamab	• Incidence of anti-tarlatamab antibody formation

Estimand(s) for Primary Objective(s)

ORR by BICR per RECIST 1.1 in Chinese subjects with advanced SCLC who have progressed on or recurred following 1 platinum-based regimen as 1L therapy (including a PD-1/ PD-[L]1) and at least 1 other prior line of therapy (re-treatment with a platinum based regimen is considered a second-line of therapy) prior to start of new cancer therapy (while-on-treatment strategy).

Estimand(s) for Key Secondary Objective(s)

Not applicable.

2.2 Hypotheses and/or Estimations

No statistical hypotheses will be tested.

3. Study Overview

3.1 Study Design

This is a phase 2a, multicenter, single arm, open-label study in Chinese subjects with advanced SCLC who have progressed on or recurred following 1 platinum-based regimen as 1L therapy (including a PD-1/PD-[L]1) and at least 1 other prior line of therapy (re-treatment with a platinum-based regimen is considered a second line of therapy). The study consists of a 21-day screening period, a treatment period, a safety follow-up (SFU) period, and a long-term follow-up (LTFU) period.

A SFU visit will occur 60 (+ 5) days after the last dose of tarlatamab regardless of initiation of subsequent anticancer therapy within that period. After the SFU visit,

subjects will be followed in LTFU for survival every 12 weeks (+/-14 days) for up to 1 year after the **last** subject's last dose of tarlatamab or 5 years from the first subject enrolled, whichever occurs first.

3.2 Sample Size

Approximately 30 subjects will be enrolled in the study. With 30 subjects enrolled at the target dose, the probability that the observed ORR will be greater than **different thresholds are presented in Table 3.2-1**.

Table 3.2-1. Probabilities of Observed ORR Greater Than Thresholds With Sample Size of 30

True ORR	Probability of Observed ORR > 25 %	Probability of Observed ORR > 30%
0.35	88%	64%
0.4	96%	82%

With 30 subjects, there is a 79% to 96% probability of observing at least 1 adverse event if the true event rate is 5% to 10%.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

The relationship between relevant covariates and efficacy endpoints may be explored if appropriate. The following baseline covariates may be summarized as appropriate.

- Race
- Sex
- Age at enrollment in years
- ECOG performance status at baseline
- Prior lines of therapy
- Metastatic
- Sum of diameters of target lesions at baseline based on investigator assessment (mm)

4.2 Subgroups

Not applicable.

5. Definitions

5.1 General Definitions

Baseline

For any variable, unless otherwise specified, baseline is the last non-missing assessment taken prior to the first administration of tarlatamab. Where baseline measurements are taken on the same day as the tarlatamab administration and no time is present, it is assumed that these measurements are taken prior to tarlatamab administration.

Change from Baseline

Change from baseline = post-baseline value – baseline value.

Percent Change from Baseline

Percent change from baseline = 100*(post-baseline value – baseline value) / baseline Value

Body Mass Index (BMI)

BMI (kg/m^2) = weight (kg) / [height (cm) / 100]^2

Investigational Product (IP)

Investigational product refers to tarlatamab.

Study Day

Study day = (date - date of study day 1) + x; where

x = 1 if date is after study day 1;

x = 0 if date is before study day 1.

Study Day 1

Study day 1 is defined as the date of the first dose of tarlatamab administration to the Subject.

Treatment Duration

Treatment duration (weeks) = (last dose date – first dose date + 1) / 7.

Relative Dose Intensity

Relative dose intensity (%) = 100*(Actual cumulative dose / Planned cumulative dose);

Actual cumulative dose = sum of received doses.

Planned cumulative dose = planned dose accumulated over the actual treatment duration,

i.e., 10 mg x (number of records in exposure dataset - 1) + 1 mg; 1 mg is the step dose on C1D1.

Actual and planned cumulative dose up to the study visit are considered.

Last Known Alive Date

Last known alive date is the latest date of the following dates before death date. Other Case Report Form (CRF) data may be explored to get the last known alive date. Last know alive date should be imputed the first day of the month for the partial date when the month and year are available, but day is missing.

