INTEGRATED STATISTICAL ANALYSIS PLAN

Integrated Summary of Safety for Second-line Tarlatamab Filing

Protocol Number :	**20160323, 20200491, 20210004**
Version*:*	**2.0**
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Does this Integrated Statistical Analysis Plan document any analysis with the objective to claim prespecification?

☑ Yes

☐ No

Version Number	**Date (DDMMMYYYY)**	**Summary of Changes, including rationale for changes**
Original (v1.0)	22OCT2024	Not applicable
Amendment 1 (v2.0)	**06FEB2025**	• **Update studies under the scope of ISS** • **Include additional table for ICANS** • **Update MedDRA version** • **Add EOI category Hypersensitivity narrow events [Hypersensitivity (SMQ Narrow) / Anaphylactic reactions (SMQ Narrow)]** • **Add table participants incidence of hospitalization due to treatment-emergent CRS (AMQ Narrow) during cycle 1 day 1 and cycle 1 day 8 doses by grade**

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Table of Abbreviations

Term/Abbreviation	Definition/Explanation
AE	Adverse Event
AMQ	Amgen MedDRA Query
AST	Aspartate Aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOI	Event of Interest
FDA	US Food and Drug Administration
eIV	Extended Intravenous
hr	Hour
ICANS	Immune Effector Cell-associated Neurotoxicity Syndrome
iSAP	Integrated Statistical Analysis Plan
ISS	Integrated Summary of Safety
KM	Kaplan-Meier

MedDRA	Medical Dictionary for Regulatory Activities
PA	Primary Analysis
PD-1	Programmed Death Protein 1
PD-L1	Programmed Death Protein 1 Ligand
Q3W	Every 3 Weeks
QTcB	Bazett-corrected QT Interval
QTcF	Fridericia-corrected QT Interval
RR	Respiratory Rate
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TRAE	Treatment-related Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
WHO DRUG	World Health Organization Drug

1. INTRODUCTION

The objective of this Integrated Statistical Analysis Plan (iSAP) is to describe the analysis of Integrated Summary of Safety (ISS) that will be performed on all relevant safety data to support second-line tarlatamab filing.

Studies under the scope of ISS are:

- Monotherapy cohorts of 20160323 (Parts A, D, E, F and G) :
  A Phase 1 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Tarlatamab in Participants With Small Cell Lung Cancer.
- 20200491 (Parts 1, 2, 3):
  A Phase 2 Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of Tarlatamab in Participants with Relapsed/Refractory Small Cell Lung Cancer After Two or More Prior Lines of Treatment.
- Tarlatamab arm of 20210004:
  A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Participants With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy.

Safety data from study 20200491**,** monotherapy cohorts of study 20160323 and tarlatamab arm of study 20210004 will be integrated and analyzed. **If needed, additional studies may be added after data are available.**

Output headers are shown below:

Table 1. Output Header

Study 20160323	**Studies 20210004, 20200491, and 20160323**	**Studies 20200491 and 20160323**	**Studies 20210004, 20200491, and 20160323**
Tarlatamab < 10 mg (N = xx) n (%)	**Tarlatamab 10 mg (N = xx) n (%)**	**Tarlatamab > 10 mg (N = xx) n (%)**	**Tarlatamab All Doses (N = xx) n (%)**

D = Day; eIV = Extended IV; hr = Hour; Q3W = Every 3 weeks.

Tarlatamab < 10 mg includes study 20160323 cohorts 1-7. **Tarlatamab 10 mg** includes study 20210004 1->10 mg; study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); study 20160323 cohorts 8, 32 and 35. **Tarlatamab > 10 mg** includes study 20200491 1->100 mg (part 1 randomized arm); study 20160323 cohort 9 (1->30 mg), cohorts 10, 30, (1->100 mg), cohort 11 (tarlatamab + dexamethasone), cohort 34 (1->100 mg 24-hr outpatient), cohorts 26 (

mg eIV-[redacted] mg), cohorts 27 and 31 ([redacted] mg eIV-[redacted] mg), 2-step dosing cohort 23 ([redacted] mg), cohort 37 ([redacted] mg Q3W 21 day/cycle), and cohort 38 ([redacted] mg D1/D8 21 day/cycle). **Tarlatamab All Doses** includes all participants who receive any dose of tarlatamab monotherapy from studies 20210004, 20200491, and 20160323.

