STATISTICAL ANALYSIS PLAN

STUDY TITLE: A RANDOMIZED, MULTICENTER, PHASE Ib/III STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF ATEZOLIZUMAB SUBCUTANEOUS COMPARED WITH ATEZOLIZUMAB INTRAVENOUS IN PATIENTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

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STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 2, 26 October 2020.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
3	See electronic date stamp on the last page of this document.	Version 6, 25 February 2022
2	25 March 2022	Version 6, 25 February 2022
1	10 November 2021	Version 5, 10 February 2021

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) for Study BP40657 (IMscin001) has been amended to incorporate the following changes.

- The name of Population PK analysis set has been changed to PK evaluable set.

- Minor updates have been made to the definition of Per Protocol PK population and PK evaluable population to improve clarity.

- Confirmed duration of response evaluable population has been added to the analysis set in Section 4.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	Anti-drug antibodies
AE	Adverse event
$AUC_{0-21 d}$	Area under the concentration-time curve from 0 to 21 days
CCOD	Clinical cutoff date
C-DOR	Confirmed Duration of response
CI	Confidence interval
CIT	Cancer immunotherapy
CSR	Clinical Study Report
C_{trough}	Trough plasma concentration
CTSQ	Cancer Therapy Satisfaction Questionnaire
CV	Co-efficient of variation
DOR	Duration of response
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
ER	Exposure-response
GMR	Geometric mean ratio
HCP	Health care professional
HR	Hazard ratio
ICE	Intercurrent event
ICH	International Council on Harmonization
IL57	Interleukin 57
IRF	Independent Review Facility
IV	Intravenous
IxRS	Interactive voice/web-based response system
JMC	Joint monitoring committee
Ln	Natural logarithm
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMPA	National Medical Products Administration
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
popPK	Population pharmacokinetics
PRO	Patient-reported outcomes

Abbreviation or Term	Description
PK	Pharmacokinetic
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SWT	Satisfaction with therapy

1.   INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Part 2 (Dose Confirmation) of Study BP40657 (hereinafter IMscin001). The data in Part 1 of the study was analyzed on an ongoing basis to inform and justify the dose selection, site of administration for subsequent cohorts, and for the Part 2 dose thus will not be in scope of this SAP. The analysis for Part 1 was performed previously (Data Memo submitted to the FDA for dose justification) and will be reported in the CSR. For detailed background information on the study, refer to Protocol Section 1.

1.1   OBJECTIVES AND ENDPOINTS ESTIMANDS

This study will evaluate the pharmacokinetics, safety, and efficacy of atezolizumab subcutaneous (SC) compared with atezolizumab intravenous (IV) in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not been exposed to cancer immunotherapy (CIT) (i.e., "CIT-naive") and for whom prior platinum- based therapy has failed. The study is comprised of two parts, as follows:

- Part 1 (Phase Ib, dose finding) will aim to identify the dose of atezolizumab SC that yields drug exposure that is comparable to that of atezolizumab IV

- Part 2 (Phase III, randomized, dose confirmation) will aim to demonstrate the non-inferiority of observed drug exposure following treatment with atezolizumab SC at the identified dose compared with drug exposure following treatment with atezolizumab IV

Definitions used in Part 2 of this study are outlined in Table 1.

Specific objectives for Part 2 of the study and corresponding endpoints are outlined in Table 2.

Table 1   Study Definitions

Atezolizumab	Atezolizumab monoclonal antibody as a molecule, irrespective of its formulation
Atezolizumab SC	Ready-to-use SC formulation of atezolizumab co-formulated with 2,000 U/mL rHuPH20
Atezolizumab IV	Currently approved formulation of atezolizumab for IV infusion in its 1200 mg vial configuration

IV = intravenous; SC = subcutaneous.

Table 2   Objectives and Corresponding Endpoints

Primary Pharmacokinetic Objectives	Corresponding Endpoint(s)
The primary PK objective for Part 2 is to demonstrate non-inferiority of exposure to atezolizumab SC compared with atezolizumab IV based on the corresponding co-primary endpoints.	• Observed serum C_{trough} at Cycle 1 (predose Cycle 2) • Model-predicted area under the concentration-time curve (AUC) from 0 to 21 days ($AUC_{0-21 d}$) at Cycle 1

Following the estimand framework introduced in the ICH-E9 addendum (ICH 2020), the estimand for the primary analysis follows a principal stratum strategy based on the following attributes:

Definition of Co-Primary Estimand 1:

o **Population:** Patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed. The analysis population will consist of the Per Protocol PK population, with patients grouped according to their received treatment.

o **Variable:** The Cycle 1 observed serum C_{trough} (predose Cycle 2), using the measured concentration from the PK sample.

o **Treatment:** Atezolizumab IV or atezolizumab SC, at the determined dose at baseline. All randomized patients are expected to receive the baseline infusion or SC injection.

o **Intercurrent Events and Handling Strategy:**

o **Premature discontinuation from treatment:** Every effort will be made to ensure all randomized patients will receive the treatment at baseline and will have the PK sample collected appropriately. Treatment will start within 5 days of randomization. Withdrawal after randomization, prior to baseline treatment is not expected. In case of such an event, those patients are excluded from the analysis population and those patients will not be replaced.

o **Premature discontinuation from study:** Some patients could discontinue the study prior to the time point of predose Cycle 2 due to death or other reasons. Considering the short interval between randomization and Cycle 2, this situation is expected to be exceptional. Those patients are excluded from the population.

o **Missing or outside of window PK samples:** Some patients could have a Cycle 1 C_{trough} PK sample missing or outside of the accepted window, due to early withdrawal or other reasons. Every effort will be made to collect PK samples on schedule. Those patients are excluded from the analysis population.

Summary measure: Geometric mean ratio (GMR) and 90% CI of atezolizumab SC versus atezolizumab IV of Cycle 1 C_{trough}. The non-inferiority would be established if the lower bound of the 90% CI is ≥ 0.8.