- Date of consent signed, and date of consent withdrawn from additional consents/withdrawals of consent form
- Date of Enrollment date on Subject Enrollment CRF
- Date First Taken, Date Last Taken on Concomitant Medications CRF
- Date Performed on MUGA/ECOG Performance Status, Vital Signs, Echocardiogram, Electrocardiogram, Surgical Procedures, Procedure CRFs
- Admission Date, Discharge Date on Hospitalizations CRF, Date of Examination on Physical Measurement CRF
- Date Collected on Reproductive Status and Pregnancy Test (Local Lab), Chemistry (Local Lab), Hematology (Local Lab), Coagulation (Local Lab) CRFs, Urinalysis (Local Lab) and in central lab data
- Start Date, Stop Date on Product Administration CRF
- Start Date, Stop Date on Other Protocol Required Therapy CRF
- Date Started and Date Ended on Events CRF for non-fatal events
- Tumor response and NYHA Classification date
- Target/non-target assessment date
- CRS Symptoms and ICANS date

- End of study, end of safety follow-up and end of administration date where end reason is not death or lost to follow-up
- Start date, Stop date on On-Study Radiotherapy, Anti-Cancer Therapies (Subsequent) CRF
- Subject Status Date if status is Alive on Survival Status CRF
- Assessment Date of CT or MRI
- Date of Liver biopsy
- Neurological Evaluation date
- Date of Clinical Outcome Assessments
- If death happened, then last known alive date is death date minus 1.
- Date of Anti-body sample
- Date of PK sample
- Date/Time of Tumor Measurement
- Date/Time of Tumor Identification
- Date/Time of Response Assessment

End of IP Administration

End of IP administration for each subject is defined as the date the decision was made to end IP as recorded on the End of Product Administration eCRF page.

End of Study Date (End of Trial)

The end of study date for the entire study is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit) including any additional parts in the study (eg, LTFU, antibody testing), as applicable.

End of Study (Individual Subject)

End of study for each subject is defined as the date the subject last completed a protocol specified procedure. The date will be recorded on the End of Study eCRF page.

Safety Follow-up (SFU)

Upon permanent discontinuation from the study treatment for any reason, a safety follow up visit will be performed approximately 60 (+ 5) days after the end of the last dose of tarlatamab, regardless of initiation of subsequent anticancer therapy within that period.

Long Term Follow-up (LTFU)

Following the SFU visit (60 [+ 5] days), subjects will enter the LTFU period for clinical evaluation of disease status and survival. Subjects will be followed via telephone, clinic visit, or chart review to assess for survival and/or the commencement of subsequent cancer therapy every 12 weeks (± 14 days) from the SFU visit or last imaging visit, whichever is later, for up to 1 year after the last subject's last dose of tarlatamab or 5 years from first subject enrolled, whichever occurs first.

5.2 Efficacy Endpoint-related Definitions

Best Overall Response (BOR)

The subject's best response assignment depends on the findings of both target and non-target disease and also takes into consideration the appearance of new lesions and confirmation of response based on the findings from MRI/CT scans. Confirmation of progressive disease is not required. BOR is based on all post-baseline disease assessments that occur prior to the initiation of subsequent anticancer treatment. At least 5 weeks from the first dose of IP must elapse without radiological disease progression to meet the minimum criteria for SD duration in order to assign a BOR of SD. In general, subjects not classifiable under the RECIST 1.1 response categories due to inadequate data or early death are classified as not evaluable (NE) for BOR but will be counted in the denominator of all response rate calculations. BOR per RECIST 1.1 has the following possible categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE). The rules for deriving the BOR are detailed in Appendix B.

Objective Response (OR)

OR is defined as a BOR of CR or PR per RECIST 1.1. Subject without a post-baseline tumor assessment is considered non-responder.

Objective Response Rate (ORR)

ORR is defined as proportion of subjects with BOR of CR or PR per RECIST 1.1.

Disease Control (DC)

DC is defined as a BOR of CR or PR or SD per RECIST 1.1.

Disease Control Rate (DCR)

DCR is defined as proportion of subjects with a BOR of CR or PR or SD per RECIST 1.1.

Duration of Disease Control (DoDC)

DoDC is defined as time from **the date of first dose of tarlatamab** until the first documentation of disease progression or death due to any cause, whicheve ccurs first. Only subjects with a BOR of confirmed response (CR/PR) or SD are evaluated for DoDC.

DoDC (Months) = (earlier of progressive disease date or death date – **date of first dose of tarlatamab** + 1) × 12 / 365.25

DoDC is censored following the same censoring rules as PFS (Appendix C).

