Statistical Analysis Plan

Protocol Title:	A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Bemarituzumab Monotherapy and Combination with other Anti-Cancer Therapy in Subjects with Squamous-Cell Non-Small-Cell Lung Cancer (FORTITUDE-201)
Short Protocol Title:	A phase 1b study of bemarituzumab monotherapy and combination with other anti-cancer therapy in SqNSCLC with FGFR2b overexpression (FORTITUDE-201)
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	**10MAR2023**	**The first version of a document.**
Amendment 1 (V2.0)	**25JUN2024**	**1) Removed subgroups as no planned subgroup analysis.** **2) Updated the definition of study day 1 for not dosed subjects.**

		3) Updated definitions of duration of treatment, actual dose intensity, average dose per cycle and relative dose intensity **4) Updated the definition of TEAE for events related to lung cancer or disease progression.** **5) Updated Demographic and Baseline Characteristics.** **6) Changes in requirement of various lab shift and summary tables.** **7) Added parameters in vital signs** **8) Added language for ECG in part 4 and updated summary language for part 3.** **9) Updated Analytical Windows Appendix.** **10) Removed Appendix C.**

Table of Contents

List of Tables

No table of figures entries found.

List of Figures

No table of figures entries found.

List of Abbreviations

Abbreviation	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Clotting Time
AST	Aspartate Aminotransferase
ATC	**Anatomical Therapeutic Chemical**
AUC	Area Under the Concentration Time Curve
BOR	Best Overall Response
BSA	Body Surface Area
CBD	Clinical Biomarkers and Diagnostics
CI	Confidence Interval
C_{max}	Maximum Observed Concentration
CPMS	Clinical Pharmacology, Modeling and Simulation
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Observed Concentration at the End of a Dose Interval
DC	Disease Control
DCR	Disease Control Rate
DCO	Data Cutoff
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI(s)	Event(s) of Interest
EOS	End of Study
EU	European Union
FDA	Food and Drug Administration
FGFR2b	Fibroblast Growth Factor Receptor Isoform 2b
GFR	**Glomerular filtration rate**

GSO-DM	Global Study Operations-Data Management
IHC	Immunohistochemistry
INR	International Normalized Ratio
IP	Investigational Product
IPD	Important Protocol Deviation
IV	Intravenous
KM	Kaplan-Maier
LTFU	Long-Term Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mTPI	Modified Toxicity Probability Interval Method
NCI	National Cancer Institute
NE	Not Evaluable
Non-IP	Non-Investigational Product
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin time
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QTc	Corrected QT Interval
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
ROW	Rest of World
RP3D	Recommended Phase 3 Dose
SAP	Statistical Analysis Plan
SD	Stable Disease
SFU	Safety Follow-Up
SqNSCLC	Squamous Non-Small Cell Lung Cancer
SSAP	Supplemental Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event
TPS	Tumor Proportion Score

US	United States
WHO DRUG	World Health Organization Drug Dictionary

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 for study 20210102, Bemarituzumab (AMG 552) dated **27 April 2023**. The scope of this plan includes the interim analysis in the form of Dose Level Review Meeting (DLRMs), the primary analysis and the final that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. Pharmacokinetic (PK), pharmacodynamic, and biomarker analyses will be performed by Clinical Pharmacology, Modeling and Simulation (CPMS) or the Clinical Biomarkers & Diagnostics (CBD) group.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of bemarituzumab monotherapy and combination with other anti-cancer therapies • To determine the recommended phase 3 dose of bemarituzumab in combination with other anti-cancer therapies	• Dose-limiting toxicities (DLTs), treatment-emergent adverse events, and clinically significant changes in vital signs, physical examinations, clinical laboratory tests, and visual acuity
Secondary	
• To characterize the pharmacokinetics (PK) of bemarituzumab monotherapy and in combination with other anti-cancer therapies	• PK parameters for bemarituzumab including, but not limited to, area under the concentration time curve (AUC), maximum observed concentration (C_{max}), and observed concentration at the end of a dose interval (C_{trough})
• To evaluate preliminary anti-tumor activity of bemarituzumab monotherapy and in combination with other anti-cancer therapies	• Objective response [defined as complete response (CR) + partial response (PR)] as determined by investigator per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1] • Duration of response, defined as the time from first response to disease progression (as determined by investigator per RECIST v1.1) or death from any cause, whichever comes first

	• Disease control defined as CR + PR + stable disease (SD) • Progression free survival (PFS), defined as time from first dose of investigational product until disease progression or death from any cause. Subjects alive without progression will be censored at their last evaluable disease assessment. Progression will be based on assessment by investigator per RECIST v1.1 • Overall survival (OS), defined as time from first dose of investigational product until death from any cause. Subjects still alive will be censored at the date last known to be alive
Exploratory	
• To characterize the immunogenicity of bemarituzumab	• Anti-bemarituzumab antibody formation
• To evaluate the expression of biomarkers in tumor samples	• Expression of biomarkers, including, but not limited to FGFR2b and [redacted]
• To evaluate the relationship between exploratory biomarkers and efficacy	• Correlation of biomarkers, including [redacted] and FGFR2b overexpression status with efficacy endpoints
• To explore protein and nucleic acid biomarkers in blood and tissue	• Changes in protein and nucleic acid biomarkers in blood and in tumor biopsies pre-treatment, on-treatment, and at progression

2.2 Hypotheses and/or Estimations

No statistical hypothesis will be tested.