In addition, Cytokine Release Syndrome (CRS) data from study 20200491, monotherapy cohorts of study 20160323 and tarlatamab arm of study 20210004 will be integrated and analyzed for participants who received tarlatamab and were enrolled from monotherapy cohorts of study 20160323 part F and tarlatamab arm of study 20210004 under PA3 with mandatory 6 to 8 hours monitoring post-infusion at cycle 1 day 1 and cycle 1 day 8 and participants who received tarlatamab with more than mandatory 6 to 8 hours monitoring post-infusion at cycle 1 day 1 and cycle 1 day 8 may. Output headers are shown below:

Table 2. Output Header for 6 to 8 Hours Cohorts

Studies 20210004, 20200491, and 20160323, More Than 6 to 8 Hours Monitoring	Studies 20210004 and 20160323, With 6 to 8 Hours Monitoring	Study 20160323, With 6 to 8 Hours Monitoring	Study 20210004, With 6 to 8 Hours Monitoring	Study 20210004, More Than 6 to 8 Hours Monitoring	Overall
Tarlatamab 10 mg (N = xx) n (%)	Tarlatamab 10 mg (N = xx) n (%)	Tarlatamab 10 mg (N = xx) n (%)	Tarlatamab 10 mg (N = xx) n (%)	Tarlatamab 10 mg (N = xx) n (%)	Tarlatamab 10 mg (N = xx) n (%)

Studies 20210004, 20200491, and 20160323, more than 6 to 8 hours monitoring includes participants who receive 10 mg of tarlatamab monotherapy from studies 20210004, 20200491, and 20160323 and were monitored for more than 6 to 8 hours. **Studies 20210004 and 20160323, with 6 to 8 hours monitoring** includes study 20210004 under protocol amendment 3 with mandatory 6 to 8 hours monitoring post-infusion at cycle 1 day 1 and cycle 1 day 8 and study 20160323 part F. **Study 20160323, with 6 to 8 hours monitoring** includes study 20160323 part F. **Study 20210004, with 6 to 8 hours monitoring** includes study 20210004 under protocol amendment 3 with mandatory 6 to 8 hours monitoring post-infusion at cycle 1 day 1 and cycle 1 day 8. **Study 20210004, more than 6 to 8 hours monitoring** includes participants who receive 10 mg of tarlatamab monotherapy from study 20210004 and were monitored for more than 6 to 8 hours. **Overall** includes all participants who received 10 mg of tarlatamab monotherapy from studies 20210004, 20200491, and 20160323, regardless of monitoring period.

2. OBJECTIVES

The safety profile of tarlatamab will be evaluated through various analyses including, but not limited to, a description of overall exposure to tarlatamab, summaries of Treatment-

emergent Adverse Events (TEAEs), treatment-related TEAEs (TRAEs), electrocardiogram (ECG), clinical laboratory tests, physical measurements and vital signs.

3. DEFINITIONS

Baseline

For any variable, unless otherwise specified, the baseline is the last nonmissing assessment taken prior to the first administration of tarlatamab treatment or other protocol-required therapies. Where baseline measurements are taken on the same day as the tarlatamab administered and no times are present, it will be assumed that these measurements are taken prior to the study specified treatment being administered.
For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the earliest date of first administration of tarlatamab or other protocol-required therapies, the baseline value is the value from the screening period measured closest to the earliest date of first administration of tarlatamab or other protocol-required therapies. In the event that multiple assessments are done on the same day as the earliest date of first administration of tarlatamab or other protocol-required therapies and there is no time associated with the assessments, the value associated with the last clinically planned event before the earliest date of first administration of tarlatamab or other protocol-required therapies will be used as the baseline value.

