Official Title: A Randomized, Multicenter, Open-Label Cross-Over Study to Evaluate Participant and Healthcare Professional Reported Preference for Subcutaneous Atezolizumab Compared with Intravenous Atezolizumab Formulation in Participants with Non-Small Cell Lung Cancer

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PARTICIPANT AND HEALTHCARE PROFESSIONAL REPORTED PREFERENCE FOR SUBCUTANEOUS ATEZOLIZUMAB COMPARED WITH INTRAVENOUS ATEZOLIZUMAB FORMULATION IN PARTICIPANTS WITH NON-SMALL CELL LUNG CANCER**
STUDY NUMBER:	MO43576
STUDY NAME:	IMscin002
VERSION NUMBER:	1.0
ROCHE COMPOUND:	Atezolizumab (RO5541267)
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PLAN PREPARED BY:	[redacted], MSc; [redacted], MSc

STATISTICAL ANALYSIS PLAN APPROVAL

See electronic signature on the final page of this document.

SPONSOR: **LEGAL REGISTERED ADDRESS:**	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp on the last page of this document.

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This statistical analysis plan (SAP) was developed based on Roche SAP model document v2.0 (26 October 2020).

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	See electronic date stamp on the last page of this document.	Version 3, 7 March 2023

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
CI	confidence interval
COVID	coronavirus disease
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organization for the Research and Treatment of Cancer
FAS	Full Analysis Set
HCP	healthcare professional
HRQoL	health-related quality of life
ICH	International Council on Harmonization
IV	intravenous
IxRS	interactive voice/web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small cell lung cancer
PPQ	patient preference questionnaire
PRO	patient-reported outcomes
PK	pharmacokinetic
SAE	serious adverse events
SAP	Statistical Analysis Plan
SC	subcutaneous
TASQ-IV	Therapy Administration Satisfaction Questionnaire - intravenous
TASQ-SC	Therapy Administration Satisfaction Questionnaire - subcutaneous
ULN	upper limit of normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study MO43576 (IMscin002), a randomized, multicenter, open-label cross-over study to evaluate participant and healthcare professional (HCP) reported preference for subcutaneous (SC) atezolizumab compared with intravenous (IV) atezolizumab formulation in participants with non-small cell lung cancer (NSCLC). More detailed background information for the study can be found in the protocol.

1.1 OBJECTIVES, ENDPOINTS AND ESTIMANDS

This study will evaluate participant- and HCP-reported preference for atezolizumab SC compared with atezolizumab IV in patients with resected Stage II, IIIA, and selected IIIB (T3-N2) NSCLC who have completed adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence, and chemotherapy-naive participants with Stage IV NSCLC.

The primary study objective and corresponding endpoint is expressed using the estimand framework in Table 1, in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020).

Table 1 Primary Objective and Corresponding Estimands

Primary Objective	Estimand Definition
• Evaluate participant preference for atezolizumab SC compared with atezolizumab IV	Estimand components for the endpoint: • Population: Patients with resected Stage II, IIIA, and selected IIIB (T3–N2) NSCLC who have completed adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence, and chemotherapy-naive participants with Stage IV NSCLC • Variable: Question 1 of the Patient Preference Questionnaire (PPQ) on Cycle 6 Day 1 or after at least two consecutive administrations of each treatment in case of treatment discontinuation before Cycle 6 Day 1 • Treatments: o Atezolizumab 1875 mg subcutaneous injection every 3 weeks and o Atezolizumab 1200 mg intravenous infusion every 3 weeks irrespective of the treatment sequence • Intercurrent events and handling strategies: o Death prior to providing an answer to Question 1 of the PPQ: patients will be excluded from the analysis population o Early discontinuation of study treatment prior to providing an answer to Question 1 of the PPQ: patients will be excluded from the analysis population o Patients who never received any study treatment: patients will be excluded from the analysis population • Population-level summary: Proportion of patients preferring the SC administration, over the total number of patients with non-missing data