3. Study Overview

3.1 Study Design

This is a phase 1b, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of bemarituzumab monotherapy and combination across different lines of therapy in subject locally advanced/metastatic SqNSCLC. This study will explore the addition of bemarituzumab to the established standard of care immune-chemotherapy in the first-line treatment setting and the addition to chemotherapy in the second line or later setting.

The study consists of a pre-screening period to collect tissue for FGFR2b testing (Parts 2, 3, and 4 only), a 28-day screening period, a treatment period, a safety follow-up (SFU) visit, and a long-term follow-up (LTFU) period. Subjects who discontinue bemarituzumab will undergo SFU approximately 28 (+3) days after the last dose of study treatment. In addition, subjects will undergo LTFU for survival approximately every 3 months (± 1 month) for up to 2 years from the first dose of bemarituzumab. Subjects will receive study treatment with bemarituzumab until disease progression, unacceptable toxicity, subject request, or death (whichever occurs first).

Radiographic assessments will be performed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and will be performed every 6 weeks (Q6W) (± 7 days) until week 54 and then every 12 weeks (± 14 days). After discontinuation of study treatment for reasons other than radiographic disease progression or withdrawal of consent, tumor assessments will continue until radiographic progression or initiation of additional anticancer therapy.

The study consists of 4 Parts:

- Part 1: Combination dose exploration with docetaxel
- Part 2: Combination dose expansion with docetaxel
- Part 3: Monotherapy
- Part 4: Combination with carboplatin, paclitaxel or nab-paclitaxel, and pembrolizumab

Part 1

Part 1 of the study will explore the dosing of bemarituzumab in combination with docetaxel. During dose exploration, subjects will be enrolled in groups of 3 to 6 dose limiting toxicity (DLT) evaluable subjects per cohort, and escalation will be guided primarily by safety responses to different doses.

The planned dose levels are:

- Dose Level 1: bemarituzumab 22 mg/kg IV cycle 1 day 1 followed by 15 mg/kg IV day 22 and Q3W thereafter
- Dose Level 2: bemarituzumab 30 mg/kg IV cycle 1 day 1 followed by 22 mg/kg IV day 22 and Q3W thereafter

An additional Dose Level 1a of bemarituzumab 15 mg/kg IV Q3W plus 1 additional 7.5 mg/kg dose on cycle 1 day 8 only may be explored if dose de-escalation is required from Dose Level 1.

At each dose level, and on each planned dosing day, docetaxel will be administered at 75 mg/m2 IV Q3W (or 60 mg/m^2 IV Q3W for subjects from sites in Japan).

Part 1 will begin with Dose Level 1. The study DLT period is 21 days following the first dose. Once 3 to 6 subjects enrolled at a certain dose level are followed for safety for 21 days, a Dose Level Review Team (DLRT) meeting will be convened.

The mTPI-2 escalation/de-escalation guideline for each dose cohort is derived with a target toxicity probability of 0.30, acceptable toxicity probability interval of (0.25, 0.33). A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT (i.e., the elimination boundary).

Dose exploration will continue until:

- a maximum of 18 subjects in Part 1 is reached; or
- 9 subjects have been treated a specific dose level; or
- the lowest dose level exceeds the elimination boundary

Part 2

Once a dose level has been declared safe by the DLRT, a dose level can enter Part 2 of the study. Part 2 enrollment will be limited to subjects with prospectively identified FGFR2b overexpression status. A minimum of 10 response-evaluable subjects and a maximum of 30 response-evaluable subjects will be treated per dose level in Part 2 to better understand the safety profile and preliminary efficacy of the combination and to enable selection of recommended phase 3 dose (RP3D). Up to 2 dose levels consisting of 10 to 30 subjects each can be expanded in Part 2 of the study. For Part 2, subjects can receive 1 dose of docetaxel during pre-screening or screening if initiation of treatment is deemed urgent by the investigator.

Part 3

Part 3 of the study will explore bemarituzumab monotherapy at the dose of 15 mg/kg IV Q2W plus 1 additional 7.5 mg/kg dose on cycle 1 day 8. One cycle of treatment will consist of 14 days. Part 3 enrollment will be limited to subjects with prospectively

identified tumor FGFR2b overexpression status. A minimum of 10 response-evaluable subjects and a maximum of 30 response-evaluable subjects will be treated in Part 3 to better understand the safety profile, PK, and preliminary efficacy of monotherapy bemarituzumab in FGFR2b+ SqNSCLC. Part 3 may enroll subjects concurrently with Parts 1 and 2 and 4.

Part 4

Once a dose level has been declared safe by the DLRT for Part 1, a dose level can enter the Part 4 safety run-in. During the safety run-in, 6 subjects will be evaluated with a 21-day DLT period and once the dose has been declared safe in the first-line setting with immune-chemotherapy combination, then Part 4 enrollment can proceed with dose expansion. Dose de-escalation may occur in Part 4, independently of the recommendation in Part 1. Part 4 enrollment will be limited to subject with prospectively identified FGFR2b overexpression status. A minimum of 10 subjects and a maximum of 30 subjects, including the 6 subjects in the safety run-in, will be treated in Part 4 to better understand the safety profile and preliminary efficacy of the combination and to enable the selection of the RP3D. Up to 2 dose levels consisting of 10 to 30 subjects can be expanded in Part 4 of the study. Subjects will receive up to 4 cycles of bemarituzumab, pembrolizumab, and chemotherapy followed by bemarituzumab and pembrolizumab maintenance. In addition to bemarituzumab administered on day 1 of every 21-day treatment cycle, subject will be administered pembrolizumab 200mg day 1 for up to 35 cycles and, for the first four cycles only, the combination of carboplatin 6mg/mL/min and either paclitaxel 200 mg/m^2 on day 1 or nab-paclitaxel 100 mg/m^2 on days 1, 8, and 15. For Part 4 expansion (and not in safety run-in), subjects can receive 1 dose of carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab during pre-screening or screening if initiation of treatment is deemed urgent by the investigator. This bridging dose is not a requirement of the study and is not considered part of the clinical study.

