# Statistical Analysis Plan

NCT Number: NCT05590377

Title: A Phase 1/2a Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Modakafusp Alfa in Combination With Daratumumab Subcutaneous in Patients With Relapsed or Refractory Multiple Myeloma.

Study Number: TAK-573-2001

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# STATISTICAL ANALYSIS PLAN

Study Number: TAK-573-2001

**A Phase 1/2a Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Modakafusp Alfa in Combination With Daratumumab Subcutaneous in Patients With Relapsed or Refractory Multiple Myeloma**

**Phase 1/2a**

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Statistics and Quantitative Sciences

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|---|---|---|
| Original Version | Not Applicable | Not Applicable |

## TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES

## ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| ADA | antidrug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the serum concentration-time curve |
| $AUC_{\tau}$ | area under the concentration-time curve during a dosing interval |
| $AUC_{\infty}$ | area under the serum concentration-time curve from time 0 to infinity |
| $AUC_{last}$ | area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration |
| BLQ | below the limit of quantitation |
| CBR | clinical benefit rate |
| CI | confidence interval |
| CL | total clearance after administration |
| $C_{max}$ | maximum observed serum concentration |
| CR | complete response |
| DCR | disease control rate |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EOT | end of treatment |
| FLC | free light chain |
| ICF | informed consent form |
| ICU | intensive care unit |
| IDMC | independent data monitoring committee |
| Ig | immunoglobulin |
| IMWG | International Myeloma Working Group |
| IRC | Independent review committee |
| IRR | Infusion-related reaction |
| IV | intravenous(ly) |
| κD | dissociation constant |
| LLOQ | lower limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MM | multiple myeloma |
| MRD | measurable (minimal) residual disease |
| MRD[-] | MRD negative |
| MTD | maximum tolerated dose |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| OBD | optimal biological dose |
| ORR | objective response rate |

| Abbreviation | Term |
|---|---|
| PD | progressive disease; disease progression |
| PFS | progression-free survival |
| PoS | probability of success |
| PI | Proteasome inhibitor |
| PK | pharmacokinetic(s) |
| PO | orally |
| PPOS | posterior probability of success |
| PR | partial response |
| PT | preferred term |
| QD | once daily |
| QTcF | QT interval with Fridericia correction method |
| RBC | red blood cells |
| RP2D | recommended phase 2 dose |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| sCR | stringent complete response |
| SD | stable disease |
| SOC | system organ class |
| SPEP | serum protein electrophoresis |
| $t_{1/2}$ | terminal disposition phase half-life |
| TEAE | treatment-emergent adverse event |
| $t_{max}$ | time of first occurrence of maximum observed serum modakafusp alfa concentration |
| TTP | Time to progression |
| TTR | Time to response |
| ULN | upper limit of normal |
| UPEP | urine protein electrophoresis |
| VGRP | very good partial response |
| $V_{ss}$ | volume of distribution at steady state |
| $\lambda_z$ | terminal disposition phase rate constant |

# 1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

## 1.1 Objectives

### 1.1.1 Primary Objective

The primary objectives are:

Phase 1 Dose Escalation

- To determine the safety and tolerability of modakafusp alfa in combination with daratumumab SC.

Phase 2a Dose Finding

- To inform the RP2D of modakafusp alfa in combination with daratumumab SC.
- To provide a preliminary evaluation of the clinical efficacy of modakafusp alfa in combination with daratumumab SC as measured by ORR.

### 1.1.2 Secondary Objective(s)

Phase 1 Dose Escalation

- To characterize the PK profile of modakafusp alfa and daratumumab in the combination setting.
- To characterize antimyeloma activity as measured by ORR, DOR, PFS, and overall survival (OS).
- To characterize the immunogenicity of modakafusp alfa in combination with daratumumab SC.
- To characterize measurable (minimal) residual disease (MRD) negativity rate and duration of MRD negativity.

Phase 2a Dose Finding

- To determine DOR, clinical benefit rate (CBR), duration of clinical benefit (DCB), disease control rate (DCR), duration of disease control, time to progression (TTP), time to response (TTR), time to next treatment (TTNT), PFS, and OS.
- To further characterize safety and tolerability of modakafusp alfa in combination with daratumumab SC.
- To collect PK data for modakafusp alfa to support population PK and E-R analysis.
- To collect PK data for daratumumab SC to assess any potential impact of immunogenicity on daratumumab PK.

- To further characterize the immunogenicity of modakafusp alfa in combination with daratumumab SC.
- To characterize MRD negativity rate and duration of MRD negativity.