Duration of Response (DOR)

DOR is defined as time from first documentation of CR or PR per RECIST 1.1 until the first documentation of progressive disease or death due to any cause, whichever occurs first. Only subjects who with a BOR of confirmed response (CR/PR) are evaluated for DOR.

DOR (Months) = (earlier of progressive disease date or death date – response start date + 1) × 12 / 365.25

DOR is censored following the same rules as PFS (Appendix C).

Progression-free survival (PFS)

PFS is defined as time from **the date of first dose of tarlatamab** to the earlier of progressive disease per RECIST 1.1 or death due to any cause, whichever occurs first.

PFS (Months) = (earlier of progressive disease date or death date – **date of first dose of tarlatamab** + 1) × 12 / 365.25

Appendix C details the censoring rules for PFS.

Overall Survival (OS)

OS is defined as time from **the date first dose of tarlatamab** until event of death due to any cause. Subjects still alive are censored at the date last known to be alive. If the date

last known to be alive is after the date that triggers the analysis (i.e., the data cut-off date), the subject is censored at the data cut-off date.

OS (Months) = (death date –**date of first dose of tarlatamab**+ 1) × 12 / 365.25

5.3 Safety Endpoint-related Definitions

Treatment-Emergent Adverse Event (TEAE)

TEAE is defined as adverse events starting on or after first dose of tarlatamab as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events eCRF, and up to and including 65 days after the last dose of tarlatamab excluding the events reported after End of Study date. Events that are directly related to lung cancer or disease progression (including, but not limited to, preferred terms “Small cell lung cancer”, “Disease progression” etc.) will be excluded from TEAE analysis.

Treatment-related Adverse Event (TRAE)

TRAE is defined as TEAE with the relationship flag on the Events eCRF indicating there is a reasonable possibility that the event may have been caused by tarlatamab. Event with missing relationship with tarlatamab is assumed to be treatment-related.

6. Analysis Sets

6.1 Full Analysis Set

Not applicable.

6.1.1 Primary Analysis Set

Not applicable.

6.2 Safety Analysis Set

Safety analysis set consists of all subjects who received at least 1 dose of tarlatamab.

The analysis of all safety endpoints and efficacy endpoints, unless noted otherwise, are conducted using safety analysis set.

6.3 Per Protocol Analysis Set(s)

Not applicable.

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

Not applicable.

6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

Pharmacokinetic (PK) analysis set consists of all subjects who received at least 1 dose of tarlatamab and have at least 1 pharmacokinetic sample collected. These subjects are evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing. Analysis of PK data, unless otherwise specified, is conducted using pharmacokinetic analysis set.

6.6 Interim Analyses Set(s)

Not applicable

6.7 Study-specific Analysis Set(s)

6.7.1 RECIST 1.1 Evaluable by Blinded Independent Central Reviewer Analysis Set

RECIST 1.1 evaluable by blinded independent central reviewer analysis set consists of all subjects who received at least 1 dose of tarlatamab, have measurable baseline disease per RECIST 1.1 as assessed by blinded independent central reviewer. This analysis set is used for RECIST 1.1 related endpoints assessed by central reviewer for sensitivity analyses.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Not applicable.

7.2 Primary Analysis

The primary analysis is planned **after** all subjects have been enrolled and have had opportunity to **confirm an objective response** after **the** first post-treatment scan **or up to 13 weeks of follow-up, whichever occurs first**

The data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the primary analysis will be locked. It is expected that outstanding data issues are resolved ahead of the lock to the extent possible.

7.3 Final Analysis

The final analysis will occur when enrollment is complete and each subject completes the study, including long-term follow-up.

The data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the final analysis wili be locked to prevent future changes. It is expected that all outstanding data issues are resolved ahead of the final lock.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will receive and store all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

Partially missing dates for adverse event, concomitant medication, new anti-cancer therapy initiation and death will be imputed as outlined in Appendix A.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations (IPD). The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

Descriptive statistics will be used to identify potential outliers in key variables. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6 Distributional Characteristics

The assumptions underlying the proposed statistical methodologies will be assessed as appropriate. If required data transformations or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

For proportions, 95% CI will be estimated using an exact method proposed by Clopper-Pearson (Clopper and Pearson, 1934). Kaplan-Meier methods will be used to estimate the median and percentiles for time-to- event endpoints with CI calculated using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method. Kaplan-Meier methods will be used to estimate landmarks for time-to-event endpoints (eg, 1-year OS) with the Greenwood formula (Kalbfleisch and Prentice, 1980) used to estimate the standard error used in CI calculation. Kaplan-Meier curves will be constructed for time to- event endpoints.