For Part 4 only, subjects may continue treatment beyond initial RECIST v1.1 progressive disease (PD), as assessed by the investigator, as long as they meet the following criteria:

- Investigator assessed clinical benefit
- Tolerance of study drug
- Stable Eastern Cooperative Oncology Group (ECOG) performance status

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (ie, central nervous system [CNS] metastases)

A dose of bemarituzumab selected in Part 1 in combination with docetaxel will enter Part 4 safety run-in in combination with pembrolizumab, carboplatin, and nab-paclitaxel/paclitaxel

3.2 Sample Size

It is anticipated that up to 180 subjects will be enrolled in this study, consisting of a maximum of 18 subjects in Part 1 and a maximum of 150 subjects in Parts 2, 3 and 4 combined. The 150 subjects include the possibility of two cohorts at 2 dose levels of bemarituzumab, consisting of 10 to 30 subjects in each of Part 2 and 4. Three to 6 Japanese subjects per dose level will be enrolled in Part 1, Part 2, and/or Part 4 either as part of the initial dose level evaluation, or as backfill once RP3D has been determined.

With 3, 6, or 9 subjects in a dose level cohort in Part 1, there is a 58%, 82%, and 93% probability, respectively, of observing at least 1 DLT if the true DLT rate is 25%.

With a minimum of 10 subjects each in Parts 2, 3 and 4, there is an approximate 95% probability of observing at least 1 DLT if the true DLT rate is 25%, the lower end of the acceptable toxicity interval. Up to 30 subjects may be enrolled to gain further safety and preliminary efficacy data.

3.3 Adaptive Design

The mTPI-2 design will be employed to guide the DLRT on dose escalation and de-escalation decisions.

4. Covariates and Subgroups

4.1 Planned Covariates

This phase 1b study has no prespecified covariate analyses.

4.2 Subgroups

No subgroup analysis is planned for the study.

5. Definitions

Area Under the Curve (AUC)

The area under the plasma drug concentration-time curve (AUC) reflects the actual body exposure to drug after administration of a dose of the drug.

Actual cumulative dose (mg) =

$$\sum_{i}^{\#\ cycles} \textbf{total dose given at cycle i (mg)}$$

Actual cumulative dose (mg/kg) =

$$\left(\sum_{i}^{\#\ cycles} \textbf{total dose given at cycle i (mg)/weight (kg)}_i\right)$$

Actual cumulative dose (mg/m^2) =

$$\left(\sum_{i}^{\#\ cycles} \textbf{total dose given at cycle i (mg)/ BSA (m}^2\textbf{)}_i\right)$$

Actual cumulative dose (min*mg/mL) =

$$\left(\sum_{i}^{\#\ cycles} \textbf{total dose given at cycle i (mg)/ GFR (mL/min)}_i\right)$$

Average dose per cycle administered

Bemarituzumab (mg/kg)	**Actual cumulative dose (mg/kg) / number of cycles administered**
Docetaxel, Paclitaxel and Nab-Paclitaxel (mg/m^2)	**Actual cumulative dose (mg/m^2) / number of cycles administered**
Pembrolizumab (mg)	**Actual cumulative dose (mg) / number of cycles administered**
Carboplatin (min*mg/mL)	**Actual cumulative dose (min*mg/mL) / number of cycles administered**

Actual dose intensity

For part 1 and 2 (w=3)

	Actual dose intensity
Bemarituzumab (mg/kg)/week	**Actual cumulative dose (mg/kg) / [(Last dose date – first dose date + w*7)/7]**

	Actual dose intensity
Docetaxel (mg/m^2)/week	**Actual cumulative dose (mg/m^2) / [(Last dose date – first dose date + w*7)/7]**

For Part 3 (w=2)

	Actual dose intensity	Condition
Bemarituzumab (mg/kg)/week	**Actual cumulative dose (mg/kg) / [(Last dose date – first dose date + w*7)/7]**	**Subject began at least 2 cycles**
	Actual cumulative dose (mg/kg) / w weeks	**Subject took only C1D1 and C1D8 doses**
	Actual cumulative dose (mg/kg) / 1 week	**Subject took only C1D1 dose**

For Part 4 (w=3)

	Actual dose intensity
Bemarituzumab (mg/kg)/week	**Actual cumulative dose (mg/kg) / [(Last dose date – first dose date + w*7)/7]**
Docetaxel, Paclitaxel and Nab-Paclitaxel (mg/m^2)/week	**Actual cumulative dose (mg/m^2) / [(First dose date of the last cycle – first dose date + w*7)/7]**
Pembrolizumab (mg)/week	**Actual cumulative dose (mg) / [(First dose date of the last cycle – first dose date + w*7)/7]**
Carboplatin (min*mg/mL)/week	**Actual cumulative dose (min*mg/mL) / [(First dose date of the last cycle – first dose date + w*7)/7]**

Baseline

For any variable, unless otherwise specified, the baseline value is the last non-missing assessment taken prior to the first administration of IP**/Non-IP**. The following are eligible for baseline consideration:

- Assessments taken on the same date and the same time as the first dose of IP**/Non-IP**
- Assessments taken on the same date as the first dose of IP**/Non-IP** but with unknown time, when no assessments on the same date with known time are available.

