Official Protocol Title:	A Phase 2 Study to Evaluate Patient Reported Preference for Subcutaneous Pembrolizumab Coformulated with Hyaluronidase (MK-3475A) Over Intravenous Pembrolizumab Formulation in Participants With Multiple Tumor Types
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TITLE PAGE

STATISTICAL ANALYSIS PLAN

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Protocol Title: A Phase 2 Study to Evaluate Patient Reported Preference for Subcutaneous Pembrolizumab Coformulated with Hyaluronidase (MK-3475A) Over Intravenous Pembrolizumab Formulation in Participants With Multiple Tumor Types

Protocol Number: F11

Compound Number: MK-3475A

Sponsor Name:
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TABLE OF CONTENTS

LIST OF TABLES

1 INTRODUCTION

The SAP is a companion document to the protocol. While Section 9 of the protocol provides the principal features of the analyses for this study, this SAP provides additional statistical analysis details/data derivations and may document modifications or additions to the protocol-specified analysis plan that are not principal in nature and/or result from information that was not available at the time of protocol finalization.

2 SUMMARY OF CHANGES

This is the initial version of the SAP.

3 ANALYTICAL AND METHODOLOGICAL DETAILS

This section outlines the principal statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in an amendment of the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

3.1 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as a randomized, open-label study, i.e., participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule(s) for study treatment assignment. The algorithm for the randomized allocation of participants will be implemented in an IVRS by a study vendor.

3.2 Hypotheses/Estimation

Objectives of the study are stated in Section 3 of the protocol.

There are no hypotheses associated with any of the objectives.

3.3 Analysis Endpoints

Participant preference and satisfaction measure endpoints and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

3.3.1 Participant Preference and Satisfaction Measure Endpoints

Primary

- Participant preference assessed by response of MK-3475A SC on PPQ question 1

Secondary

- Participant responses to question 3 of the patient preference questionnaire
- Participant responses to question 1 of the TASQ SC and TASQ IV
- Participants' choice of MK-3475A SC for the study treatment Continuation Period

Exploratory

- Healthcare provider preference assessed by HCP question (HCPQ)

3.3.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory test results, and vital signs. Safety measurements are provided in Section 4.2.1.2 and Section 8 of the protocol.

3.4 Analysis Populations

3.4.1 Participant Preference and Satisfaction Measure Analysis Populations

The FAS population will serve as the primary population for the analysis of participant preference and satisfaction measure data in this study. The FAS population consists of all randomized participants who:

- Receive all three doses of MK-3475A subcutaneous during the treatment crossover period
- Receive all three doses of Pembrolizumab intravenous during the treatment crossover period
- Answered at least question 1 of the PPQ at C6D1

The FAS population will be used for the analysis of the following primary and secondary endpoints:

- Participant preference assessed by response of MK-3475A SC on PPQ question 1
- Participant responses to question 3 of the patient preference questionnaire
- Participant responses to question 1 of the TASQ SC and TASQ IV

All randomized participants who choose to receive treatment intervention in the continuation period, will serve as the analysis population for the following secondary endpoint:

- Participants' choice of MK-3475A SC for the study treatment Continuation Period

3.4.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population.

Analyses of laboratory test results and vital signs will include only participants with at least one measurement obtained after at least one dose of study intervention. If the analysis will assess change from baseline, a baseline measurement is also required.

3.5 Statistical Methods

This is an estimation study. Since there are no hypotheses associated with any endpoints, there is no type I error control strategy.

3.5.1 Statistical Methods for Participant Preference and Satisfaction Measure Analyses

The primary objective of this study is to evaluate participant preference for MK-3475A SC based on the participant preference rate (PPR). PPR is defined as the proportion of participants indicating an overall preference for MK-3475A SC in question 1 of the PPQ. The point estimate of PPR will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934]. Additionally, PPR will be descriptively summarized by treatment arm as a supportive analysis.