9.2 Participant Accountability

The number and percent of subjects who were enrolled, received investigational product, completed investigational product, discontinued from investigational product (including reasons for discontinuation), completed study, discontinued the study (including reasons for discontinuation) will be summarized. Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

9.3 Important Protocol Deviations

Important protocol deviations (IPD) categories are defined by the study team before the

first subject's initial visit and will be updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

The final IPD list is used to produce the summary of IPDs table and the list of subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations may be provided.

9.4 Demographic and Baseline Characteristics

Descriptive summaries of the demographic and baseline characteristics will be produced for the following based on the safety analysis set:

- Race. If multiple races have been reported for a subject, the subject will be categorized as 'Multiple'
- Sex
- Age at enrollment in years
- ECOG performance status at baseline
- Weight (kg)
- Height (cm)
- BMI (kg/m2)
- Time from initial diagnosis to enrollment (months)
- Prior lines of therapy
- Metastatic
- Sum of diameters of target lesions at baseline based on investigator assessment (mm)

9.5 Efficacy Analyses

The following efficacy analysis will be performed.

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

Table 9-1. Example Primary Efficacy Endpoint/Estimand Summary Table

Endpoint/Estimand	Primary Summary and Analysis Method	Sensitivity Analysis
ORR based on BICR	Proportion of subjects with OR, corresponding Clopper-Pearson (Clopper and Pearson, 1934) exact 95% CI.	Repeat summary on RECIST 1.1 evaluable by blinded independent central reviewer analysis set.

The efficacy analyses of primary endpoint will be conducted on the safety analysis set, unless otherwise specified. the proportion of subjects with a BOR of PR or better per RECIST 1.1 based on BICR with corresponding Clopper-Pearson 95% CI will be Presented.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)/Estimand(s)

Table 9-2. Example Secondary Efficacy Endpoint/Estimand Summary Table

Endpoint/Estimand	**Primary Summary and Analysis Method**	**Sensitivity Analysis**
DCR based on BICR	Proportion of subjects with DC, corresponding Clopper-Pearson (Clopper and Pearson, 1934) exact 95% CI.	Repeat summary on RECIST 1.1 evaluable by blinded independent central reviewer analysis set.
DoDC, DOR, PFS based on BICR	Distribution of DoDC, DOR, PFS, corresponding median and percentiles using Kaplan-Meier (KM) method with 95% CI calculated using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	Repeat summary on RECIST 1.1 evaluable by blinded independent central reviewer analysis set.
ORR, DCR based on investigator assessment	Proportion of subjects with OR, DC, corresponding Clopper-Pearson (Clopper and Pearson, 1934) exact 95% CI.	None
DoDC, DOR, PFS based on investigator assessment	Distribution of DoDC, DOR, PFS, corresponding median and percentiles using Kaplan-Meier (KM) method with 95% CI calculated using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	None

Endpoint/Estimand	Primary Summary and Analysis Method	Sensitivity Analysis
OS	Distribution of OS, corresponding median and percentiles using Kaplan-Meier (KM) method with 95% CI calculated using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method.	None

The efficacy analyses of secondary endpoints will be conducted on the safety analysis set, unless otherwise specified.

For ORR based on investigator assessment, the proportion of subjects with PR or better and corresponding Clopper-Pearson 95% CI will be presented. For DCR based on BICR and DCR based on investigator assessment, the proportion of subjects with DC and corresponding Clopper-Pearson 95% CI will be presented.

The distribution of DoDC, DOR, and PFS (per RESIST 1.1 based on BICR) and the distribution of OS, including median and percentiles using Kaplan-Meier (KM) method with 95% CI calculated using the Brookmeyer and Crowley will be presented. Landmarks at selected time points (e.g. 3, 6, 9 and 12 months) with 95% CI calculated using the Greenwood formula (Kalbfleisch and Prentice, 1980) to estimate the standard error in CI calculation will be provided. For DoDC, percentages of subjects with DoDC ≥ 4 months will also be provided.