If a subject is enrolled but does not receive IP**/Non-IP**, the baseline value is the last non-missing assessment taken on or prior to enrollment (e.g., at screening).

Best Overall Response (BOR)

Best overall response (BOR) for a subject is the best confirmed response from disease assessments recorded from the start of the IP administration until the initiation of subsequent anticancer treatment. Confirmation of response by a repeat scan is required after 4 weeks from the first documentation of response. Overall response assessments occurring after the start of the first subsequent anticancer therapy will not be included.

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 v1.1 response categories due to inadequate data or early death will be classified as non-evaluable (NE) for BOR but will be counted in the denominator of all response rate calculations.

Body Mass Index (BMI)

Body Mass Index will be calculated using the following formula:

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

Body Surface Area (BSA)

BSA measures the total surface area of the body and is used to calculate drug dosages and medical indicators or assessments. In addition to BSA derivation provided by site, the internal derivation may be provided using the formula:

$$BSA\ (m^2) = 0.007184\ \text{x}\ weight\ (kg)^{0.425}\ \text{x}\ height\ (cm)^{0.725}$$

Change from Baseline

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

Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value) /Baseline Value] x 100

C_{max}

C_{max} is defined as the maximum observed drug concentration.

C_{min}

C_{min} is defined as the minimum observed drug concentration.

C_{trough}

C_{trough} is defined as the observed concentration at the end of a dose interval.

Disease Control

Disease control is defined as complete response (CR) or partial response (PR) or stable disease (SD) per RECIST v1.1.

Disease Control Rate (DCR)

DCR is defined as proportion of subjects with CR, PR or SD per RECIST v1.1.

Dose Limiting Toxicity (DLT)

Dose limiting toxicities are defined as any of the corresponding adverse events listed in the protocol during the DLT evaluation period (21 days) considered by the investigator to be at least possibly related to bemarituzumab.

Duration of Response (DOR)

Duration of response is defined as the time from the first documentation of objective response (as determined by investigator per RECIST v1.1) until the first documentation of disease progression or death due to any cause, whichever occurs first.

DOR = (min(PD date, death date) - response start date + 1) ×12 / 365.25

Only subjects who have achieved OR will be evaluated for DOR. DOR will be censored at the last evaluable post-baseline tumor assessment prior to subsequent anticancer

therapy; otherwise, at date of first documentation of objective response (i.e., assign a one-day interval).

Duration of Treatment

Duration of treatment (weeks) = (date of last dose – date of first dose + 1)/7

Enrollment Date

Date of Enrollment on Subject Enrollment CRF.

End of Study (EOS)

An individual subject is considered to have completed the study if they have completed the last visit shown in the Schedule of Activities of the protocol.

End of Study Date

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 (i.e., last subject last visit), including any additional parts in the study (e.g., long-term follow-up, antibody testing), as applicable.

Investigational Product (IP)

The term ‘investigational product’ is used in reference to bemarituzumab.

Last Known Alive Date

In analysis of overall survival, subjects still alive are censored at last known alive date, defined as the latest date of the following dates.

- Assessment dates from on-study procedures
- Dosing start and stop dates of IP, non-IP, or concomitant medications
- Event start and stop dates
- Survival status date in LTFU
- Date ending IP, non-IP, or study

Non-Investigational Product (non-IP)

The term ‘non-investigational product’ is used to reference docetaxel, carboplatin, paclitaxel, nab-paclitaxel and pembrolizumab.

Objective Response (OR) as per RECIST 1.1

Objective response is defined as best overall response of confirmed complete response (CR) or confirmed partial response (PR), as defined by RECIST 1.1. Response will be assessed by investigator per RECIST v1.1 and recorded in the 'Overall Response' field on the Tumor Response (RECIST 1.1) eCRF.

Objective Response Rate (ORR)

ORR is defined as the proportion of subjects with a best overall response of OR.

Overall Survival (OS)

OS is defined as the time from the date of first dose of IP until event of death due to any cause through the analysis cutoff (DCO) date.

OS = (Date of death– date of first dose of IP + 1) ×12 / 365.25

Subjects still alive will be censored at the date last known to be alive through the DCO date.

Progressive Disease (PD) Date

Imaging Date entered on the Tumor Response (RECIST 1.1) eCRF that supports progressive disease status for Overall Response.

Progression-Free Survival (PFS)

Progression-free survival is defined as the time from date of first dose of IP until the first documentation of radiologic disease progression or death due to any cause, whichever occurs first, in the absence of subsequent anticancer therapy.

PFS (months) = (min(PD date, death date) - first dose date + 1) x 12 / 365.25

PFS will be censored at the last evaluable post-baseline tumor assessment prior to subsequent anticancer therapy; otherwise, at first dose of IP. Progression will be based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (derived utilizing investigator tumor assessments).