Baseline ECG

Baseline ECG is the cycle 1 day 1 pre-dose assessment.

- If multiple ECGs are available, the mean of all ECGs will be calculated for baseline.
- If only one ECG is available, this assessment will be used.

If cycle 1 day 1 pre-dose ECG assessment is missing, the last nonmissing assessment taken prior to the first administration of tarlatamab treatment will be used as the baseline ECG. If multiple nonmissing assessments are available at the same date, the mean of all assessments will be used as baseline ECG.

Postbaseline ECG

The calculation follows the same rule as the baseline ECG.

Bazett-corrected QT Interval (QTcB)

The Bazett correction will be calculated from the investigator reported QT (msec) and RR interval (msec) if available, as follows:

$$QTcB=QT/(RR/1000)^{0.5}$$

QTcB will be only summarized if RR is collected.

Change from Baseline

Change from baseline is the arithmetic difference between post-dose assessments and baseline assessment.

Change (absolute) from baseline = postbaseline value – baseline value

Duration of Adverse Event

Duration of resolved adverse events (days) = (event end date – event start date) + 1

Exposure-Adjusted Event Rate of TEAE

Exposure-adjusted event rate will be calculated as:

(Total number of TEAEs) / (total participant years of exposure of tarlatamab)*100

Fridericia-corrected QT Interval (QTcF):

The Fridericia correction will be calculated from the investigator reported QT (ms) and RR interval (ms) if available, as follows:

$$QTcF=QT/(RR/1000)^{0.33}$$

QTcF will be only summarized if RR is collected.

Long Term Follow-Up

Each study will follow their own definition, which are specified in the individual SAPs.

Relative Dose Intensity

Relative dose intensity (%) is calculated as (actual cumulative dose / planned cumulative dose)*100, where

- Actual cumulative dose is the total dose of tarlatamab given up to the data cutoff. For participants who did not take any drug the actual cumulative dose is 0 mg.
- Planned cumulative dose is the planned dose of tarlatamab accumulated over the actual duration on study treatment.

Safety Follow-Up

Each study will follow their own definition, which are specified in the individual SAPs.

Study Day

Post study day: study day = (date - date of study day 1) + 1

Pre-study day: study day = (date – date of study day 1)

Study Day 1

Study day 1 is defined as the first day that any of tarlatamab or other protocol-required therapies is administered to the participant.

Time to Adverse Event Resolution

Time to resolution is defined as the interval from the event start date to event end date. Unresolved events are censored at last dose of tarlatamab date + 65 days, end of study date, death date or analysis cutoff date, whichever occurs earlier.

Time to First Onset of Event of Interest (EOI) from First Tarlatamab Administration

Time to first onset of EOI will be derived as the number of days from first tarlatamab administration to start date of EOI.

Time to first onset of EOI from first tarlatamab administration (days) = (date of EOI - date of first tarlatamab administration) + 1

Time to first onset of EOI from first tarlatamab administration (hours) = datetime of EOI - datetime of first tarlatamab administration

Time to First Onset of Event of Interest (EOI) After Each Dose from Last Prior Tarlatamab Administration

Time to first onset of EOI will be derived as the number of days from the last prior tarlatamab administration start date to the start date of EOI.

Time to first onset of EOI from last prior tarlatamab administration (days) = (date of EOI - date of last prior tarlatamab administration) + 1

Time to first onset of EOI from last prior tarlatamab administration (hours) = datetime of EOI - datetime of last prior tarlatamab administration

Treatment-Emergent Adverse Event (TEAE)/Treatment-Related TEAE (TRAE)

Each study will follow their own definition, which are specified in the individual SAPs. 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.

4. COVARIATES AND SUBGROUPS

Not applicable.

5. ENDPOINT CATEGORIES AND ANALYSES

5.1 Endpoints

- Exposure to tarlatamab
- Participant incidence of treatment-emergent adverse events (TEAEs)
- Participant incidence of treatment-related TEAEs (TRAEs)
- Electrocardiogram (ECG)
- Clinical laboratory tests
- Physical measurements
- Vital signs

5.2 Hypothesis/Estimation

No formal hypothesis testing will be performed.