Definition of Co-Primary Estimand 2:

o **Population:** Patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed. The analysis population will consist of the PK Evaluable population, with patients grouped according to their received treatments.

o **Variable:** Model-predicted Cycle 1 $AUC_{0-21\,d}$ derived from the popPK model.

o **Treatment:** same as for co-primary endpoint Cycle 1 observed serum C_{trough}

o **Intercurrent Events and Handling Strategy:**

   o **Absence of post-treatment PK blood sample:** Some patients could discontinue the study following their Cycle 1 dose prior to providing a post-baseline PK blood sample or PK blood samples could not be collected. Considering the short interval between the first study drug treatment (Cycle 1) and the first PK blood sample (8+/- 2 hours) as well as the numerous PK blood samples collected on study, these situations are expected to be exceptional. Those patients are excluded from the analysis population.

   o **Premature discontinuation from treatment:** Every effort will be made to ensure all randomized patients will receive the study drug treatment and corresponding PK sample collected. Treatment will start within 5 days of randomization. Withdrawal after randomization, prior to baseline treatment is not expected. In case of such an event, those patients are excluded from the analysis population and those patients will not be replaced

   o **Missing or inaccurate time and date reported for treatment administration or PK blood samples:** Every effort will be made to ensure all randomized patients will receive the treatment and will have the time and date of dosing and PK blood samples reported accurately. Missing or inaccurate dosing time and date can occur during any cycle however, it is very rare. In case of such an event, only such affected samples are excluded, and patients are retained as long as they have a single reportable dose and corresponding PK sample, regardless of the cycle.

o **Summary measure:** GMR and 90% CI of atezolizumab SC versus atezolizumab IV of Cycle 1 model predicted AUC_{0-21d}. The non-inferiority would be established if the lower bound of the 90% CI is ≥0.8.

Secondary Pharmacokinetic Objectives	Corresponding Endpoints
The secondary PK objectives for Part 2 are to descriptively compare between atezolizumab SC and IV based on:	• Model-predicted C_{trough} at Cycle 1 ($C_{trough\ Cycle\ 1}$) • Model-predicted C_{trough} at steady state ($C_{trough,ss}$) • Model-predicted AUC at steady state (AUC_{ss})
Secondary Safety Objective	**Corresponding Endpoints**

A secondary objective for Part 2 is to evaluate the safety of atezolizumab SC compared with atezolizumab IV based on the following endpoints:	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Overall patient-reported adverse event burden over time, as assessed by the patient global impression of cancer treatment side effects burden item from the European Organization for Research and Treatment of Cancer (EORTC) IL57
Secondary Efficacy Objectives	**Corresponding Endpoints**
A secondary objective for Part 2 is to evaluate the efficacy of atezolizumab SC compared with atezolizumab IV based on the following endpoints:	• ORR, defined as the proportion of patients with a complete response (CR) or partial response (PR), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) • PFS, defined as the time from study entry to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • OS, defined as the time from study entry to death from any cause • Duration of response (DOR), defined as the time from first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1

| Secondary Patient Reported Outcome (PRO) Objective	Corresponding Endpoints
An additional secondary objective for Part 2 is to evaluate patient experience with atezolizumab SC compared with atezolizumab IV based on the following endpoints:	• Functioning and global health status over time, as assessed by the physical functioning, role functioning, and global health status/quality of life scales of the EORTC IL57 • Overall satisfaction with treatment over time, as assessed by the modified satisfaction with therapy (SWT) scale of the Cancer Therapy Satisfaction Questionnaire (CTSQ)
Secondary Immunogenicity Objective	**Corresponding Endpoints**
A secondary objective for Part 2 is to evaluate the incidence of ADAs to the tested molecules based on the following endpoints:	• Incidence of ADAs to atezolizumab after SC administration or IV administration relative to the prevalence of ADAs at baseline • Incidence of ADAs to rHuPH20 after SC administration relative to the prevalence of ADAs at baseline
Exploratory Pharmacokinetic Objective	**Corresponding Endpoint**
The exploratory PK objective for Part 2 is to descriptively compare between atezolizumab SC and IV based on:	• Exploratory exposure–response analyses may be performed to link atezolizumab exposure (e.g., C_{trough}, C_{max}, and AUC Cycle 1) to safety (Grade 3–5 adverse events, adverse events of special interest) and efficacy (ORR and OS) endpoints.
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
An exploratory objective for Part 2 is to evaluate potential effects of ADAs based on the following endpoint:	• Relationship between post-baseline ADA status and PK, safety, or efficacy endpoints

Exploratory Biomarker Objective	Corresponding Endpoint
The exploratory biomarker objective for Part 2 is to evaluate biomarkers that may be predictive of response to atezolizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab, can provide evidence of atezolizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology. They will be evaluated based on the following endpoint:	• Relationship between biomarkers in tumor tissue (listed in Protocol Section 4.5.7) and efficacy, or other biomarker endpoints

Health Care Professional-Reported Experience Utility Objective	Corresponding Endpoints
The secondary utility objective for Part 2 is to evaluate health care professional (HCP)-reported experience with administration of atezolizumab SC and atezolizumab IV, based on the following endpoints:	• Convenience, potential time savings, and overall satisfaction with atezolizumab SC compared with atezolizumab IV, as assessed by the HCP SC versus IV Perspective Questionnaire • Convenience, ease of administration, and overall satisfaction with atezolizumab SC, as assessed by the HCP Subcutaneous Perspective Questionnaire

ADA = anti-drug antibodies; AUC$_{ss}$ = area under the curve at steady state; AUC 0-21 d = area under the time-concentration curve from 0 to 21 days; C$_{trough}$ = trough plasma concentration; CI = confidence interval; CIT = Cancer immunotherapy; CSR = Clinical Study Report; EORTC = European Organization for Research and Treatment of Cancer; GMR = geometric mean ratio; IV = intravenous; IL57 = Interleukin-57; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; popPK = population pharmacokinetics; PK = pharmacokinetic; SC = subcutaneous

1.2 STUDY DESIGN

The study schema for Part 2 is shown in Figure 1.