Relative dose intensity (%)

For part 1 and 2

IP	**Q3W Dose Level 1 (Part 1)**

Bemarituzumab	**{ Actual cumulative dose (mg/kg) / Expected dose (mg/kg) } * 100** **If last dose date = C1D1 then Expected dose = 22** **If last dose date > C1D1 then Expected dose = 22 + {(last dose date – second dose date +21)*15}/21**

IP	**Q3W Dose Level 2 (Part 1 and Part 2)**
Bemarituzumab	**{ Actual cumulative dose (mg/kg) / Expected dose (mg/kg) } * 100** **If last dose date = C1D1 then Expected dose = 30** **If last dose date > C1D1 then Expected dose = 30 + {(last dose date – second dose date +21)*22}/21**
Non-IP	**Q3W**
Docetaxel	$\frac{Actual\ cumulative\ dose(mg/m^2)}{[Last\ dose\ date - first\ dose\ date + 21] * \frac{75\ mg/m^2}{21}} * 100$

(The expected dose level for docetaxel is 60mg/m^2 in case of Japanese subjects.)

For Part 3

Relative dose intensity (%)

IP	**Q2W**
Bema	**{ Actual cumulative dose (mg/kg) / Expected dose (mg/kg) } * 100** **If last dose date = C1D1 then Expected dose = 15** **If last dose date = C1D8 then Expected dose = 15 + {(last dose date – first dose date) * 7.5}/7** **If last dose date > C1D8 then Expected dose = 7.5 + {(last dose date – first dose date +14) * 15}/14**

For Part 4

Relative dose intensity (%)

IP	**Q3W**

Bema	$\frac{Actual\ cumulative\ dose\ (mg/kg)}{I(Last\ dose\ date \geq Study\ Day\ 1)[(Last\ dose\ date - first\ dose\ date + 21) * \frac{22\frac{mg}{kg}}{21} + 8\ mg/kg)]\} * 100}$
Non-IP	**Q3W**
Pembrolizumab	$\frac{Actual\ cumulative\ dose(mg)}{[Last\ dose\ date - first\ dose\ date + 21] * \frac{200\ mg}{21}} * 100$
Carboplatin	$\frac{Actual\ cumulative\ dose(min * mg/mL)}{[Last\ dose\ date - first\ dose\ date + 21] * \frac{dose\ (min * mg/mL)}{21}} * 100$
Paclitaxel	$\frac{Actual\ cumulative\ dose(mg/m^2)}{[Last\ dose\ date - first\ dose\ date + 21] * \frac{200\ mg/m^2}{21}} * 100$
Nab-Paclitaxel	$\frac{Actual\ cumulative\ dose(mg/m^2)}{[First\ dose\ date\ of\ the\ last\ cycle - first\ dose\ date + 7] * \frac{100\ mg/m^2}{7}} * 100$

(The expected dose level for docetaxel is 60mg/m^2 in case of Japanese subjects.)

Study Day

For a given visit, the study day for a subject is defined as:

Study Day = (Visit Date – Study Day 1 date) + 1, if the visit is on or after Study Day 1.

Study Day = (Visit Date - Study Day 1 date), if the visit is prior to Study Day 1.

Study Day 1

A subject's study day 1 is defined as the date of the first dose of IP/Non-IP administration after enrollment. **Enrollment date can be used as study day 1 if a subject is not dosed with IP and non-IP.**

Treatment Emergent Adverse Events (TEAE) (General)

TEAE are adverse events starting on or after first dose of IP 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 the earlier of 28days after the last dose of investigational product and EOS date. **Events that are directly related to lung cancer or disease progression (including, but not limited to, preferred terms "Non-small cell lung cancer", "Disease progression" etc.) will be excluded from TEAE analysis.**

Treatment Emergent Adverse Events (TEAE) (Ocular)

Ophthalmological events as indicated by the Event Category = 'Ocular Event' **or pertaining to an eye-related EOI** starting on or after first dose of IP 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 the earlier of 100 days after the last dose of bemarituzumab and EOS date.

Treatment-Related AE

A treatment-related AE is any TEAE with the relationship flag on the Events eCRF page indicating there is a reasonable possibility that the event may have been caused by the investigational product.

6. Analysis Sets

6.1 Enrolled Analysis Set

The enrolled analysis set will consist of all enrolled subjects.

6.2 Safety Analysis Set

All subjects who have received at least one dose of bemarituzumab. The safety analysis set will also serve as the full analysis set.

6.3 DLT Analysis Set

All subjects that are enrolled in Part 1 who received at least one dose of bemarituzumab and Docetaxel; and met either of the following: 1) experienced a DLT; or 2) completed the 21-day DLT evaluation period, 3) received 100% of their planned dose

6.4 Pharmacokinetic Analyses Set

The PK Analysis Set includes all subjects who have received at least 1 dose of bemarituzumab (AMG 552) and have at least 1 PK sample collected. These subjects will be 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. The PK analysis set will be used to conduct the analysis of PK data, unless otherwise specified.

6.5 Interim Analyses Set(s)

Not applicable

6.6 Study-specific Analysis Sets

Not applicable

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Part 3 may enroll simultaneously with Parts 1, 2, and 4; and Parts 2 and 4 may enroll simultaneously. Therefore, the timing of the DLRMs described below may be adjusted so data from multiple study parts can be reviewed at a single meeting. Interim analyses

will be based on as-is database snapshots (ie, data that have gone through routine data cleaning).

Part 1

During DLRMs, Amgen, in consultation with the site investigators, will review all available cumulative data (safety, tolerability, laboratory, PK and efficacy) by cohort prior to making dose escalation or dose de-escalation recommendations. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRM and considered in all enrollment and dosing decisions. A DLRM will occur during dose exploration and 21 days following last subject enrolled in a dose cohort (every 3 to 6 subjects enrolled at a given dose level).