5.3 Analysis Subset(s)

5.3.1 Safety Analysis Set

The safety analysis set is defined as all participants who receive at least 1 dose of tarlatamab. Participants will be analyzed according to the actual dose received. Analysis of all the safety endpoints will be conducted on the safety analysis set.

5.4 Analysis Methods

5.4.1 General Considerations

Descriptive statistics will be provided for exposure and safety endpoints. Descriptive statistics on continuous data will include means, medians, standard deviations, Q1, Q3, minimum, and maximum; while categorical data will be summarized using frequency counts and percentages. For time to safety event variables, Kaplan-Meier (KM) estimates and corresponding two-sided 95% confidence interval will be provided.
Data derivation from each study will follow their own principles specified in the individual study SAPs.

Imputation for missing or incomplete data may be performed if required. Incomplete adverse event and death dates will be imputed as described in Appendix A.

5.4.2 Participant Accountability

The number and percent of participants who were enrolled, received tarlatamab, completed tarlatamab, discontinued from tarlatamab (including reasons for discontinuing), completed study and discontinued study (including reasons for discontinuing) will be summarized.

5.4.3 Exposure to Tarlatamab

Descriptive statistics will be produced to describe the exposure to tarlatamab. Number of doses of tarlatamab, cumulative dose (mg), relative dose intensity and treatment duration (weeks) will be summarized. Treatment duration (months) will be summarized for ≥ 3, ≥ 6, ≥ 9 and ≥ 12 months. Additionally, a listing of the delay of tarlatamab administration will be provided.

5.4.4 Adverse Events

5.4.4.1 All Adverse Events

The MedDRA version **27.0** or later will be used to code all events categorized as adverse events to a system organ class and a preferred term. The severity of each adverse event will be graded using CTCAE version 5.0 for study 20200491 and tarlatamab arm of study 20210004. The severity of each adverse event for monotherapy cohorts of study 20160323 will be converted from CTCAE version 4.0 to 5.0 where possible. CRS and ICANS events from study 20200491 and tarlatamab arm of study 20210004 are graded according to ASTCT 2019. CRS and ICANS events from monotherapy cohorts of study 20160323 will be converted from Lee et al. 2014 to ASTCT 2019 where possible.

The participant incidence of adverse events will be summarized for all TEAEs, treatment-related TEAEs, serious TEAEs, grade 3 or higher TEAEs, fatal TEAEs, TEAEs leading to dose interruption and/or reduction of tarlatamab and TEAEs leading to discontinuation of tarlatamab.

Worst grade is derived as the maximum grade (per the applicable grading scale CTCAE / ASTCT) for each preferred term per participant.

Detail on the derivation of worst grade at event level will be provided in the TFL shell document.

Participant incidence of all TEAEs and TRAEs will be summarized as outlined in the Table 3. When applicable, rows are sorted by system organ class (alphabetically) and

preferred term within system organ class (in descending order of frequency).
Overall summary of exposure-adjusted event rate of all TEAEs, serious TEAEs, grade 3 or higher TEAEs, fatal TEAEs, TEAEs leading to dose interruption and/or reduction of tarlatamab and TEAEs leading to discontinuation of tarlatamab will be produced. A separate overall summary of exposure-adjusted event rate of serious TEAEs will be provided.
Listing of TEAEs, listing of deaths during the studies will be produced with all the relevant fields.
Events that are directly related to small cell lung cancer/disease progression are excluded in analysis of integrated summary of safety for all TEAEs and TRAEs summaries above because these are not considered as TEAEs. These events are identified by Global Safety Officer using preferred terms coded MedDRA version **27.0** or later. Additional overall summary of TEAEs including events of small cell lung cancer/disease progression, participant incidence of all TEAEs including events of small cell lung cancer/disease progression by preferred term, participant incidence of fatal TEAEs including events of small cell lung cancer/disease progression by system organ class and preferred term will be summarized.