Supplementary estimand: • Evaluate participant preference for atezolizumab SC compared with atezolizumab IV	Estimand components for the endpoint: • Population: Patients with resected Stage II, IIIA, and selected IIIB (T3–N2) NSCLC who have completed adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence, and chemotherapy-naive participants with Stage IV NSCLC • Variable: Question 1 of the Patient Preference Questionnaire (PPQ) on Cycle 6 Day 1 or after at least one administration of each treatment in case of treatment discontinuation before Cycle 6 Day 1 • Treatments: o Atezolizumab 1875 mg subcutaneous injection every 3 weeks and o Atezolizumab 1200 mg intravenous infusion every 3 weeks irrespective of the treatment sequence • Intercurrent events and handling strategies: o Death prior to providing an answer to Question 1 of the PPQ: patients will be excluded from the analysis population o Early discontinuation of study treatment prior to providing an answer to Question 1 of the PPQ: patients will be excluded from the analysis population o Patients who never received any study treatment: patients will be excluded from the analysis population • Population-level summary: Proportion of patients preferring the SC administration, over the total number of patients with non-missing data

Specific objectives not expressed in an estimand framework and corresponding endpoints for the study are outlined in Table 2.

Table 2 Other Secondary/Exploratory Objectives and Corresponding Endpoints

Secondary Objectives	Corresponding Endpoints
• Evaluate participant-reported satisfaction with atezolizumab SC and atezolizumab IV	• Question 1 of the Therapy Administration Satisfaction Questionnaire (TASQ) SC or TASQ IV on Day 1 of Cycle 3 or Cycle 6 depending on the arm
• Evaluate participants' choice of atezolizumab SC for the treatment continuation period	• Selection of atezolizumab SC for the treatment continuation period
• Evaluate HCP perception of time/resource use and convenience for administration with atezolizumab SC and IV	• HCP responses to the Healthcare Professional Questionnaires (HCPQs), by individual question
• Evaluate HRQoL with atezolizumab SC and atezolizumab IV	• Change in symptoms and function from baseline and over time as assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) scores

	• Mean and mean changes from baseline score in HRQoL by cycle as assessed by the Global Health Status/Quality of Life (GHS/QoL) scale (items 29 and 30) of the EORTC QLQ-C30
• Monitor the ongoing clinical benefit of atezolizumab	• Proportion of participants with continuing clinical benefit after 16 cycles of atezolizumab, as assessed by the investigator according to local standard of care
Safety Objectives	**Corresponding Endpoints**
• Evaluate the overall safety and tolerability of atezolizumab SC and atezolizumab IV	• Incidence, severity, and nature of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0) • Safety laboratory values • Vital signs • ECG
• Evaluate the safety of switching from atezolizumab SC to atezolizumab IV and from atezolizumab IV to atezolizumab SC	• Incidence, severity, and nature of adverse events, with severity determined according to NCI CTCAE v5.0 during the study Treatment Cross-over Period by treatment arm • Safety laboratory values during the study Treatment Cross-over Period by treatment arm • Vital signs during the study Treatment Cross-over Period by treatment arm • ECG during the study Treatment Cross-over Period by treatment arm
Exploratory Pharmacokinetic Objective	**Corresponding Endpoint**
• Characterize the exposure of atezolizumab when given intravenously or subcutaneously	• Serum atezolizumab concentration at specified timepoints during SC and IV administration
Exploratory Immunogenicity Objective	**Corresponding Endpoints**
• Evaluate the immune response to atezolizumab	• Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline and incidence of ADAs to atezolizumab after initiation of study treatment • Evaluation of safety and PK by ADA status
Health Status Utility Objective	**Corresponding Endpoint**
• Evaluate health status utility scores of participants treated with atezolizumab SC compared with atezolizumab IV	• Change from baseline over time in EuroQol EQ-5D-5L index-based and visual analogue scale (VAS) scores

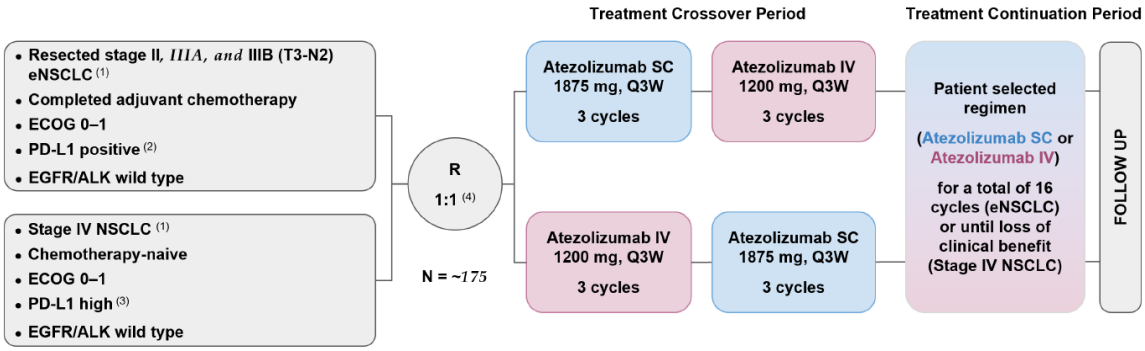
ADA = anti-drug antibody; ECG = electrocardiogram; HRQoL = health-related quality of life; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SC = subcutaneous; TASQ = Therapy Administration Satisfaction Questionnaire.