Parts 2, 3, and 4

Amgen, in consultation with site investigators, will review the data as detailed above 4 months after the 10th subject has been enrolled, in each of Parts 2, 3 and 4.

Additional administrative analyses may be performed for Parts 2, 3 and 4 before the primary analysis in order to plan for additional studies.

7.2 Primary Analysis

Refer to the final analysis.

7.3 Final Analysis

The final analysis will be based on a cleaned database lock and will occur after all subjects have ended the study.

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 provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

Missing and incomplete dates will be imputed as outlined in Appendix A. Partial or missing death dates will be imputed prior to derivation of any endpoint that utilizes the date of death.

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 IPD.

If applicable, the methods to detect bias are describe in the analyses of particular endpoints.

8.5 Outliers

PK concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard PK evaluation practice.

For non-PK analyses, any suspected outliers at the time of analyses will be investigated by the study team and will be included in analyses unless determined to be an error or there is supporting evidence or explanation to justify the exclusion. Any outliers excluded from the analysis will be discussed in the Clinical Study Report (CSR), including the reasons for exclusion and the impact of their exclusion on the study.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed which in most of the cases are normal distribution. If required data transformations or alternative non-parametric methods of analyses will be performed.

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.

Additional statistical software may be used to perform exploratory/ad-hoc analyses.

9. Statistical Methods of Analysis

9.1 General Considerations

Data will be summarized by cohort. Continuous variables will be described with the mean, standard deviation, median, quartiles, minimum, and maximum. Categorical data

will be summarized with frequency counts and percentages. Unless otherwise specified, data will be summarized using the Safety Analysis Set.

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

9.2 Subject Accountability

The number and percent of subjects who were screened, enrolled, received at least one dose of IP, discontinued from IP or non-IP (including reasons for discontinuing), discontinued the study (including reasons for discontinuing), and completed study will be summarized. The number and percent of subjects enrolled will be tabulated by study site and country. Key study dates for the first subject enrolled, last subject enrolled, **last subject ended IP, last subject ended study,** and data cut-off date for analysis will be presented.

9.3 Important Protocol Deviations

Eligibility deviations are defined in the protocol. Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and 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. A listing of IPDs will be provided.

9.4 Demographic and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by treatment groups using descriptive statistics for the safety analysis set as well as the pharmacokinetic analysis set for all the **four** parts of the study.

These include, but not limited to the following:

- Baseline demographics:
    - Age at enrollment
        - As a continuous variable
        - As a categorical variable: (< 65 vs ≥ 65 years)

- **As categorical variable: (18 - 64 years vs 65 - 74 years vs 75 - 84 years vs ≥ 85 years)**

- Sex (Male, Female)
- Race
  - White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, **Multiple** and Other
  - Asian (Japanese, Asian Indian, Chinese, Korean and Other)
- Region (US/EU, Asia, rest of world [ROW])
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

- Baseline characteristics:
  - Weight (kg)
  - Height (cm)
  - Body surface area (m^2)
  - **Body mass index (kg/m^2)**
  - ECOG performance status (0 vs 1 **vs 2**)
  - Time since initial diagnosis **to** study entry (months)
  - **Prior anti-cancer therapy category setting (as per eCRF data)**
  - **Prior lines of anti-cancer therapy (first line, second line, third line, fourth line, fifth line, sixth line, seventh line, not reported)**
  - **Prior radiotherapy for current malignancy setting (as per eCRF data)**
  - **Prior surgical procedures for current malignancy intent (as per eCRF data)**
  - TNM Staging at screening **(as per eCRF data)**
  - Disease status at screening (metastatic, locally advanced, locally recurrent)
  - **Disease status at initial diagnosis (metastatic; locally advanced, unresectable; locoregional, resectable)**
  - History of CNS involvement (yes vs no)
  - Tumor FGFR2b IHC staining score of 2+ or 3+ (**positive, negative, missing**)

- **Differentiation at screening (well differentiated vs moderately differentiated vs poorly differentiated)**
- **Histopathology type at screening (adenocarcinoma, squamous Cell carcinoma, large Cell Carcinoma, adenosquamous carcinoma, undifferentiated, sarcomatoid, other)**
- **Liver metastasis (yes, no)**
- **Smoking history**
- **Alcohol history**

9.5 Efficacy Analyses

Analysis of efficacy endpoints will be based on the Safety Analysis Set unless otherwise specified.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Not Applicable

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The number and percentage of subjects with objective response and disease control will be presented along with 95% CI.

For subjects treated at the RP3D, KM curves, KM quartiles with 95% CIs, and KM estimates with 95% CIs at landmark time points will be estimated for the following endpoints: duration of objective response (for only responding subjects), PFS, and OS.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or later will be used to code all events categorized as adverse events, to a system organ class and a preferred term.

The handling of incomplete adverse event start and/or end dates is detailed in Appendix A.

Subject incidence of all treatment-emergent adverse events, grade 3 or higher TEAEs, grade 4 or higher TEAEs, fatal adverse events, serious adverse events, adverse events leading to investigational product interruption, and adverse events leading to investigational product withdrawal will be tabulated by alphabetical order of system organ class and then by preferred term in descending order of frequency.

Subject incidence of treatment-emergent adverse events will be tabulated by preferred term in descending order of frequency, and also by system organ class, preferred term, and grade.