Table 3. TEAE Summary

	Overall	Preferred Term	System Organ Class and Preferred Term	System Organ Class Preferred Term and Worst Grade
Overall summary of TEAEs/TRAEs	x			
All TEAEs		x	x	x
Serious TEAEs		x	x	
Grade 3 or higher TEAEs		x	x	
Fatal TEAEs		x	x	
TEAEs leading to dose interruption and/or reduction of tarlatamab		x	x	
TEAEs leading to discontinuation of tarlatamab		x	x	
TEAEs occurring in ≥ 5% of participants		x		
All TRAEs		x		
Serious TRAEs		x		
Grade 3 or higher TRAEs		x		
Fatal TRAEs		x		
TRAEs leading to dose interruption and/or reduction of tarlatamab		x		
TRAEs leading to discontinuation of tarlatamab		x		
TRAEs occurring in ≥ 5% of participants		x		

5.4.4.2 Event of Interest (EOI)

EOIs identified for tarlatamab:

Cytokine Release Syndrome (AMQ Broad), Cytokine Release Syndrome (AMQ Narrow), Neutropenia (AMQ Broad), Neutropenia (AMQ Narrow), Immune effector Cell Associated Neurotoxicity Syndrome (ICANS) and associated neurological events (AMQ Broad), Neurological Events [Nervous system disorders (SOC) / Psychiatric disorders (SOC)], Hypersensitivity **broad** events [Hypersensitivity (SMQ Broad) / Anaphylactic reactions (SMQ Narrow)], **Hypersensitivity narrow events [Hypersensitivity (SMQ Narrow) / Anaphylactic reactions (SMQ Narrow)]**.

For the list of EOIs mentioned above, the participant incidence of treatment-emergent adverse events of interest (Amgen MedDRA Queries), grade ≥ 2, grade ≥ 3, grade ≥ 4, serious, fatal, events leading to dose interruption and/or reduction of tarlatamab and events leading to discontinuation of tarlatamab will be summarized.

Summary of all treatment-emergent EOIs, treatment-emergent serious EOIs, grade 3 or higher treatment-emergent EOIs, treatment-emergent fatal EOIs, treatment-emergent EOIs leading to dose interruption and/or reduction of tarlatamab and treatment-emergent EOIs leading to discontinuation of tarlatamab by their categories and preferred term will be provided. Similar summaries will be repeated for treatment-related treatment-emergent adverse events of interest.

Additionally, summaries of time to first onset of treatment-emergent EOIs from first tarlatamab administration (days), time to first onset of treatment-emergent EOIs after each dose from last prior tarlatamab administration (days), and duration of treatment-emergent EOIs (days) will be provided. Summaries of time to first onset of treatment-emergent EOIs from first tarlatamab administration (hours), and time to first onset of treatment-emergent EOIs after each dose from last prior tarlatamab administration (hours) will be provided for CRS (AMQ Narrow) only. Summaries of treatment-emergent CRS (AMQ Narrow) by dose, time from onset of grade 1 treatment-emergent CRS (AMQ Narrow) to grade 2 or higher treatment-emergent CRS (AMQ Narrow) by dose, time from onset of grade 1 treatment-emergent CRS (AMQ Narrow) to grade 2 treatment-emergent CRS (AMQ Narrow), duration of treatment-emergent CRS (AMQ Narrow) for participants that required tocilizumab, participant incidence of treatment-emergent CRS (AMQ Narrow) treated with tocilizumab, participant incidence of recurrent treatment-emergent CRS (AMQ Narrow), summary of treatment-emergent CRS (AMQ Narrow) rebound incidence in participants following recommended tarlatamab dosage for restarting therapy after dose delay, participant incidence of intervention utilization in relation to treatment-emergent CRS (AMQ Narrow), participant incidence of intervention utilization within and after 24 hours of last prior dose at cycle 1 day 1 and cycle 1 day 8 for grade 2 or higher treatment-emergent CRS (AMQ Narrow), participant incidence and time to onset for grade 2 or higher treatment-emergent CRS (AMQ Narrow) by dose will be presented, other analyses for CRS (AMQ Narrow) may be provided as well if needed.