1.2 STUDY DESIGN

This is a Phase II, randomized, multi-center, multinational, open-label, cross-over study in adult participants with PD-L1–positive NSCLC.

The study will evaluate participant- and HCP-reported preference for atezolizumab SC compared with atezolizumab IV.

Figure 1 Study Schema



eNSCLC = early non-small cell lung cancer; IV = intravenous; PD-L1 = programmed death-ligand 1; Q3W = every 3 weeks; R = randomization; SC = subcutaneous; TC = tumor cells; TPS = tumor proportion score.

(1) Histological or cytological diagnosis per UICC/AJCC staging system, 8th Ed.

(2) PD-L1 positive defined as minimum TC ≥ 1% by VENTANA PD-L1 (SP263) IHC assay or TPS ≥ 1% by Dako PD-L1 IHC 22C3 pharmDx assay performed by a local or central laboratory.

(3) PD-L1 high defined as minimum TC ≥ 50% by VENTANA PD-L1 (SP263) IHC assay, minimum TPS ≥ 50% by Dako PD-L1 IHC 22C3 pharmDx assay, or TC3 or IC3 by VENTANA PD-L1 (SP142) IHC assay, performed by a local or central laboratory.

(4) Stratification: disease stage and type of surgery.

Two populations will be included: participants with resected Stage II, IIIA and selected IIIB (T3-N2) NSCLC who have completed adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence, and chemotherapy-naive participants with Stage IV NSCLC.

Participants whose tumors have an EGFR mutation or ALK rearrangement will be excluded from enrolment. Participants with tumors of non-squamous histology with unknown EGFR or ALK mutational status will be required to be tested at prescreening/screening centrally if the local test cannot be done or does not meet the required criteria.

Eligibility will be assessed within a 28-day screening period. A pre-screening period will be available for those participants who need to assess their eligibility in terms of PD-L1 expression, EGFR mutation, or ALK rearrangement.

Participants who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion, provided all initial and subsequent screening assessments are performed within 56 days prior to Day 1. Re-screened participants must meet all eligibility criteria and re-sign the Informed Consent Form prior to re-screening. The investigator will record reasons for screen failure.

Participants must have PD-L1-positive or high NSCLC to be enrolled in the study. Participants that do not have prior PD-L1 testing will be prospectively tested for PD-L1 expression by central testing at prescreening/screening.

Participants will undergo a tumor assessment at baseline to confirm eligibility criteria. Subsequent tumor assessments will be conducted as per local standard of care.

Participants with Early-Stage NSCLC

Eligible participants with early-stage NSCLC will have had a complete resection of NSCLC and must be adequately recovered from surgery and adjuvant chemotherapy. Prior to treatment with adjuvant atezolizumab, all participants should have received up to four cycles of adjuvant platinum-based chemotherapy, with no evidence of disease relapse/recurrence.

Chemotherapy-Naive Participants with Stage IV NSCLC

Participants with Stage IV NSCLC will be eligible to join the study if they have not received prior chemotherapy for advanced NSCLC and satisfy the eligibility criteria described.

1.2.1 Treatment Assignment

This is a randomized, open-label study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from the interactive voice or web-based response system (IxRS).

Participants will be randomly assigned to one of two treatment arms: Arm A (atezolizumab SC followed by atezolizumab IV) or Arm B (atezolizumab IV followed by atezolizumab SC). Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by disease stage (II, III, IV) and type of surgery (no surgery, pneumonectomy, any other lung surgery).

1.2.2 Independent Review Facility

No Independent Review Facility (IRF) will be used for this study.