The distribution of DoDC, DOR and PFS per RESIST 1.1 based on investigator assessment will be summarized using the same methods as that of DoDC, DOR, and PFS (per RESIST 1.1 based on BICR) on safety analysis set. In addition, percent change from baseline in target lesion sum of diameters will be plotted for BICR and investigator assessment respectively.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Not applicable.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Not applicable.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or later is used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all TEAEs, TRAEs, serious TEAEs, grade 3 or higher TEAEs, fatal TEAEs, TEAEs leading to withdrawal of tarlatamab, TEAEs leading to interruption and/or reduction of tarlatamab. Subject incidence summary by system organ class and preferred term in descending order of frequency will be provided for all TEAEs, TRAEs, serious TEAEs, grade 3 or higher TEAEs, fatal TEAEs, TEAEs leading to withdrawal of tarlatamab, TEAEs leading to interruption and/or reduction of tarlatamab. Where appropriate the summary will also be provided by worst grade. Above summaries will not be created if two or fewer subjects experience the AE, subject-level data may be provided instead.

Severity of CRS and ICANS events will be graded using American Society for Transplantation and Cellular Therapy (ASTCT) (Lee et al, 2019) criteria. Severity of tumor lysis syndrome (TLS) will be graded using CTCAE version 5.0 but will be managed based on Cairo Bishop criteria (Coiffier et al, 2008). Severity of all other adverse events will be graded using CTCAE version 5.0.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen Medical Queries) will also be summarized according to their categories and preferred term if appropriate.

Adverse Events of Interest (EOI):

The summary of subject incidence of treatment-emergent adverse events of interest standardized MedDRA queries and/or Amgen Medical Queries such as cytokine release syndrome, hypersensitivity, immune effector cell associated neurotoxicity syndrome (ICANS) and associated neurological events, neutropenia, and neurological events will be summarized. The summary will include grade≥2, grade≥3, grade≥4, serious, fatal, and events leading to interruption and/or reduction and discontinuation of IP.

The subject incidence of above treatment-emergent EOIs, serious treatment-emergent EOI, grade 3 or higher treatment-emergent EOI, fatal treatment-emergent EOI, treatment-emergent EOI leading to discontinuation of investigational product and treatment-emergent EOI leading to interruption and/or reduction of

investigational product will be tabulated by preferred term. CRS and immune-effector cell-associated neurotoxicity syndrome (ICANS) will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) (Lee et al, 2019).

The summaries of time to onset of EOI from first dose, time to onset of EOI after each dose from last prior dose, and duration of treatment-emergent EOI will be provided. Additionally, summaries of time to onset and duration of EOI will be provided for grade 2 or higher and grade 3 or higher EOIs respectively.

9.6.3 Exposure to Investigational Product

Subject exposure to tarlatamab will be summarized using descriptive statistics for the following: number of doses, cumulative dose (mg), relative dose intensity (%), treatment duration (weeks) and number and percent of subjects with dose modifications (e.g dose reductions, dose interruptions) and reason for modification. Subject-level data may be provided instead of the summary if the subject incidence is low, or a single dose is given. Listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

9.6.4 Laboratory Test Results

Laboratory data will be summarized using standard descriptive statistics at each scheduled time point in the study. Summaries of the absolute value and/or changes from baseline at each scheduled assessment will be provided for selected laboratory parameters of interest.

Shift tables indicating the change between the baseline and the worst on-study increased and/or decreased grade will be provided for selected laboratory parameters of interest. Unscheduled assessments will be included in the shift tables.

The subject incidence of potential cases of Hy's Law will be summarized. Hy's law cases have the following three components: **A potential Hy's Law case is defined as any postbaseline total bilirubin elevation to ≥ 2 x ULN occurring on or within 30 days after a postbaseline ALT or AST elevation to ≥ 3 x ULN and concurrent ALP < 2 x ULN.** A listing of AST, ALT, and Total Bilirubin values at each time point may be produced for the subjects suspected of fulfilling the criteria for Hy's law.

9.6.5 Vital Signs

Vital signs including systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry and temperature will be summarized by summary statistics over time and

changes from baseline over time using descriptive statistics. The incidence and percentage of abnormal changes in vital signs will be tabulated.

9.6.6 Physical Measurements

The analysis will include descriptive summary at baseline.

9.6.7 Electrocardiogram

The ECG measurements are performed as per SOC for routine safety monitoring, rather than for assessment of potential QTc effect. No statistical analyses of ECG measurements are planned.

9.6.8 Antibody Formation

The incidence and percentage of subjects who develop anti-tarlatamab antibodies at any time will be tabulated.

9.6.9 Exposure to Non-investigational Product(s)/Auxiliary Medicinal Product(s)

Not applicable.