### 1.1.3 Additional Objective(s)

*1.1.3.1 Exploratory Objectives*

[redacted]

## 1.2 Endpoints

Patients' responses to the treatment will be determined per International Myeloma Working Group (IMWG) criteria in the current study.

### 1.2.1 Primary Endpoint(s)

The primary endpoints are:

Phase 1 Dose Escalation

- DLT incidences.
- Frequency and severity of TEAEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.

Phase 2a Dose Finding

- ORR, defined as the proportion of patients who achieved a confirmed response of PR or better during the study as assessed by the investigator.

### 1.2.2 Secondary Endpoint(s)

The secondary endpoints are:

Phase 1 Dose Escalation

- Summary statistics by dose level and cycle day for the following PK parameters for modakafusp alfa for Cycles 1 and 2:
  - Single-dose maximum observed serum concentration ($C_{max}$).
  - Time of first occurrence of $C_{max}$ ($t_{max}$).

  - Area under the serum concentration-time curve from time 0 to infinity ($AUC_{\infty}$).
  - Area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration ($AUC_{last}$).
  - Apparent serum modakafusp alfa terminal disposition rate constant.
  - Apparent serum modakafusp alfa terminal disposition phase half-life.
  - Clearance.
  - Volume of distribution at steady state after intravenous (IV) administration.
- Summary statistics by dose level and cycle day for the following PK parameters for daratumumab for Cycles 1 and 2:
  - Single-dose $C_{max}$.
  - $t_{max}$.
  - Single-dose and multiple-dose observed concentration at the end of a dosing interval ($C_{trough}$).
  - $AUC_{\infty}$.
  - $AUC_{last}$.
- ORR by the investigator.
- DOR by the investigator.
- PFS by the investigator.
- OS.
- ADA incidence and characteristics (eg, titer and specificity) and neutralizing antibody (NAb).
- Rate of MRD negative (MRD[-]) CR, at a threshold of $10^{-5}$, with CR assessed by the investigator.
- Rate of MRD[-], at a threshold of $10^{-5}$.
- Duration of MRD negativity, at a threshold of $10^{-5}$.

<u>Phase 2a Dose Finding</u>

- DOR by investigator.
- CBR response of sCR, CR, very good partial response (VGPR), PR, or minimal responses (MR) by investigator.
- DCB by investigator.
- DCR (CBR + stable disease [SD]) by investigator.

- Duration of disease control by investigator.
- TTP by investigator.
- TTR by investigator.
- TTNT.
- PFS by investigator.
- OS.
- Frequency and severity of TEAEs according to the NCI CTCAE, Version 5.0.
- ADA incidence and characteristics (eg, titer and specificity) and NAb.
- Rate of MRD[-] CR, at threshold of $10^{-5}$, with CR assessed by the investigator.
- Rate of MRD[-], at a threshold of $10^{-5}$.
- Duration of MRD negativity, at a threshold of $10^{-5}$.

### 1.2.3 Exploratory Endpoint(s)

[redacted]

## 1.3 Estimand(s)

Not applicable.

## 2.0 STUDY DESIGN

This is a global multicenter, open-label, phase 1/2a study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of modakafusp alfa in combination with daratumumab subcutaneous (SC) in patients with relapsed or refractory multiple myeloma (RRMM). The study will begin with a phase 1 dose escalation to evaluate the safety and tolerability of modakafusp alfa in combination with daratumumab SC. Two dose levels of modakafusp alfa in combination with daratumumab SC will be selected to be further explored in the randomized phase 2a dose finding part of the study. Patients will be randomized in a 1:1 ratio across 2 dose levels (DL1 or DL2) of modakafusp alfa in combination with daratumumab SC. The confirmed ORR assessed by the investigator per IMWG criteria will be determined as the primary efficacy endpoint of the phase 2a dose finding. The optimized recommended phase 2 dose (RP2D) of modakafusp in combination with daratumumab SC will be selected on the basis of integrated safety, efficacy, PK, and PD data from the current study and other relevant stud(ies).

**Phase 1 Dose Escalation**

The study will begin with a phase 1 dose escalation to evaluate the safety and tolerability of modakafusp alfa in combination with daratumumab SC during the Cycle 1 (28 days per cycle) dose-limiting toxicity (DLT) evaluation period and beyond. The proposed population in the phase 1 dose escalation will be patients with RRMM with at least 3 prior lines of therapy, including at least 1 proteasome inhibitor (PI), 1 immunomodulatory imide drug (IMiD), and 1 anti-CD38 monoclonal antibody (mAb) drug; or who are triple refractory to a PI, an IMiD, and an anti-CD38 mAb drug, regardless of the number of prior line(s) or therapy.