1.2.3 Data Monitoring

No data monitoring will be conducted for this study.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The primary objective for this study is to evaluate participant- and HCP-reported preference for atezolizumab SC compared with atezolizumab IV.

There will be no formal hypothesis test for the primary endpoint.

2.2 SAMPLE SIZE DETERMINATION

The planned total sample size of 175 participants is based on an assumed rate of 70% of participants preferring atezolizumab SC compared with atezolizumab IV. To achieve a distance of approximately ±8% from the estimated proportion to 95% CI limits, a total of 126 participants are needed for the evaluation of preference. The final target sample size will be increased to approximately 175 participants to allow for 28% of the participants not providing an evaluable preference assessment.

Approximately 175 participants from approximately 40–50 study sites worldwide will be randomized in the study. Up to one-third of the study population will comprise chemotherapy-naive participants with Stage IV NSCLC; this proportion may be increased if sufficient participants with early-stage NSCLC are not recruited. Participants who withdraw from the study following randomization will not be replaced.

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 3.

Table 3 Participant Analysis Sets

Participant Analysis Set	Definition
Full Analysis Set (FAS)	All randomized participants.
Safety-Evaluable	All participants who received at least one dose of study treatment.
PK-Evaluable	All participants who received at least one dose of study treatment and had at least one post-baseline quantifiable PK sample available.
ADA-Evaluable	All randomized patients who have received at least one dose of study treatment and have at least one post-treatment ADA result.

ADA = anti-drug antibody; IxRS = interactive voice or web-based response system; PK = pharmacokinetic.

4. STATISTICAL ANALYSES

The analyses described in this SAP will supersede those specified in the Protocol Version 3, 7 March 2023 or thereafter.

4.1 GENERAL CONSIDERATIONS

The primary analysis will take place when all study participants have completed their last study treatment administration in the Treatment Cross-over Period. Summaries of secondary study endpoints, including PK and ADA measurements, participant-reported TASQ and EORTC QLQ-C30 responses, selection of treatment administration method for the Treatment Continuation Period, HCP reported HCPQ responses, and safety endpoints will be included in the primary analysis, based on all data up to the clinical cut-off date.

The final study analysis that includes all secondary endpoints including all questionnaires, PK, ADA, and safety endpoints will be conducted after the end of the study (i.e., when all patients have received 16 cycles of atezolizumab or discontinued study treatment).

Summaries of participants' preference, analysis of PROs, including the primary endpoint, HCP reported outcomes and clinical benefit, as well as sensitivity analysis for preference and satisfaction, will be based on the FAS, according to the treatment sequence assigned.

All safety analyses will be performed in the safety-evaluable population, unless otherwise specified. Participants will be analyzed according to the treatment they actually received. In case of protocol deviations leading to a treatment sequence with more than one treatment switch, participants will be analyzed according to the treatment sequence assigned.

Continuous variables will be summarized by the mean, standard deviation, median and range (minimum and maximum). Categorical variables will be summarized by number/percentage of participants.

Unless otherwise stated, baseline values are the last available data obtained prior to the patient receiving the first dose of study treatment (or at screening, for patients who were not treated).

4.2 PRIMARY OBJECTIVE

Analysis will be done for all patients and, as a part of exploratory analysis when applicable, separately among participants with early-stage NSCLC and chemotherapy-naive participants with Stage IV NSCLC.

The primary objective of this study is to evaluate participant preference for atezolizumab SC based on the proportion of participants indicating an overall preference for atezolizumab SC compared with atezolizumab IV in Question 1 of the PPQ. Question 1 of the PPQ is as follows: "All things considered, which route of administration did you prefer?".

4.2.1 Definition of Primary Estimand

The evaluation of participant preference for atezolizumab SC compared with atezolizumab IV will be analyzed as defined in Table 1 of Section 1.1 of the SAP.

4.2.2 Main Analytical Approach for Primary Estimand

Patient preference will be summarized and presented by overall and by randomized treatment sequence using FAS. As stated in Table 1, for intercurrent events such as patients who died, early discontinued from treatment or never received any study treatment, as well as patients lost to follow-up prior to providing an answer to Question 1 of the PPQ will be excluded from the analysis. Responses to Question 1 of the PPQ collected before at least two consecutive administrations of treatment, with each treatment administration route, were received by the patient will not be included in the analysis.