Subject incidence of all treatment-emergent treatment-related adverse events, grade 3 or higher TEAEs, grade 4 or higher TEAEs, fatal adverse events, serious adverse events, adverse events leading to investigational product interruption, and adverse events leading to investigational product withdrawal will be tabulated by alphabetical order of system organ class and then by preferred term in descending order of frequency.

Treatment-emergent events of interest (EOIs) (including ocular events) will be summarized by EOI category and preferred term. In addition, the subject incidence of all treatment-emergent EOIs, grade 3 or higher treatment-emergent EOIs, grade 4 or higher treatment-emergent EOIs, serious EOIs, EOIs leading to investigational product interruption, and EOIs leading to investigational product withdrawal will be tabulated. Time to onset, duration, number of resolved events will be summarized for select EOIs, including ocular events.

If a subject experiences repeated episodes of the same AE, then the subject will be counted once when tabulating subject incidence and, where applicable, the highest severity grade and strongest causal relationship to investigational product will be selected.

Serious TEAE and fatal TEAE for the safety population will be listed.

9.6.3 Ophthalmologic Exam Results

Visual acuity (logMAR equivalent) will be summarized **for baseline, worst post-baseline, maximum increase, and last post-baseline visits** in the Safety Analysis Set. The **same will be summarized for** subjects with changes in visual acuity related to abnormal corneal findings **on study** as indicated on the Ophthalmology Examination eCRF. The times per day of ocular lubricant usage will be summarized. **Unilateral and bilateral** intraocular pressure **and change from baseline** will be summarized by visit. Compliance of the performance of slit lamp, dilated retinal exam, 3-field retinal photographs, ocular surface staining, and optical coherence tomography results will be summarized by visit.

In addition, shift tables between baseline and the worst on-study value will be provided according to visual toxicity grades for unilateral and bilateral cases.

9.6.4 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time. The number and percentage of subjects with abnormal changes in **select** laboratory endpoints will be summarized for the Safety Analysis Set.

Shift tables between baseline and the worst on-study value in select laboratory **will be performed. Lab parameters will be evaluated in the increasing and/or decreasing direction. The parameters** will be provided according to the NCI CTCAE toxicity grades and the unscheduled assessments will be included in the shift tables.

9.6.5 Vital Signs

The number and percentage of subjects with abnormal changes in systolic blood pressure, diastolic blood pressure, heart rate, **respiration rate,** body temperature **and oxygen saturation** will be summarized at baseline for the Safety Analysis Set. In addition, minimum post-baseline and maximum post-baseline values will be summarized using descriptive statistics.

9.6.6 Physical Measurements

Physical measurements including height, weight and BSA will be summarized at baseline using descriptive statistics. In addition, minimum post-baseline and maximum post-baseline weight will be summarized using descriptive statistics.

9.6.7 Electrocardiogram

In Part 1, 2 **and 4**, the ECG measurements will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

In Part 3, **summaries over time and/or changes from baseline over time will be provided for all ECG parameters with descriptive statistics**. In addition, the maximum post-baseline and maximum change from baseline in QT interval, **QTcF interval, QTcB interval** will be categorized and the number and percentage of subjects in each group will be summarized. ECG data **may** be listed and select parameters may be plotted.

9.6.8 Antibody Formation

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

9.6.9 Exposure to Investigational Product

The number of days on investigational product, the total dose of investigational product, and dose intensity will be summarized using descriptive statistics.

Descriptive statistics will be produced to describe the exposure to IP by cohort. The number of cycles of protocol-specified therapy administered will be summarized. In addition, the duration of therapy in weeks, the cumulative dose, , actual dose intensity and relative dose intensity will be summarized. The number and percent of subjects with

dose modifications (e.g., dose change/withheld, dose delay or dose interruptions) and reason for modification will be summarized.

List of manufacturing lot number will be provided.

9.6.10 Exposure to Non-investigational Product

The exposure to non-IP will be summarized in a similar way to the summary of the exposure to IP.

List of manufacturing lot number will be provided for Amgen supplied non-IP.

9.6.11 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications from Study Day 1 will be summarized **by ATC text and** by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary. The number and proportion of subjects receiving concomitant medications of interest will be summarized **by ATC text and by preferred term** for each cohort.

9.7 Other Analyses

Other analyses in the study include analyses for PK and biomarker endpoints, which may be specified in separate analysis plans.

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Nominal sampling times will be used for individual concentration-time plots and tables. Actual dose administered, and actual sampling times will be used for the calculation of PK parameters for each subject. Bemarituzumab serum concentrations with values below the lower limit of quantification will be set to zero for analysis. The reasons for excluding any sample from the analyses will be provided.

Individual concentration-time data will be tabulated and presented graphically. Summary of PK concentration over time and PK parameters will be provided. Mean concentration-time profiles for each dose will be provided.

PK parameters will include AUC, maximum observed concentration (C_{max}), and observed concentration at the end of a dose interval (C_{trough}) for bemarituzumab.

For Bema, PK parameters will be determined from the time concentration profile using the current version of Phoenix WinNonlin based on the PK Analysis Set. PK parameters will be summarized using descriptive statistics including, but not limited to means, standard deviations, medians, minimums, and maximums.

Based on review of the data, analyses to describe the relationship between bemarituzumab exposure and either pharmacodynamic effect and/or clinical outcome may also be performed.

Above analyses will be conducted by Amgen CPMS.