Participant incidence of treatment-emergent ICANS and associated neurological events by last prior tarlatamab administration, participant incidence of treatment-emergent ICANS and associated neurological events by last prior tarlatamab administration visit and worst grade, participant incidence of recurrent treatment-emergent ICANS and

associated neurological events**, summaries of time to first onset of treatment-emergent ICANS from first tarlatamab administration (days), time to first onset of treatment-emergent ICANS after each dose from last prior tarlatamab administration (days), and duration of treatment-emergent ICANS (days)** will be presented. Summaries of time to onset of treatment-emergent EOIs and duration of treatment-emergent EOIs will be provided for grade 2 or higher and grade 3 or higher treatment-emergent EOIs respectively.

Listing of recurrent treatment-emergent CRS (AMQ Narrow) will be produced with all the relevant fields.

Overall summary of treatment-emergent CRS (AMQ Narrow) and treatment-related treatment-emergent CRS (AMQ Narrow), time to first onset of treatment-emergent CRS (AMQ Narrow) from first tarlatamab administration (days), time to first onset of treatment-emergent CRS (AMQ Narrow) after each dose from last tarlatamab administration (days and hours), duration of treatment-emergent CRS (AMQ Narrow) (days), treatment-emergent CRS (AMQ Narrow) by dose, time from onset of grade 1 treatment-emergent CRS (AMQ Narrow) to grade 2 or higher treatment-emergent CRS (AMQ Narrow) by dose, time from onset of grade 1 treatment-emergent CRS (AMQ Narrow) to grade 2 treatment-emergent CRS (AMQ Narrow)**, and participants incidence of hospitalization due to treatment-emergent CRS (AMQ Narrow) during cycle 1 day 1 and cycle 1 day 8 doses by grade** among participants who received tarlatamab and were enrolled from monotherapy cohorts of study 20160323 part F and tarlatamab arm of study 20210004 under PA3 with mandatory 6 to 8 hours monitoring post-infusion at cycle 1 day 1 and cycle 1 day 8 and participants who received tarlatamab with more than mandatory 6 to 8 hours monitoring post-infusion at cycle 1 day 1 and cycle 1 day 8 may be summarized side by side if there is sufficient number of participants, other analyses for CRS (AMQ Narrow) may be provided as well if needed.

5.4.5 Electrocardiogram

Participants' maximum change from baseline in QTcF and QTcB will be categorized and the number and percentage of participants in each group will be summarized for study 20200491 and monotherapy cohorts of study 20160323 only. Unscheduled assessments will be included in the determination of the maximum change. The categories are $\leq$ 30 msec, $>$ 30 – 60 msec, $>$ 60 msec.

Participants' maximum post baseline values will also be categorized and the number and percentage of participants in each group will be summarized for study 20200491 and

monotherapy cohorts of study 20160323 only. The categories are ≤ 450 msec, > 450 – 480 msec, > 480 – 500 msec, > 500 msec.

No statistical analyses of ECG measurements are planned for tarlatamab arm of study 20210004.

5.4.6 Clinical Laboratory Tests

Shift tables between the worst postbaseline and baseline grades of selected laboratory parameters will be presented. Participant incidence of toxicity change of more than 3 grades from baseline will be summarized. Laboratory abnormalities that worsened from baseline will be summarized by all grades and grade 3 to 4.

Participant incidence of suspected Hy's law cases will be summarized using the following criteria:

- ALT or AST > 3 x ULN at baseline and on-study.
- Total bilirubin > 2 x ULN at baseline and on-study.
- (ALT or AST) > 3 x ULN and (Total bilirubin > 2 x ULN) and (ALP < 2 x ULN) at baseline and on-study or within 30 days after a postbaseline ALT or AST (transaminases) elevation

Summaries of time from first tarlatamab administration (days) to first onset of grade 3 or higher increased will be provided for ALT, AST and total bilirubin, time from first tarlatamab administration (days) to first onset of grade 3 or higher decreased will be provided for hemoglobin, platelets and total neutrophils.