Figure 1 Study Schema
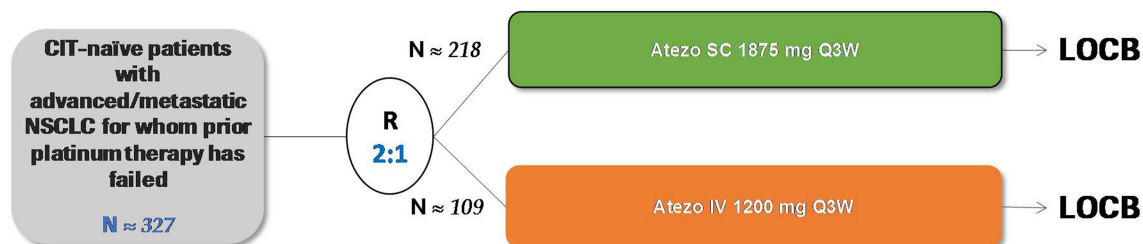
LOCB = loss of clinical benefit; NSCLC = non-small cell lung cancer; Q3W = every three weeks; R = randomization; CIT = Cancer immunotherapy; IV = intravenous

Part 2 will be initiated once a dose has been identified based on the cumulative data collected from Part 1 (see Section 3.3.1 of the Protocol). In Part 2, patients will be randomized in a 2:1 ratio to receive monotherapy with either 1875 mg of atezolizumab SC Q3W or 1200 mg of atezolizumab IV Q3W, respectively, starting on Day 1 of each 21-day cycle.

Part 2 of this study will initially enroll approximately 327 participants (later increased to ~355, see Appendix 1) across approximately 150 sites in a global enrollment phase. For further details on study design, refer to Protocol Section 3.

1.2.1 Treatment Assignment and Blinding

This is an open-label study. Patients should receive their first dose of study drug the day of randomization for Part 2, if possible. If this is not possible, the first dose should occur within 5 days after randomization.

Patients in Part 2 will be randomly assigned to one of two treatment arms: atezolizumab SC or atezolizumab IV. Randomization will occur in a 2:1 ratio using a permuted-block randomization method to ensure more patients are assigned to the SC arm. Although Part 2 is open-label, Sponsor's standard operating procedures for blinding and unblinding will be followed.

To ensure a patient population representative of standard clinical practice, the Sponsor will periodically evaluate the prevalence of *epidermal growth factor receptor* (*EGFR*) mutation and limit the number of patients with *EGFR*-positive mutation to a maximum of approximately 10% of all randomized patients if required.

1.2.2 Independent Review Facility

Not applicable.

1.2.3   Data Monitoring

A Joint Monitoring Committee (JMC) will be convened to evaluate safety data and PK for formulation comparability and sample size consideration during Part 2 of the study. The JMC will be composed of internal and external members; further details on the composition, roles and responsibilities, and meeting schedule of the JMC are documented in the JMC charter.

2.   STATISTICAL HYPOTHESES

The primary objective of Part 2 is to demonstrate non-inferiority of the PK of atezolizumab SC compared with atezolizumab IV based on two co-primary endpoints, Cycle 1 observed serum trough plasma concentration (C_{trough}) (predose Cycle 2) and model-predicted area under the time-concentration curve from 0 to 21 days ($AUC_{0-21\,d}$).

A statistical hypothesis test will be performed on the GMR of C_{trough} following SC administration ($C_{trough,SC}$) to C_{trough} following IV administration ($C_{trough,IV}$), both values taken from data observed in Cycle 1: $C_{trough,SC}/C_{trough,IV}$.

The null and alternative hypotheses will be as follows:

- *H_0: The SC dose is inferior to the IV dose with a non-inferiority margin less than 0.8 (i.e., the geometric mean ratio (GMR) $C_{trough,SC}/C_{trough,IV}$ is less than 0.8), versus*

- *H_1: The SC dose is non-inferior to the IV dose (i.e., the GMR $C_{trough,SC}/C_{trough,IV}$ is equal or greater than 0.8).*

Model-predicted $AUC_{0-21\,d}$ in Cycle 1 is the other co-primary endpoint used for the primary objective of Part 2. The model-predicted AUC in Cycle 1 after atezolizumab SC administration will be compared with the model-predicted $AUC_{0-21\,d}$ in Cycle 1 after IV administration.

A statistical hypothesis test will be performed on the GMR of $AUC_{0-21\,d}$ following SC administration ($AUC_{0-21d,SC}$) to IV administration ($AUC_{0-21\,d,IV}$), both values taken from data predicted in Cycle 1: $AUC_{0-21\,d,\,SC}/AUC_{0-21\,d,\,IV}$.

The null and alternative hypotheses will be as follows:

- *H_0: The SC dose is inferior to the IV dose with a non-inferiority margin less than 0.8 (i.e., the GMR $AUC_{0-21\,d,\,SC}/AUC_{0-21\,d,\,IV}$ is less than 0.8), versus*

- *H_1: The SC dose is non-inferior to the IV dose (i.e., the GMR $AUC_{0-21\,d,\,SC}/AUC_{0-21\,d,\,IV}$ is equal to or greater than 0.8)*

2.1 MULTIPLICITY ADJUSTMENT

Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted $AUC_{0-21 d}$ will be tested using the Hochberg procedure (Hochberg and Tamhane 1987; FDA 2017). In step 1 of this procedure, if the lower bounds of the 90% CI for both the GMR $C_{trough,SC}/C_{trough,IV}$ and the GMR $AUC_{0-21 d, SC}/AUC_{0-21 d, IV}$ are ≥ 0.8, both null hypotheses will be rejected. In this case, it will be concluded that SC administration is non-inferior to IV administration in terms of C_{trough} and AUC in Cycle 1.

If in Step 1 the null hypotheses are not rejected, the procedure continues to Step 2. In Step 2, if the 95% CI for one GMR (i.e., either $C_{trough,SC}/C_{trough,IV}$ or $AUC_{0-21 d, SC}/AUC_{0-21 d, IV}$) is ≥ 0.8, the corresponding null hypothesis will be rejected. In this case, it will be concluded that SC administration is non-inferior to IV administration in terms of C_{trough} or AUC in Cycle 1.