Patient preference will be summarized by presenting the number and proportion of patients in each category (SC, IV and No preference). A point estimate with associated exact Clopper-Pearson binomial 95% CI for the proportion of patients who preferred atezolizumab SC will be calculated and will be displayed by randomized treatment sequence and overall.

4.2.3 Supplementary Estimand

An analysis will be done for the evaluation of participant preference for atezolizumab SC compared with atezolizumab IV based on the FAS. All the attributes are similar to the primary estimand except the variable attribute where now patients who discontinued earlier to the study treatment but received at least one dose of each treatment route will be analyzed (cf. Table 1). Patients who died, never received any treatment or are lost to follow-up prior to providing an answer to Question 1 of the PPQ will be excluded from the analysis.

4.2.4 Subgroup Analyses for the Primary Objective

As a part of exploratory analysis, patient preference will also be summarized by presenting the number and proportion of patients in each category (SC, IV and No preference) by stratification factors: disease stage (II, III, IV) and type of surgery (no surgery, pneumonectomy, any other lung surgery) according to Table 1.

4.2.5 Secondary Endpoints Analyses

4.2.6 Patient responses to questions of the TASQ-SC and TASQ-IV

The TASQ is a 12-item questionnaire measuring the impact of the mode of treatment administration on five domains: Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction. The Physical Impact domain comprises of 3 items (Q2: Pain experience, Q3: Swelling experience, Q4: Redness experience), the Psychological Impact domain contains one item (Q5: Feeling restricted by SC injection/IV infusion), The Impact on Activities of Daily Living contains one item (Q8: Lost/gained time), The Convenience domain contains 2 items (Q6: Is it convenient to get SC injection/IV infusion, Q7: Bothered by the amount of time to get SC injection/IV infusion), and the Satisfaction domain includes 2 items (Q1: How satisfied or dissatisfied are you with the SC injection/IV infusion, Q12: Would you recommend the way you received the treatment). All 9 TASQ items included in the above domains have five response options:

- Reverse-coded response values will be created for eight of the TASQ items (Q1, Q2, Q3, Q4, Q5, Q6, Q7 and Q12)

In addition, there are three questions in the TASQ (Q9, Q10, Q11) that are not part of the above domains. These three questions will be analyzed separately and presented descriptively.

Participant assessed satisfaction with atezolizumab SC and atezolizumab IV will be based on participant responses to Question 1 of the TASQ-SC and TASQ-IV respectively.

The patient satisfaction will be described by randomized treatment sequence and overall, as a categorical variable with the number and proportion of patient responses to each modality of the question (very satisfied, satisfied, …, very dissatisfied).

In addition, responses of the TASQ-SC and TASQ-IV will be summarized by domain (physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction).

For the three domains that contain more than one item (Physical Impact, Convenience and Satisfaction), the algorithm will be the following:

If there are no missing responses, the domain will be scored using the formula:

$$Domain\ Score = \frac{\left[\frac{Sum\ of\ completed\ item\ response}{\text{Number of completed items}} - 1\right] \times 100}{\text{Max possible item response value} - \text{Min possible item response value}}$$

However, if there are any missing responses within a domain then the domain will not be scored (i.e., a missing value is assigned to the domain).

Since the maximum possible item response value is 5 and the minimum possible response value is 1 for all TASQ items, a simpler way to represent the above formula for the TASQ domains is:

$$TASQ\ Domain\ Score = [\text{Mean of completed item responses} - 1] \times 25$$

Descriptive statistics will be computed for these three domains by randomized treatment sequence and overall.

The two domains that contain only one item (Psychological Impact and Impact on Activities of Daily Living) will be described by randomized treatment sequence and overall, in the same way as the patient satisfaction in Question 1: first as a categorical variable with the number and proportion of patient responses to each modality of the question, and secondly as a continuous variable with descriptive statistics.

The three descriptive questions (Q9, Q10, Q11) that are not part of the above domains will be summarized individually by the number and proportion of patient responses to each modality of the question.

The proportion of responses will be based on the number of patients who answered the respective question. All TASQ analyses will be performed on the FAS. The analysis will be done for all patients and as an exploratory analysis, as applicable, separately among participants with early-stage NSCLC and chemotherapy-naive participants with Stage IV NSCLC.

4.2.7 Patient's Choice of Treatment for the Treatment Continuation Period

The number and proportion of patients who select each treatment administration route for the Treatment Continuation Period will be summarized on the FAS. Results will be displayed by randomized treatment sequence and overall. The proportion of responses will be based on the number of patients who started the treatment continuation period.