9.7.2 Analyses of Clinical Outcome Assessments

Not applicable

9.7.3 Analyses of Health Economic Endpoints

Not applicable

[redacted]

9.7.5 Analysis of COVID-19 Impact

The following summaries to assess the impact of COVID-19 may be provided:

- Listing of all subjects impacted by COVID-19 related study disruptions

- Subject incidence of IPD and non-important protocol deviation due to COVID-19 control measures by protocol deviation category, which may include:
  - alternative IP administration process
  - alternative lab/imaging data process
  - alternative site visits
  - alternative procedures or methods not included in original study design and not identified
  - missed/partial missed visits
  - missed IP/non-IP
  - early end of study
  - early end of treatment with IP and non-IP
  - early end of safety follow-up
- Subject incidence of COVID-19 related dose change/withheld

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Brookmeyer R and Crowley J. A Confidence Interval for the Median Survival Time. *Biometrics.* 2984;38:29-41.

Clopper CJ and Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika.* 1934;26:404-413.

Guo W, Wang S-J, Yang S, et al. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. *Contemp Clin Trials*. 2017;58:23-33.

Kalbfleisch, J.D. and Prentice, R.L. (1980) The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons.

12. Prioritization of Analyses

Not applicable

13. Data Not Covered by This Plan

Pharmacokinetic, pharmacodynamic, exposure-response and biomarker analyses will be performed by Clinical Pharmacology, Modeling and Simulation (CPMS) or Clinical Biomarker & Diagnostics (CBD). Further analysis of clinical outcome assessments may be provided in a separate Supplemental Statistical Analysis Plan (SSAP).

14. Appendices

Appendix A Handling of Date, Incomplete Date and Missing Dates

A1. Imputation Rules for Partial or Missing Start Dates for Concomitant Medications and Adverse Events

The reference date for the following rules is the date of first dose IP (non-IP if a subject never took IP)

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	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 or first day of year if month is also missing.

A2. Imputation Rules for Partial Diagnosis or Procedure Date (Medical History)

- If the month and year are present, impute the first day of that month.
- If only the year is present, impute January 1 of that year.
- If the date is entirely missing, do not impute.

A3. Imputation Rules for Partial or Missing Stop Dates (Medical History, Concomitant Medications, Adverse Events)

Initial imputation

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.

- If the stop date is entirely missing, assume the event or medication is ongoing.

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the death date, impute as death date.

If the imputed stop date is after the end of study date, impute as the end of study date.

A4. Imputation Rules for Partial or Missing Death Dates

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

- If yyyymm for the **derived** date last known to be alive equals yyyymm for death date, set death date to the day after the **derived** date last known to be alive.
- If yyyymm for the **derived** date last known to be alive is less than the yyyymm for death date, set death date to the first day of the death month.
- If yyyymm for the **derived** date last known to be alive is greater than yyyymm for death date, assume **the derived** date last known to be alive is in error, set death date to the first day of the death month; **leave derived date last known to be alive as is.**

If month and day are missing and year of death is known:

- If yyyy for the **derived** date last known to be alive equals yyyy for death date, set death date to the **derived** day after last known to be alive date.
- If yyyy for the **derived** date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.
- If yyyy for the **derived** date last known to be alive is greater than yyyy for death date, assume **the derived** date last known to be alive is in error, set death date to the first day of the death year; **leave derived date last known to be alive as is.**

If a death date is totally missing:

Set death date to the day after the derived date last known to be alive.

Appendix B. Analytical Windows

Analytical Windows for **Ophthalmology exams** are shown below. If more than one visit falls within the same defined window, the visit closets to the target day will be considered for analysis. If two assessment dates are the same distance from the target day, then the latest visit will be considered for analysis.

Analysis windows for **Ophthalmology Exams** (except for retinal exams)

Week	Target Day	Study Day Window Start	Study Day Window End	Window Length (Days)
Baseline	1	-28	1	30
6	43	2	64	63
12	85	65	106	42
18	127	107	148	42
24	169	149	197	49
32	225	198	253	56
40	281	254	309	56
48	337	310	365	56
56	393	366	421	56
64	449	422	477	56
72	505	478	533	56
80	561	534	589	56
88	617	590	645	56
96	673	646	701	56
104	729	702	757	56
112	785	758		
. .				
Week x	**x*7+1**	**Week [x-8] Study Day Window End + 1**	**Min(Last dose date of IP + 42, Week [x-8] Study Day Window End + 1 + 55)**	**(Study Day Window End - Study Day Window Start) + 1**
Safety follow-up	**Last dose date of IP/non-IP + 28**	**Last dose date of IP/non-IP + 1**	**Last dose date of IP/non-IP + 31**	**31**

Analysis windows for Retinal Exams

Week	Target Day	Study Day Window Start	Study Day Window End	Window Length (Days)
Baseline	1	-28	1	30
12	85	2	127	126
24	169	128	225	98
40	281	226	337	112
56	393	338	449	112
72	505	450	561	112
88	617	562	673	112
104	729	674		
. .				
Week x	**x*7+1**	**Week [x-16] Study Day Window End + 1**	**Min(Last dose date of IP + 42, Week [x-16] Study Day Window End + 1 + 111)**	**(Study Day Window End - Study Day Window Start) + 1**
Safety follow-up	**Last dose date of IP/non-IP + 28**	**Last dose date of IP/non-IP + 1**	**Last dose date of IP/non-IP + 31**	**31**