3. <u>SAMPLE SIZE DETERMINATION</u>

A total of ~327 patients (later increased to ~355, see Appendix 1) were planned to be randomized in Part 2 of the study. This sample size will provide sufficient power for the statistical hypothesis test for the co-primary endpoints, based on the following assumptions:

- 2:1 randomization ratio
- True GMR ≥ 0.95 for Cycle 1 C_{trough}
- True GMR ≥ 0.95 for Cycle 1 AUC_{0-21d}
- One-sided significance level 0.05
- Coefficient of variation (CV%) of geometric mean C_{trough} in Cycle 1 is $< 55\%$; this value is based on the results observed after atezolizumab SC co-mix administration in Part 1 of the study (Clinical cutoff date[CCOD] 10 March 2020)
- CV% of geometric mean Cycle 1 AUC_{0-21d} is $< 45\%$; this value is based on the results observed after atezolizumab SC co-mix administration in Part 1 of the study (CCOD 10 March 2020)
- Positive correlation between Cycle 1 AUC_{0-21d} and Cycle 1 $C_{trough} > 0.8$; this value is based on the results observed after atezolizumab SC co-mix administration in Part 1 of the study (CCOD 10 March 2020)

Under these assumptions, a sample size of ≥ 261 pharmacokinetic (PK)-evaluable patients in the atezolizumab SC and atezolizumab IV arms would provide at least 80% power to conclude non-inferiority of Cycle 1 $C_{trough,SC}$ and $AUC_{0-21 d, SC}$ with a non- inferiority margin of 0.8 for the GMR, or more concisely: $C_{trough,SC} > 0.8\ C_{trough,IV}$ and $AUC_{0-21 d, SC} > 0.8\ AUC_{0-21 d, IV}$ (see Table 3).

It is expected that up to 20% of randomized patients will need to be excluded from the Per Protocol PK population. The total number of 327 patients was chosen to ensure the

Per Protocol PK population will be large enough to meet the primary study objective and to assess comparable safety and efficacy data.

The total number of patients to be enrolled in Part 2 of the study was planned to be either increased or decreased, after taking into account the actually observed PK variability during the blinded sample-size re-estimation (once approximately 210−250 patients have been randomized). For example, for a coefficient of variation of 70% for Cycle 1 C_{trough}, the number of patients enrolled in Part 2 would be increased to 477 in order to ensure sufficient power for the non-inferiority test (see Table 3).

Table 3 Statistical Power of Test of Non-Inferiority of C_{trough} and AUC_{0-21d}

Coefficient of Variation for Cycle 1 C_{trough}	PK-Evaluable Patients	Probability to reject the null hypothesis for both co-primary endpoints	Estimated Required Randomized Patients [a]
50%	234	80%	293
55%	**261**	**80%**	**327**
60%	297	80%	372
65%	336	80%	420
70%	381	80%	477

[a] Assuming up to 20% not PK-evaluable.

After conducting the blinded estimation of the CV% and of the remaining parameters used in the initial sample size as planned, the highest CV% observed was around 55% while the rate of not PK-evaluable patients was higher as compared to the initial assumption (24% vs 20%). As a consequence of this change in the initial assumption, a larger number of randomized patients was required than initially planned to ensure 80% power for both hypotheses test. Hence, the Sponsor decided to increase the sample size to approximately 355. The details of this calculation are summarized in Appendix 1

4.   ANALYSIS SETS

The following analysis sets are defined for the analysis of Part 2:

Population	Definition
Per Protocol PK evaluable	All patients randomized to the atezolizumab SC and atezolizumab IV treatment arms who do not have protocol deviations[a] that could affect Cycle 1 observed C_{trough} results.
PK evaluable	All patients randomized to the atezolizumab SC and atezolizumab IV treatment arms with at least one post-baseline PK sample.
Full Analysis Set (FAS)	All patients who were randomized, with patients grouped according to their assigned treatment.
Response evaluable	All patients included in the FAS and with measurable disease at baseline.
Duration of Response (DOR) evaluable	All patients with a measurable disease at baseline and with a post-baseline objective response.
Confirmed Duration of Response (C-DOR) evaluable	All patients with a measurable disease at baseline and with a post-baseline confirmed objective response.
Safety evaluable	All randomized patients who received at least one dose of protocol treatment.
Post-treatment ADA evaluable	All randomized patients who have received at least one dose of protocol treatment and have at least one post- treatment ADA result.

ADA = anti-drug antibodies; IV = intravenous; SC = subcutaneous; PK = pharmacokinetic.

[a] Reasons for exclusion from the Per Protocol PK-evaluable may include, but may not be limited to:

- lack of the Cycle 1 C_{trough} (predose Cycle 2) PK sample,
- a C_{trough} sample collected outside the pre-specified window (day 21 +/- 2 days),
- administration of a dose amount that deviates from the planned dose by >20% at Cycle 1,
- use of an injection site other than the thigh at Cycle 1,
- duplicate times of collection for the Cycle 1 C_{trough} sample.

5. STATISTICAL ANALYSES

The analyses outlined in this SAP supersede those specified in Protocol Version 6, 25 February 2022 or thereafter.

The data in Part 1 of the study was analyzed on an ongoing basis to inform the dose selection for subsequent cohorts, and for Part 2. The analysis for Part 1 may be found in the Data Memo submitted to the FDA for dose justification.

In Part 2, the analysis of the co-primary endpoints, Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted $AUC_{0-21\ d}$, will be performed when the planned number of patients has been randomized and the last required data point has

been reported. The cutoff for the primary analysis will therefore be approximately one month after randomizing the last patient in Part 2. Analyses of available data on secondary and exploratory endpoints up to this time point will also be presented.

After that, patients will continue to be followed until the end of the study, approximately 33 months after randomizing the last patient in the global enrollment phase, or when all patients have discontinued from the study, whichever occurs first. An additional analysis will be performed at the end of study to evaluate the longer-term efficacy and safety data for atezolizumab SC.