The secondary participant preference and satisfaction measure variables will be summarized descriptively. For participant responses to question 3 of the patient preference questionnaire, number and percentage of participants selecting each reason will be provided. For participant responses to question 1 of the TASQ SC and TASQ IV questionnaire, number and percentage of participants selecting each option for the 12 questions will be provided. The proportion of participants who choose MK-3475A SC for the study treatment continuation period will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 1 Analysis Strategy for Key participant preference and satisfaction measure Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint Analysis				
Proportion of participants who prefer MK-3475A SC with treatment preference assessed by PPQ question 1	P	Estimation: point estimate, 95% CI using exact binomial method proposed by Clopper and Pearson	FAS	Not Applicable

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Key Secondary Endpoints Analysis				
Participant responses to question 3 of the patient preference questionnaire	P	Frequency (%)	FAS	Participants with missing data are considered to have no response
Participant responses to question 1 of the TASQ SC and TASQ IV	P	Frequency (%)	FAS	Participants with missing data are considered to have no response
Proportion of participants who choose MK-3475A SC for the study treatment Continuation Period	P	Point estimate, 95% CI using exact binomial method proposed by Clopper and Pearson	Participants who choose to receive a treatment in continuation period	Not Applicable
FAS=Full Analysis Set. [a] P=Primary approach				

3.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results and vital signs. Adverse events will be summarized by MedDRA term, appropriate MedDRA levels (system organ class [SOC] and preferred term [PT]), and when specified by NCI CTCAE grade. For each participant, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

3.5.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by treatment intervention for cycles 1-3 and cycles 4-6 in the Crossover Period, and by treatment arm in the overall study. An adverse event will be attributed to the treatment received on or before the AE start date. Adverse events that started during the first three cycles of the Crossover Period and continued into subsequent three cycles (even if the AE changed severity grade) will be summarized by the route of administration during which it first occurred. These AEs will be flagged in listings.

The overall safety endpoints include the number and percentage of participants with at least one AE, drug-related AE, serious AE, serious, drug-related AE, Grade 3-5 AE, AEOSI, who discontinue from study intervention due to an AE, or with an AE resulting in death. The number and percentage for injection-site reactions will be provided for participants who receive MK-3475A SC treatment. Point estimates and 95% CIs for the differences between treatment groups (i.e., treatment interventions for cycles 1-3 in the Crossover Period,

treatment interventions for cycles 4-6 in the Crossover Period and treatment arms in the overall study) in the percentages of participants with the event will be provided based on the criteria described below for specific AEs.

The number and percentage of participants with specific AEs will also be provided. Point estimate and 95% CIs for the difference between treatment groups in the percentage of participants with specific AEs will be provided if at least 10% of participants in any treatment group exhibit the event. The threshold of at least 10% of participants was chosen because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, difference in the percentage of participants with specific Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will also be summarized by point estimate and 95% CIs.

CIs for between treatment group differences will be provided using the Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985]. CIs that are not adjusted for multiplicity should only be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance of between-group differences.

The number and percentage of participants with laboratory toxicity grade increased from baseline will be summarized by the post-baseline maximum toxicity grade per CTCAE V5.0 for each gradable laboratory test**.**

For continuous safety measures, such as change from baseline in laboratory, vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment arm.

3.5.2.2 Assessment of Safety Topics of Special Interest

AEs that are immune-mediated or potentially immune-mediated will be evaluated separately. These events have been characterized consistently throughout the pembrolizumab clinical development program. Point estimates and 95% CIs for between-group difference is not expected to add value to the safety evaluation, and hence only number and percentage of participants with such pembrolizumab AEOSI will be provided, as well as the number and percentage of participants with corticosteroids administration to treat an AEOSI. Summary statistics will be provided for the analysis of time from first dose to the onset of an AEOSI.

Table 2 summarizes analysis strategy for safety endpoints in this study.