A listing of ALT, AST, ALP, and total bilirubin values at each time point will be produced for the participants suspected of Hy's law case.

5.4.7 Physical Measurements

Physical measurement data will be listed and reviewed for each participant.

5.4.8 Vital Signs

The incidence and percentage of abnormal changes in all vital signs (including systolic/diastolic blood pressure, heart rate, respiratory rate, oxygen saturation and body temperature) will be tabulated.

5.4.9 Antibody Formation

The incidence and percentage of participants who develop anti-tarlatamab antibodies at any time will be tabulated. Summaries of positive anti-tarlatamab antibody test results over time may be provided. Overall summary of TEAEs and incidence of TEAEs by system organ class and preferred term may be tabulated by anti-tarlatamab antibodies.

5.4.10 Exposure to Concomitant Medication

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

5.5 Postmarketing Requirement

In order to meet the postmarketing requirement from FDA, analyses of adverse events for different periods, severity, and outcome of the known serious risks of CRS and ICANS will be further characterized based on the integrated safety analysis of data from participants with extensive stage SCLC. A comprehensive analysis will be included from all available data sources including but not limited to participant-level and pooled analyses of study 20200491 and monotherapy cohorts of study 20160323 and tarlatamab arm of study 20210004.

Summaries of all EOIs, serious EOIs, time to onset of EOIs from first tarlatamab administration (days), time to onset of serious EOIs from first tarlatamab administration (days), time to onset of EOIs from last prior tarlatamab administration (days), time to onset of serious EOIs from last prior tarlatamab administration (days), duration of EOIs (days) and duration of serious EOIs (days) will be provided by following periods:

- Period 1: From cycle 1 day 1 to 90 days after cycle 1 day 1 or end of treatment, whichever occurs earlier.
- Period 2: From 90 days after cycle 1 day 1 to end of treatment.
- Period 3: From end of treatment to end of safety follow up.
- Period 4: From end of safety follow up to end of long term follow up or end of study, whichever occurs later .

Similar summaries above will be repeated for pituitary dysfunction events by period 3 and period 4. Pituitary dysfunction events are identified by Global Safety Officer using preferred terms coded MedDRA version **27.0** or later.

Severity and outcome of the known serious risk of CRS, ICANS and neurologic toxicity are mentioned in section 5.4.4.2.

6. REFERENCES

Literature citations and references are detailed in the individual SAPs.

7. APPENDICES [AS APPROPRIATE]

Appendix A. Handling of Incomplete Dates and Missing Dates for Adverse Events and Death

Below imputation rules will be used to impute start date and stop date of adverse events.

Table 4. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date: Complete: *yyyymmdd* $< 1^{st}$ dose	Stop Date: Complete: *yyyymmdd* $\geq 1^{st}$ dose	Stop Date: Partial: *yyyymm* $< 1^{st}$ dose *yyyymm*	Stop Date: Partial: *yyyymm* $\geq 1^{st}$ dose *yyyymm*	Stop Date: Partial: *yyyy* $< 1^{st}$ dose *yyyy*	Stop Date: Partial: *yyyy* $\geq 1^{st}$ dose *yyyy*	Stop Date: missing
Partial: *yyyymm*	$= 1^{st}$ dose *yyyymm*	2	1	2	1	n/a	1	1
	$\neq 1^{st}$ dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	$= 1^{st}$ dose *yyyy*	3	1	3	1	n/a	1	1
	$\neq 1^{st}$ 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 participants 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:

- For partial stop date mmyyyy, impute the last of the month.
- For partial stop date yyyy, impute December 31 of the 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. (ie. set the stop date as missing).

Imputation rules for partial or missing death dates:

- 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 participant instead of family members. Last contact date would be derived from the latest participant visit/assessment date.