5.1   GENERAL CONSIDERATION

Part 2 primary and secondary PK analyses will be performed on the Per Protocol PK- evaluable and/or PK evaluable analysis set, as appropriate, and according to the actual treatment received by patients, unless otherwise specified. All Part 2 efficacy analyses will be performed on the Full Analysis Set and according to the treatment assigned at randomization by interactive voice/web-based response system (IxRS), unless otherwise specified. All safety analyses will be performed in the safety-evaluable population and according to the actual treatment received by patients, unless otherwise specified.

5.2   PARTICIPANT DISPOSITION

A detailed study disposition of participants including the number/percentage of participants who have completed the study vs. number/percentage of participants who have prematurely withdrawn from the study, as well as the primary reasons for withdrawal will be summarized overall by treatment arm. Additionally, a summary table of survival follow-up period for participants remaining in the study until the time of final overall survival will be provided, for the Full Analysis Set.

5.3   CO-PRIMARY ENDPOINTS ANALYSIS

The primary comparisons of interest are the geometric mean ratios (GMR) and confidence intervals of PK parameters for atezolizumab SC versus atezolizumab IV. The PK objective for Part 2 is to demonstrate non-inferiority of exposure to atezolizumab SC compared with atezolizumab IV based on the following co-primary endpoints:

- Observed serum C_{trough} at Cycle 1 (predose Cycle 2)
- Model-predicted area under the concentration-time curve (AUC) from 0 to 21 days ($AUC_{0-21\ d}$) at Cycle 1

5.3.1   Definition of Co-Primary Endpoints

Following the estimand framework introduced in the ICH-E9 addendum (ICH 2020), the estimand for the primary analysis follows a principal stratum strategy based on the following attributes:

<u>**Co-Primary Estimand 1:**</u>

o **Population:** Patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed. The analysis population will consist of the Per Protocol PK population, with patients grouped according to their received treatment.

o **Variable:** The Cycle 1 observed serum C_{trough} (predose Cycle 2), using the measured concentration from the PK sample.

o **Treatment:** Atezolizumab IV versus atezolizumab SC, at the determined dose at baseline. All randomized patients are expected to receive the baseline infusion or injection.

o **Intercurrent Events and Handling Strategy:**

   ▪ **Premature discontinuation from treatment:** Every effort will be made to ensure all randomized patients will receive the treatment at baseline and will have the PK sample collected appropriately. Treatment will start within 5 days of randomization. Withdrawal after randomization, prior to baseline treatment is not expected. In case of such an event, those patients are excluded from the analysis population and those patients will not be replaced.

   ▪ **Premature discontinuation from study:** Some patients could discontinue the study prior to the time point of predose Cycle 2 due to death or other reasons. Considering the short interval between randomization and Cycle 2, this situation is expected to be exceptional. Those patients are excluded from the population.

   ▪ **Missing or outside of window PK samples:** Some patients could have a Cycle 1 C_{trough} PK sample missing or outside of the accepted window, due to early withdrawal or other reasons. Every effort will be made to collect PK samples on schedule. Those patients are excluded from the analysis population.

o **Summary measure:** Geometric mean ratio (GMR) and 90% CI of atezolizumab SC versus atezolizumab IV of Cycle 1 C_{trough}. The non-inferiority would be established if the lower bound of the 90% CI is ≥0.8.

<u>**Co-Primary Estimand 2:**</u>

o **Population:** Patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed. The analysis population will consist of thePK Evaluable population, with patients grouped according to their received treatments.

o **Variable:** Model-predicted Cycle 1 $AUC_{0-21\,d}$ derived from the popPK model.

o **Treatment:** same as for co-primary endpoint Cycle 1 observed serum C_{trough}

o **Intercurrent Events and Handling Strategy:**

   ▪ **Absence of post-treatment PK blood sample:** Some patients could discontinue the study following their Cycle 1 dose prior to providing a post-

baseline PK blood sample or PK blood samples could not be collected. Considering the short interval between the first study drug treatment (Cycle 1) and the first PK blood sample (8+/- 2 hours) as well as the numerous PK blood samples collected on study, these situations are expected to be exceptional. Those patients are excluded from the analysis population.

- **Premature discontinuation from treatment:** Every effort will be made to ensure all randomized patients will receive the study drug treatment and corresponding PK sample collected. Treatment will start within 5 days of randomization. Withdrawal after randomization, prior to baseline treatment is not expected. In case of such an event, those patients are excluded from the analysis population and those patients will not be replaced

- **Missing or inaccurate time and date reported for treatment administration or PK blood samples:** Every effort will be made to ensure all randomized patients will receive the treatment and will have the time and date of dosing and PK blood samples reported accurately. Missing or inaccurate dosing time and date can occur during any cycle however, it is very rare. In case of such an event, only such affected samples are excluded, and patients are retained as long as they have a single reportable dose and corresponding PK sample, regardless of the cycle.

o **Summary measure:** GMR and 90% CI of atezolizumab SC versus atezolizumab IV of Cycle 1 model predicted AUC_{0-21d}. The non-inferiority would be established if the lower bound of the 90% CI is ≥0.8.

5.3.2 Main Analytical Approach for Co-Primary Endpoints

The primary analysis of C_{trough} will be based on logarithmic values of observed C_{trough} in Cycle 1 to compensate the known skewness of its distribution. For natural logarithm (Ln) trough plasma concentration (C_{trough}), the statistical hypothesis will be tested using an analysis of covariance model

$$Ln(C_{trough})_{ij} = \mu + \tau_i + \varepsilon_{ij} \quad (i=SC, IV; j=1, 2, …, n_i)$$

where μ denotes the overall mean, τ_i the effect of atezolizumab route of administration i (SC or IV), n_i the number of patients in arm i (SC or IV), and ε_{ij} a random error variable assumed to be independently and identically normally distributed with mean zero and variance σ_ε^2.

The contrast $\tau_{SC} - \tau_{IV}$, its 90% confidence limits, and the variance σ_ε^2 will be estimated from the model. An estimate of the treatment effects ratio and the corresponding 90% confidence limits for the untransformed variables will be calculated by exponentiation of the estimate of contrast $\tau_{SC} - \tau_{IV}$ and the 90% confidence limits. The CV for the untransformed primary variable will be estimated using the relationship $CV_\varepsilon = sqrt(exp(\sigma_\varepsilon^2)-1)$.