Table 2 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% between-group CI
Overall Safety Assessment	Specific AEs (incidence ≥10% of participants in 1 of the treatment groups)	X	X
	Specific Grade 3-5 AE (incidence ≥5% of participants in 1 of the treatment groups)	X	X
	Specific serious AE (incidence ≥5% of participants in 1 of the treatment groups)	X	X
	Any AE	X	
	Any Grade 3-5 AE	X	
	Any Serious AE	X	
	Any Drug-related AE	X	
	Any Serious and Drug-related AE	X	
	Any Grade 3-5 and Drug-related AE	X	
	Discontinuation from Study Treatment due to AE	X	
	AE that Resulted in Death	X	
	AE that Led to Treatment Interruption	X	
	Injection-site Reaction	X	
	Specific AEs, SOCs (incidence >0% of participants in any treatment group)	X	
	Change from Baseline Results (lab toxicity shift)	X	
Assessment of safety topics of special interest	Pembrolizumab AEOSI	X	

AE = adverse event; AEOSI = adverse event of special interest; CI = confidence interval; SOC = system organ class

3.5.3 Demographic and Baseline Characteristics

The comparability of the treatment arms for each relevant demographic and baseline characteristic will be assessed using tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses,

and prior and concomitant therapies will be summarized by treatment arms either by descriptive statistics or categorical tables.

3.6 Interim Analyses

3.6.1 Participant Preference and Satisfaction Measure Interim Analyses

There are no formal interim analyses planned in this study. An interim analysis may be conducted to support a future regulatory submission. The results of this interim analysis will be evaluated by a Sponsor's Executive Oversight Committee.

The final analysis (FA) will occur when approximately 115 participants have evaluable data (i.e., participants who satisfy the FAS population definition stated in Section 3.4.1). This is expected approximately 14.5 months after first participant randomized. All the primary, secondary and exploratory objectives for participant preference and satisfaction measure will be evaluated at FA.

3.6.2 Safety Interim Analyses

There are no planned safety IAs for this study.

3.7 Multiplicity

No multiplicity adjustment is planned as there are no hypotheses in this study.

3.8 Sample Size and Power Calculations

This is an estimation study. This study will randomize 144 participants to treatment arms A or B and will allow estimation of participant preference rate among all evaluable participants with a 95% CI. Assuming ~20% dropout prior to completion of PPQ at C6D1, the expected number of evaluable participants for the primary analysis will be ~115. The ~20% dropout assumption in the overall population was calculated based on the following assumed dropout rates and planned enrollment of ~33% participants for each of the 3 tumor types:

- ~14% dropout rate for adjuvant melanoma population
- ~13% dropout rate for adjuvant renal cell carcinoma population
- ~33% dropout rate for metastatic NSCLC (PD-L1≥50%) population

Table 3 shows the two-sided 95% confidence interval for participant preference rate (PPR) with 115 evaluable participants for different observed PPR based on the method of Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

Table 3 Two-sided 95% Confidence Interval for observed PPR with 115 Evaluable Participants

Observed Number of Participants preferring MK-3475A SC	**PPR Estimates**	**95% CI of PPR (%)**
63	55%	(45, 64)
69	60%	(50, 69)
75	65%	(56, 74)
80	70%	(60, 78)

3.9 Subgroup Analyses

To determine whether the participant preference rate (PPR) is consistent across various subgroups, the estimate of PPR (with a nominal 95% CI) will be estimated and plotted within each category of the following subgroup variables:

- ECOG PS (0, 1)
- Tumor type (Melanoma, RCC, NSCLC)

For subgroups determined by the levels of a stratification factor, the derived strata based on eCRF collected information (as compared to the IRT/IVRS strata) will be used as the default. If the number of participants in a category of a subgroup variable is less than 10% of the FAS population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot.

3.10 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

3.11 Extent of Exposure

The Extent of Exposure to study treatment will be evaluated by summary statistics (N, mean, median, SD) and/or frequencies (define categories) for the “Number of Days on Therapy” by treatment arms.

4 LIST OF REFERENCES

[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[03Y75Y]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]