9.6.10 Exposure to Concomitant Medication

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Other Analyses

The following additional analysis will be provided by the Department of Clinical Pharmacology, Modeling and Simulation (CPMS). This data may be analyzed at a later date.

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

For tarlatamab, PK parameters will be determined from the time concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, exploratory analyses to describe the relationship between tarlatamab exposure and either PD effect and/or clinical outcome may also be performed. These exploratory analyses may not be part of the clinical study report.

9.7.2 Analyses of Clinical Outcome Assessments

Not applicable.

9.7.3 Analyses of Health Economic Endpoints

Medical resource utilization data collected may be used to conduct following analyses:

- Number and duration of hospitalization (total days or length of stay, including duration by wards, e.g., intensive care unit)
- Number and type of diagnostic and therapeutic tests and surgical and nonsurgical procedures.
- Reason for hospitalization (e.g., adverse event such as CRS/ICANS or other).

9.7.4 Analyses of Biomarker Endpoints

Not applicable.

10. Changes From Protocol-specified Analyses

Protocol section 9.4.2.3.7 mentions of summarizing the following for analysis of exposure to investigational product: average dose per administration. But it will not be summarized. SAP section 9.6.3 outlines the analysis. **Protocol sections 1.1 and 3.0 defined the PFS, OS and DoDC defined as time from enrollment date. But it will be considered from the date of first dose of tarlatamab. SAP section 5 outlined the analysis.**

11. Literature Citations / References

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12. Prioritization of Analyses

Not applicable.

13. Data Not Covered by This Plan

Exploratory data not included in this plan may be analyzed at a later date and/or by a different Amgen department.

14. Appendices

Appendix A. Handling of Incomplete Dates and Missing Dates for Adverse Events, Concomitant Medications, New Anti-cancer Therapy Initiation and Death

Imputation rules for partial or missing start dates of adverse events and concomitant medications:

Table 14 1. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	missing
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	2	1	n/a	1	1
	≠ 1st dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing stop dates of adverse events and concomitant medications:

- For partial stop date mmyyyy, impute the last day of that month.
- For partial stop date yyyy, impute December 31 of that year.
- For completely missing stop date, do not impute.
- If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.

- If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (i.e. set the stop date as missing).

Imputation rules for partial or missing new anti-cancer therapy initiation date:

- If the start day of new anti-cancer therapy is missing and month and year are not the same as the last dosing date of study treatment, impute the first day of that month.
- If the start day of new anti-cancer therapy is missing and month and year are same as last dosing date of study treatment, impute the last dosing date of study treatment plus 1 day.
- In other situations, do not impute.

Imputation rules for partial or missing death date:

If death year and month are available but day is missing:

  - If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
  - If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
  - If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

- If both month and day are missing for death date or a death date is totally missing, do not impute.

Note that the last contact date refers to the last contact (i.e. a visit or an assessment) with patient instead of family members. Last contact date would be derived from the latest patient visit/assessment date.

Appendix B. BOR per RECIST 1.1

BOR by investigator will be derived based on the timepoint response collected in the RECIST 1.1 CRF. BOR by central review will be derived from timepoint response shared by the central imaging vendor. At each time point, BOR will be derived based upon the evaluated timepoints up to and including the current MRI/CT assessment. The following rules will apply to BOR:

- CR is better than PR is better than SD is better than PD is better than NE
- For a BOR of SD, a duration of ≥ 35 days since the cycle 1 day 1 is required
- For a BOR of CR or PR confirmation is required. PR can be confirmed by a PR or CR. The confirmation assessment must be in a consecutive assessment ≥ 28 days after the initially observed assessment of CR or PR except the following cases:
  - An unlimited number of intermittent assessments of NE or CR <28 days can occur between the initial response and the confirmation of CR. For example, BL, CR, NE, NE, NE, CR – the CR at post-baseline 1 is confirmed at post-baseline 5. SD is not allowed between CR and subsequent confirmation CR.
  - An unlimited number of intermittent assessments of NE, SD, PR or CR <28 days can occur between the initial response and the confirmation of PR. For example, BL, PR, SD, SD, SD, PR – the PR at post-baseline 1 is confirmed at post-baseline 5.

Table 14-2 provides the BOR determination per RECIST 1.1 where confirmation of response (CR/PR) is required. Table 14-3 outlines the steps to derive Confirmed_BOR (step 1) given timepoint assessments.