If the lower confidence interval bound of $exp(Ln[C_{trough,SC}]-Ln[C_{trough,IV}])=C_{trough,SC}/C_{trough,IV}$ is equal or greater than 0.8, then the null hypothesis can be rejected (see Section 2).

The model-predicted Cycle 1 $AUC_{0-21\,d}$ is a co-primary endpoint and will be analyzed using the same method as for the other co-primary endpoint, Cycle 1 observed serum C_{trough}.

The co-primary endpoints will be statistically tested at the same α level (one-sided significance level of 0.05) using the Hochberg procedure as described in Section 2.1.

5.3.3 Supplementary Analysis for Co-Primary Endpoints

A supplementary sensitivity analysis may be conducted on Cycle 1 C_{trough} values derived from the popPK model. The aim of using predicted C_{trough} is to take into account possible deviations from the protocol (i.e., sampling schedule or dosing interval) and to reduce noise (i.e., precision of analytical measurement).

The Cycle 1 C_{trough} values derived from the popPK model is a different estimand with respect to the observed serum C_{trough}. The attributes such as treatment and summary measure have the same definition as the primary endpoint (C_{trough}), while the population and intercurrent events will be defined and handled using the same approach and strategies specified for the model-predicted Cycle 1 AUC.

5.4 SECONDARY ENDPOINTS ANALYSES

The following secondary endpoints will be analyzed outside of a hypothesis-testing framework and according to the methodology provided below.

5.4.1 PK Analyses

For secondary PK and popPK analyses, the PK evaluable population will be used. Model- predicted C_{trough} at Cycle 1 (C_{trough} Cycle 1), model-predicted C_{trough} at steady state ($C_{trough,ss}$), and model-predicted AUC at steady state (AUC_{ss}) will be descriptively compared between atezolizumab SC and IV.

The PK data will be analyzed using statistical summary measures, listings, and graphs as appropriate, documented in more detail in a Clinical Pharmacology Analysis Plan (2022), and also reported in a standalone PK report.

5.4.2 Efficacy Analyses

The Response-evaluable population will be used for key secondary endpoint analysis of objective response rate (ORR) whilst a subset who achieved objective response, will be used for duration of response (DOR). The Full Analysis Set will be used for key secondary endpoint analyses such as progression-free survival (PFS) and overall survival (OS). The analysis mentioned below will be performed at the time of primary

analysis and at the end of the study. However, efficacy endpoints at the time of primary analysis given the nature of the trial and extremely small follow-up time will be immature. Therefore, for the primary analysis, secondary endpoints will be descriptively compared between atezolizumab SC and IV, followed by more formal analysis in the final report, which will include more follow-up time.

5.4.2.1 Objective Response Rate

The analysis population for ORR will be the Response-evaluable population. Patients not meeting the criteria for ORR, including patients without any post baseline tumor assessment, will be considered non-responders.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population**: All randomized patients with measurable disease at baseline included in the Response-evaluable population.

- **Variable**: ORR, defined as the proportion of patients with a CR or PR, as determined by the investigator according to RECIST v1.1.

- **Treatment**: As defined for the primary estimand

- **Intercurrent events and Handling Strategy**:

  o Use of any non-protocol anti-cancer treatment (NPT) prior to disease progression as detailed in Protocol Section 4.4.3.

  o Discontinuation of study treatment prior to disease progression

  o **ICE Handling Strategy:** Following treatment policy, all the ICE's will be ignored, and tumor assessment data collected after the ICE will be included in the ORR analysis.

- **Population-level summary:** Difference in proportion.

The ORR and 95% confidence intervals according to Clopper-Pearson will be calculated and presented by treatment arm. For the difference in response rates, 95% two-sided confidence intervals (Hauck-Anderson) will be calculated. The above analysis will be repeated as apart of sensitivity analysis for confirmed ORR (CR or PR on two consecutive occasions $\geq$ 28 days apart, as determined by the investigator according to RECIST v1.1.)

5.4.2.2 Progression-Free Survival

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population**: All randomized patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed.

- **Variable**: PFS, defined as the time from the date of study entry to the date of documented disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever is earlier.

- **Treatment**: As defined for the primary estimand.
- **Intercurrent events and Handling Strategy**:
  - Use of any non-protocol anti-cancer treatment (NPT) prior to disease progression as detailed in Protocol Section 4.4.3.
  - Discontinuation of study treatment prior to disease progression
  - **ICE Handling Strategy:** Following treatment policy, all the ICE's will be ignored, and observations collected after the ICE will be included in the PFS analysis.
- **Population-level summary:** Median duration and corresponding 95% CI.

If participants have any intercurrent event(s), then the strategies defined above to handle the intercurrent events will be implemented. Otherwise, data for participants without the occurrence of disease progression or death as of the clinical cutoff date (CCOD) will be censored at the time of the last tumor assessment prior to the CCOD (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit). PFS will be analyzed using Kaplan-Meier methodology, including survival plots, median duration and corresponding 95% confidence intervals according to the Brookmeyer- Crowley method (Brookmeyer and Crowley, Biometrics 1982).
The proportion of patients who are PFS event-free at 6 and 12 months after study entry will be estimated at the final analysis of the study when sufficient follow-up data are available. The corresponding 95% CI will be calculated using the standard error derived from Greenwood's formula. The hazard ratio (HR), and 95% CI for descriptive comparison will be estimated using a Cox regression model.

At the time of final analysis, additional sensitivity analyses of PFS may be conducted as appropriate in order to investigate the effect of baseline characteristics imbalances (if any) on the result.

5.4.2.3   Overall Survival

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population**: All randomized patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed.
- **Variable**: OS, defined as the time from randomization to death from any cause
- **Treatment**: As defined for the primary estimand
- **Intercurrent events and Handling Strategy**:
  - Use of any non-protocol anti-cancer treatment (NPT) prior to disease progression as detailed in Protocol Section 4.4.3.
  - Discontinuation of study treatment prior to disease progression

- o **ICE Handling Strategy**: Following treatment policy, all the ICE's will be ignored, and observations collected after the ICE will be included in the OS analysis.