A consistency table with answer to question 1 of the PPQ will also be provided by randomized treatment sequence and overall. For each patient's preference category as per the question 1 of the PPQ (SC, IV and No preference), the number and percentage of patients who select each treatment administration route for the Treatment Continuation Period (SC, IV) will be summarized. The percentage of patients will be based on the number of patients who answered both PPQ question 1 and patient's choice of treatment for the treatment continuation period.

4.2.8 EORTC QLQ-C30

EORTC data will be analyzed based on the FAS, unless specified otherwise.

Summary statistics (mean, standard deviation, median, and range) of linearly transformed absolute scores and mean changes from baseline will be calculated for all

items and subscales (treatment-related symptoms and function, Global Health Status/HRQoL) of the EORTC QLQ-C30 at each assessment timepoint for each randomized treatment arm.

The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers et al. 2001). Missing data will be reported by timepoint. In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale will be considered as missing. PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by randomized treatment arm on the FAS.

4.2.9 Healthcare Professional Questionnaire (HCPQ)

Healthcare professional perception of time/resource use and convenience with atezolizumab SC will be assessed by summarizing responses to individual questions of the HCPQs on the FAS by randomized treatment sequence and overall.
The percentage of responses will be based on the number of respondents in the respective questionnaire. HCPQ will also be summarized by each healthcare professional specialty.

Healthcare Professional Questionnaire-Treatment Room

The number of HCPQs completed, the specialties of Healthcare Professional Respondents (Nurse, Pharmacy Technician, Oncologist, Gynaecologist) will be summarized overall.

Experience with atezolizumab SC injection and atezolizumab IV infusion administration

Responses to individual questions will be summarized by cycle and stratified by route of drug administration.

Impact on Clinical Management and Clinical Efficiency

Responses to individual questions 2 to 8 will be summarized overall.

Healthcare Professional Questionnaire-Drug Preparation Room

The number of HCPQs completed and the specialties of Healthcare Professional Respondents (Nurse, Pharmacist, Pharmacy Technician) will be summarized overall.

Experience with atezolizumab SC and atezolizumab IV infusion Dispensing and Preparation

Response to the question 1b "How long did it take to prepare the treatment for use?" will be summarized by cycle and stratified by route of drug administration (question 1a).

Impact on Clinical Management and Clinical Efficiency

Responses to individual questions 2 to 4 will be summarized overall.

4.2.10 Clinical Benefit after 16 Cycles

The number and percentage of participants with continuing clinical benefit after 16 cycles of atezolizumab will be summarized as per Table 2 in Section 1.1 of the SAP. Patients who did not yet reach Cycle 16 but are still ongoing at the time of the analysis will be excluded. Similarly, patients who did not receive any treatment will be excluded from the analysis. Patients who discontinued or died before Cycle 16 will be considered as having no ongoing clinical benefit.

This analysis will be based on the FAS. In addition, as a part of exploratory analysis, the analysis may also be stratified by disease stage at study entry.

4.3 SAFETY ANALYSES

Unless specified otherwise, safety analyses described below will be conducted for the safety-evaluable population.

For safety analyses, 2 treatment periods will be defined. Within the cross-over treatment period, 2 subperiods may also be used for the analysis, when appropriate.

- **Cross-over period:** maximum of 6 cycles of Atezolizumab, SC (maximum 3 cycles) and IV (maximum 3 cycles). The cross-over period consists of 2 subperiods:
  - Cycle 1 to Cycle 3
  - Cycle 4 to Cycle 6
- **Continuation period:** for patients who completed the cross-over period, the continuation period will consist of additional cycles of Atezolizumab IV or SC, up to a total of 16 cycles for early NSCLC or until loss of clinical benefit for Stage IV NSCLC.

4.3.1 Extent of Exposure

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized by treatment period and by treatment sequence (IV/SC, SC/IV) in the cross-over, as well as by treatment route (IV, SC) in the continuation period.

The total number of cycles initiated will be summarized both by descriptive statistics and by presenting the number and percentage of patients in each category. The number and percentage of patients who have received their 6th cycle will also be summarized. A patient will be considered as having initiated a cycle if at least one (non-null) dose of study drug has been administered in the corresponding cycle.