At interim analyses (if any), due to lack of sufficient follow-up time for confirmation scan, study team may choose to report both confirmed responders and unconfirmed responders (subjects had an initial PR or CR and still has potential for future confirmative scans). Interim_BOR is defined to include unconfirmed responders in addition to those who achieve Confirmed_BOR. Table 14-3 step 2 provides details to derive the unconfirmed responders.

Table 14-2. BOR per RECIST 1.1 where Confirmation of CR/PR is Required

Criterion	Timepoint T1 Response	T1 ≥ 35 days after C1D1?	Timepoint T2 Response	T2 ≥ 35 days after C1D1?	T2 ≥ 28 days after T1?	BOR_temp
C1	CR	Yes	CR	-	Yes	CR
C2			CR	-	No	SD
C3			PR, SD	-	-	Query data*

C4			PD	-	-	SD
C5			NE, No further evaluations			SD
C6		No	CR	-	Yes	CR
C7			CR	Yes	No	SD
C8			CR	No	No	NE
C9			PR, SD	-	-	Query data*
C10			PD	-	-	PD
C11			NE, No further evaluations			NE
C12	PR	Yes	CR, PR	-	Yes	PR
C13			CR, PR	-	No	SD
C14			SD	-	-	SD
C15			PD	-	-	SD
C16			NE, No further evaluations			SD
C17		No	CR, PR	-	Yes	PR
C18			CR, PR	Yes	No	SD
C19			CR, PR	No	No	NE
C20			SD	Yes	-	SD
C21			SD	No		NE
C22			PD	-	-	PD
C23			NE, No further evaluations			NE
C24	SD	Yes	CR, PR, SD, PD, NE, no more evaluation			SD
C25		No	CR, PR, SD	Yes	-	SD
C26			CR, PR, SD	No	-	NE
C27			PD	-	-	PD
C28			NE, No further evaluations			NE
C29	PD		-			PD
C30	NE	-	NE, No further evaluations			NE
C31		-	CR, PR, SD	Yes	-	SD
C32		-	CR, PR, SD	No	-	NE
C33		-	PD	-	-	PD

*If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR. A CR may also be followed by a PR when the target lesion assessment is CR and the non-target lesion assessment is NE. In both of these situations, the best response is PR.

Table 14-3. BOR Derivation Step

Step 1. Derive Confirmed_BOR at each visit

Derive Confirmed_BOR at each visit:

i) At Visit 1: Use the Visit 1 scan result and refer to Table 14-2 to derive Confirmed_BOR.

ii) At Visit 2 onward:

(a) If current visit is CR: Find last scan that is not NE and at least 28 days before current visit. If current visit is PR: Find last scan that is not NE or SD and at least 28 days before current visit. Derive BOR_temp as below:

Last scan	Current	BOR_temp
CR	CR	CR
PR	CR	PR
PR	PR	PR

b) If none of above fits, find last scan reference Table 14-2 to derive BOR_temp.

Current visit Confirmed_BOR = best of (BOR_temp, last visit confirmed_BOR). Use rule CR > PR > SD > PD > NE

Step 2. Derive Interim_BOR at last visit prior to DCO	
For subjects who discontinue tumor assessment (i.e. had PD, next therapy, or end of study): Assign Interim_BOR = Confirmed_BOR	For subjects with potential for more assessment (i.e. no PD, next therapy, or end of study), unconfirmed PR/CR can be considered responders. • If any scan is CR and haven't got the opportunity to receive next scan, then Interim_BOR = CR. • If any scan is PR and haven't got the opportunity to receive next scan, then Interim_BOR = PR. • Else, Interim_BOR = Confirmed_BOR at the latest scan.

Appendix C. PFS Censoring Rules

Situation up to DCO/EOS	Date of Event or Censor	Outcome
No evaluable post-baseline tumor assessments, no death recorded	Date of first dose date of IP	Censor
PD	Date of first detection of PD	Event
No PD, but death recorded	Date of death	Event
Start of new anti-cancer therapy prior to any PD or death	Date of last evaluable tumor assessment before or on start of new anti-cancer therapy	Censor
No PD, no death recorded, no start of new anti-cancer therapy	Date of last evaluable tumor assessment	Censor
Death or PD immediately after 2 or more missed tumor assessment (14 weeks)	Date of last evaluable tumor assessment prior to the first missing assessment [a]	Censor

[a] This supersedes the previous rules that result in PFS event at date of PD or death.