- **Population-level summary:** Median duration and corresponding 95% CI.

If participants have any intercurrent events, then the strategies defined above to handle the intercurrent events will be implemented. Otherwise, data for patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of randomization plus 1 day. OS will be analyzed using Kaplan-Meier methodology, including survival plots, median duration and corresponding 95% confidence intervals according to the Brookmeyer- Crowley method
(Brookmeyer and Crowley, Biometrics 1982). The proportion of patients alive at one and two years after study entry will be estimated at the final analysis of the study when sufficient follow-up data are available. The corresponding 95% CI will be calculated using the standard error derived from Greenwood's formula. The hazard ratio (HR), and 95% CI for descriptive comparison will be estimated using a Cox regression model.

At the time of final analysis, additional sensitivity analyses of OS may be conducted as appropriate in order to investigate the effect of baseline characteristics imbalances (if any) on the result.

5.4.2.4   Duration of Response

Analysis of DOR will include only patients who had an objective response. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population**: All patients with a measurable disease at baseline and a post-baseline objective response.

- **Variable**: DOR, defined as the time interval from the date of the first occurrence of a complete or partial response (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first.

- **Treatment**: As defined for the primary estimand

- **Intercurrent events and Handling Strategy**:

  - o Use of any non-protocol anti-cancer treatment (NPT) prior to disease progression as detailed in Protocol Section 4.4.3.

  - o Discontinuation of study treatment prior to disease progression

- o **ICE Handling Strategy:** Following treatment policy, all the ICE's will be ignored and observations collected after the ICE will be included in the DOR analysis.

- **Population-level summary:** Median duration and corresponding 95% CI.

DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis. The HR and 95% CI for descriptive comparison will be estimated using a Cox regression model.

The above analysis will be repeated for confirmed objective response as defined in Section 5.4.2.1, above.

5.4.3 Patient Reported Outcomes

An additional secondary objective for Part 2 is to evaluate patient experience with atezolizumab SC compared with atezolizumab IV, based on the following endpoints:

- Functioning and global health status over time, as assessed by the physical functioning, role functioning, and global health status/quality of life scales of the EORTC interleukin 57 (IL57)

- Overall satisfaction with treatment, as assessed by the modified satisfaction with therapy (SWT) scale of the Cancer Therapy Satisfaction Questionnaire (CTSQ)

Descriptive analyses, including summary statistics, will be performed, and presented by treatment arm for each patient-reported experience measure (item- and scale-level, as appropriate). Item-level analyses will include frequencies and proportions and change from baseline at each visit by treatment arm. Summary statistics (e.g., mean, median, minimum, maximum, interquartile range) of scale scores and score changes from baseline at each visit will be evaluated by treatment arm.

For each of the EORTC scales, a prorated scale score will be calculated if 50% or more of the constituent items in the scale are completed. The scale score will be considered missing if < 50% of the constituent items were not completed. A SWT scale score will be calculated if five or more items have been completed (out of seven). The scale score will be considered missing if fewer than five items have been completed.

PRO completion, compliance rates, and reasons for missing data will be summarized at each time point by treatment arm for each measure in full analysis set. The compliance rate will be based on the total number of patients expected to complete the questionnaire at a particular time point.

5.4.4 Safety Analysis

A secondary objective for Part 2 is to evaluate the safety of atezolizumab SC compared with atezolizumab IV on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0

- Overall patient-reported adverse event burden over time, as assessed by the patient global impression of cancer treatment side effects burden item from the European Organization for Research and Treatment of Cancer (EORTC) IL57

The safety analysis population will consist of all patients who received at least one dose of study drug and will be grouped according to actual treatment received.

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. Laboratory toxicities will be defined based on local laboratory normal ranges and NCI CTCAE, v5.0.

Overall patient-reported adverse event burden over time, as assessed by the patient global impression of cancer treatment side effects burden item from the European Organization for Research and Treatment of Cancer (EORTC) IL57 will be summarized descriptively, as described in Section 5.4.3.

5.4.5 Immunogenicity Analyses

A secondary objective for Part 2 is to evaluate the incidence of anti-drug antibodies (ADAs) to the tested molecules on the basis of the following endpoint:

- Incidence of ADAs to atezolizumab after SC administration or IV administration relative to the prevalence of ADAs at baseline

- Incidence of ADAs to rHuPH20 after SC administration relative to the prevalence of ADAs at baseline

The atezolizumab and rHuPH20 Post-treatment ADA-evaluable population will consist of all patients with at least one post-treatment ADA assessment. Patients will be grouped according to treatment received. Baseline prevalence will be summarized according to treatment received for all Safety-evaluable patients.

The number and proportion of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized for ADA-evaluable patients. When determining post-baseline incidence, patients are considered to be ADA-positive if they are ADA-negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be post-treatment ADA-negative if they are ADA-negative or have missing data at

baseline and all post-baseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

Demographic and baseline characteristics in ADA-evaluable patients will be summarized by treatment arm (as appropriate).

5.5 EXPLORATORY ENDPOINTS ANALYSIS

5.5.1 Exploratory PK Analysis

Exploratory exposure–response analyses may be performed to link atezolizumab exposure (e.g., C_{trough}, C_{max}, and AUC Cycle 1) to safety and efficacy endpoints. These analyses will be reported separately from the clinical study report (CSR).

5.5.2 Exploratory Immunogenicity Analysis

The exploratory immunogenicity objective for Part 2 is to evaluate potential effects of ADAs based on the following endpoint:

- Relationship between post-baseline ADA status and PK, safety, or efficacy endpoints

5.5.3 Exploratory Biomarker Analysis

The exploratory biomarker objective for Part 2 is to evaluate biomarkers that may be predictive of response to atezolizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab, can provide evidence of atezolizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology. They will be evaluated based on the following endpoint:

- Relationship between biomarkers in tumor tissue (listed in the Protocol Section 4.5.7) and efficacy, or other biomarker endpoints

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies, and reported separately from the primary CSR.