Study drug administration details will be summarized by descriptive statistics and will include percentage of patients with cycles delayed, average number of days delayed, percentage of patients with dose modification and percentage of patients with injection or infusion modification.

4.3.2 Adverse Events

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported.

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

To evaluate the safety of switching from atezolizumab SC to atezolizumab IV and from atezolizumab IV to atezolizumab SC, adverse event summaries will also be produced for the Treatment Cross-over Period by treatment arm and treatment period, as well as potentially by cycle. In addition, summaries of AE rate adjusted for patient-years at risk may be produced by treatment arm and treatment period.

An adverse event will be allocated to the treatment received on or before the adverse event start date.

Adverse events that started during the first three cycles of the Treatment Cross-over Period and continued into subsequent cycles (even if the adverse event changed severity grade) will be summarized under the route of administration during which it first occurred. These adverse events will be flagged in listings.

4.3.3 Additional Safety Assessments

4.3.3.1 Laboratory Data

Laboratory data will be summarized by treatment period, by treatment sequence and overall. Selected laboratory data will be graded according to NCI CTCAE v5.0 and will be summarized descriptively. Shift tables from baseline to worst post-baseline values will also be presented.

Potential Hy's law patients will be listed based on the laboratory data only: treatment-emergent elevated ALT or AST ($>3\times$ baseline value) in combination with elevated total bilirubin ($>2\times$ upper limit of normal [ULN]).

4.3.3.2 Vital Signs

Vital signs, changes in vital signs and shift table from baseline versus worst post-baseline as well as ECOG performance status will be summarized by treatment sequence over time and overall.

4.3.3.3 ECGs

Changes from baseline on ECG parameters and results of on-study ECGs will be summarized by treatment sequence and overall.

4.4 OTHER ANALYSES

When applicable, exploratory analysis will be done on all patients and separately among participants with early-stage NSCLC and chemotherapy-naive participants with Stage IV NSCLC.

4.4.1 Summaries of Conduct of Study

Enrolment, eligibility violations and participant disposition will be summarized for participants by randomized treatment arm. Reasons for participant's study treatment discontinuation and participant's reasons for study discontinuation will be listed by participant and summarized. Major protocol deviations will be summarized and listed.

Median follow-up on treatment and on study, estimated with corresponding 95% CI by the reverse Kaplan-Meier approach, will be presented for all patients.

Follow-up time on study is calculated from the date of the Cycle 1 visit. Patients who died on study are censored at the time of death. Other patients are considered to have been followed until the date of study completion or discontinuation. If neither of those dates is available, the date of the last recorded visit will be used.

Follow-up time on treatment is calculated from the date of the first study treatment to the date of last study treatment $+21$ days, date of death, or date of study discontinuation, whichever occurs first.

All analyses will be performed on the FAS.

4.4.2 Summaries of Demographics and Baseline Characteristics

Demographic variables and other baseline and disease characteristics will be summarized overall and by randomized treatment sequence using descriptive statistics on the FAS.

A summary of concordance of stratification factors determined by eCRF versus IxRS will also be reported.

4.4.3 Exploratory Pharmacokinetic Analyses

Samples will be collected for PK analyses and to compare exposure in this study with that attained in previous studies. Serum concentrations of atezolizumab will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm and cycle, when appropriate and as data allow. Individual and median serum atezolizumab concentrations will be plotted by treatment arm and day.

Atezolizumab concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the curve, as warranted by the data. Potential correlations of relevant PK parameters with safety outcomes may be explored.

PK analyses will be based on the PK-evaluable population.

4.4.4 Exploratory Immunogenicity Analyses

The immunogenicity analyses will be based on the ADA-evaluable population.

Participants will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, participants 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).

Participants are considered to be 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).

Descriptive analysis of safety and PK may be analyzed by ADA status.

4.4.5 Health Status Utility

Health economic data will be assessed by the EQ-5D-5L. The results from the health economic data analysis will be reported separately from the CSR.

4.5 INTERIM ANALYSES

No interim analyses will be planned.

5. SUPPORTING DOCUMENTATION

This section is not applicable since there is no additional supporting document.

6. REFERENCES

Fayers PM, Aaronson NK, Bjordal K, et al. on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 scoring manual (3rd Edition). Published by European Organisation for Research and Treatment of Cancer, Brussels 2001.

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