5.6 OTHER SAFETY ANALYSES

5.6.1 Extent of Exposure

The number of patients who experience a dose delay, dose interruption, dose discontinuation, and reasons for the study treatment discontinuation will be summarized by treatment arm. Descriptive statistics will be presented for number of cycles received, total cumulative dose, dose intensity, and weeks of exposure.

5.6.2 Adverse Events

Verbatim descriptions of treatment-emergent AEs will be mapped to MedDRA thesaurus terms and graded according to the NCI CTCAE v5.0. All treatment-emergent adverse events (events occurring on or after the first study drug treatment up to the data cutoff date) will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade and treatment arm. In addition, common adverse events serious adverse events, severe adverse events (Grade $\geq$ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized. Multiple occurrences of the same event will be counted once at the maximum severity.

All deaths reported during the study treatment period and those reported during the follow-up period after treatment completion or discontinuation and the causes of death will be summarized by treatment arm.

5.6.3 Laboratory Data

Clinical laboratory tests will be performed at local laboratories. Laboratory abnormalities will be defined based on local laboratory normal ranges and NCI CTCAE v5.0. Select laboratory abnormalities such as worst toxicity grade and toxicity grade shift from baseline will be summarized by treatment arm. Relevant change from baseline will be summarized by treatment arm.

Patients who meet Hy's law criteria will be listed and summarized by treatment arm.

5.6.4 Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate, and body temperature) and physical measurements (including body weight and height) recorded before administration of the study treatment will be listed and summarized with changes from baseline. Vital signs collected at unscheduled visits will be excluded from the summary table. The mean, standard deviation, median, and minimum and maximum values will be presented by treatment arm. A table of clinically significant abnormal values by time and by treatment arm will also be presented, as well as, a shift table from baseline versus worst post-baseline value will be presented by treatment arm.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

The number of patients randomized in part 2 of the study, discontinue from the study, or complete the study will be summarized. Reasons for patient discontinuations from the study treatment and from the study will be presented in listings and summary tables. Protocol deviations will be evaluated for their potential effects on the interpretation of study results, and reasons for exclusion of patients from the analyses will be presented.

5.7.2 Summaries of Treatment Group Comparability

The evaluation of treatment group comparability between the two treatment arms will include summaries of demographics and baseline characteristics, medical history, and concomitant medications.

Demographic and baseline characteristics will be summarized using descriptive statistics (e.g., means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate). Summaries will be presented by treatment arm.

Baseline will be defined as the last available assessment prior to study entry. Study entry is defined as the date they were enrolled into the study according to the IxRS.

5.7.3 Health Care Professional Reported Experience

Descriptive summaries for each item in the HCP questionnaire will be presented by country or region and by other categories, as appropriate, for all HCPs who completed at least one question in a questionnaire.

5.7.4 Analyses of Subgroups of Interest

In Part 2, data on secondary endpoints may be analyzed in patient subgroups by, e.g., demographic or baseline prognostic characteristics. These analyses will be performed in an exploratory manner.

5.7.5 Analyses of China Subpopulation

The China subpopulation will include all patients randomized at qualified sites in China. Data for the China subpopulation may be analyzed descriptively as appropriate using the same statistical methods as described in Section 5. No formal statistical analysis on the co-primary endpoints will be performed for China subpopulation. Results from these analyses may be summarized in a separate Clinical Study Report addendum.

6. SUPPORTING DOCUMENTATION

For Synopsis, Schedule of assessments, PRO forms, etc. refer to study protocol.

Appendix 1   Re-estimation of Study Sample Size

A total of 327 patients were initially planned to be randomized in Part 2 of the study. This sample size would provide sufficient power for the statistical hypothesis test for the co-primary endpoints, based on the assumptions detailed in Section 3 of the SAP.

The study protocol stated that the total number of patients to be enrolled in Part 2 of the study might be increased or decreased after comparing the values assumed for sample size calculations (CV for observed C_{trough} and model-predicted AUC, correlation between both co-primary endpoints and percentage of randomized patients not evaluable for the PK co-primary endpoints) with the values actually observed in a blinded sample-size re- estimation planned to be conducted after approximately 210−250 patients have been randomized.

This blinded estimation of PK parameters was provided by an external vendor when a total of 256 patients were randomized, 197 of whom had completed the 1st Cycle and had PK data available at the Clinical Cut-Off Date (CCOD) of November 1st, 2021. The PK-evaluable population (subset of randomized patients with PK data and no major protocol deviation) included 150 patients. The following blinded summary data was shared by external vendor, and was utilized for sample size estimation:

- Highest Coefficient of variation (CV%) of geometric mean observed Cycle 1 C_{trough} in any treatment arms: 56.8%;
- Highest CV% of geometric mean model-predicted Cycle 1 AUC_{0-21d} in any treatment arms: 39.8%;
- Positive correlation between Cycle 1 AUC_{0-21d} and Cycle 1 C_{trough}: 0.787;
- PK-unevaluable rate: 23.9%

Under the same assumptions made in the original sample size calculation and replacing the expected CV's(%) and correlation between PK endpoints with the observed values reported above, it was estimated that a total sample size of ≥ 270 pharmacokinetic (PK) evaluable patients would provide at least 80% power to conclude non-inferiority of Cycle 1 observed $C_{trough,SC}$ and model-predicted $AUC_{0-21\ d,\ SC}$ with a non-inferiority margin of 0.8 for the GMR, or more concisely: $C_{trough,SC} > 0.8\ C_{trough,IV}$ and $AUC_{0-21\ d,\ SC} > 0.8\ AUC_{0-21\ d,\ IV}$.

Further, to account for the increase in PK-unevaluable dropout rate (20% initially assumed vs. 23.9% observed (including missing samples)) in the blinded review, the minimum sample size needed for this study was increased to 355 patients. Following the process described in Joint Monitoring Committee (JMC) charter (The Joint Monitoring Committee Agreement, 14 July 2021) this decision to increase the sample size was discussed in the JMC meeting on 09 February 2022 and the JMC approval to increase the sample size was documented and archived in TMF.

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The Joint Monitoring Committee Agreement for Study BP40657, 14 July 2021.

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