The dose escalation will follow the rolling six design with data collected in the dose escalation/de-escalation phase.

**Phase 2a Dose Finding**

Two dose levels of modakafusp alfa in combination with daratumumab SC doses will be selected from phase 1 dose escalation to be explored further in phase 2a open-label dose finding. Approximately 40 patients will be randomized 1:1 across 2 different dose levels (DL1 or DL2; N = ~20 at each dose level) of modakafusp alfa in combination with daratumumab SC. Eligible patients will include patients with RRMM who have received 1 to 3 prior lines of therapy, refractory to lenalidomide, and sensitive (nonrefractory) or naive to anti-CD38 mAb. The randomization will be stratified by the number of prior lines of therapy (1 vs 2 or 3). The primary endpoint is the confirmed ORR assessed by the investigator per IMWG criteria.

## 3.0 STATISTICAL HYPOTHESES AND DECISION RULES

### 3.1 Statistical Hypotheses

Not Applicable

### 3.2 Statistical Decision Rules

Not Applicable

### 3.3 Multiplicity Adjustment

Not Applicable

## 4.0 SAMPLE-SIZE DETERMINATION

A total of approximately 58 patients will be enrolled in the study, including approximately 18 DLT-evaluable patients for the phase 1 dose escalation and approximately 40 patients (approximately 20 patients per arm) for the phase 2a dose finding.

The phase 1 dose escalation will accrue approximately 18 DLT-evaluable patients based on the algorithm of the rolling six design.

With approximately 20 patients per arm in the phase 2a dose finding, the probability of observing at least 1 AE given a different true AE rate is as follows:

| True AE rate | 5% | 10% | 15% | 20% |
|---|---|---|---|---|
| Probability of observing at least 1 AE | 64% | 88% | 96% | 99% |

With approximately 20 patients per arm in the phase 2a dose finding, the 95% exact binomial CIs associated with different observed ORR are as follows:

| Observed ORR | 60% | 70% | 80% |
|---|---|---|---|
| 95% CI | (0.361, 0.809) | (0.457, 0.881) | (0.563, 0.943) |
| Width of the 95% CI | 0.448 | 0.424 | 0.379 |

## 5.0 POPULATIONS

### 5.1 DLT-evaluable Population

The DLT-evaluable population includes all patients from the phase 1 dose escalation portion who experienced a DLT in Cycle 1 in the treatment phase of the study or have completed the Cycle 1 dose of modakafusp alfa and at least 75% of the planned dose of daratumumab SC. The DLT-evaluable population will be used to inform the 2 dose levels for modakafusp alfa to be selected in the phase 2a dose finding portion in combination with daratumumab SC.

### 5.2 Response-evaluable Population

The response-evaluable population includes all patients who receive at least 1 dose, even an incomplete dose, of any study drug, have a disease assessment at screening (baseline evaluation), and at least 1 postbaseline disease assessment. The response-evaluable population will be used

for the primary analysis for ORR in phase 1 dose escalation portion and sensitivity analysis in phase 2a dose finding portion.

### 5.3 Safety Population

The safety population will include all patients who receive at least 1 dose, even an incomplete dose, of any study drug. Patients in this set will be analyzed according to the actual treatment they received. The safety population will be used for the baseline assessment and efficacy analysis except for the endpoints of PFS, OS and TTP in Phase 2a. It will be also used for the safety analysis.

### 5.4 Per-Protocol Population

The per-protocol population is a subset of subjects in the safety population who do not have major protocol deviations that are considered to impact efficacy outcomes. The list of major protocol deviations is documented and maintained by the sponsor on an ongoing basis and will be finalized prior to database lock. The per-protocol population will be used in the sensitivity efficacy analysis for endpoint of ORR if patients excluded due to major protocol deviation are deemed to have significant impact on the analysis of primary endpoints.

### 5.5 Intent-to-treat (ITT) Population

The ITT population will include all patients who are randomized. Patients in this set will be analyzed according to the treatment they are randomized to receive, regardless of any dosing errors. The ITT population will be used for the main efficacy analysis for endpoints of PFS, OS and TTP.

### 5.6 Pharmacokinetic Population

The pharmacokinetic (PK) population includes patients from the safety population with sufficient PK data to reliably report 1 or more PK parameters.

### 5.7 Immunogenicity-evaluable Population

The immunogenicity-evaluable population includes patients who received at least 1 dose of modakafusp alfa + daratumumab SC (partial or complete) with a baseline assessment and at least 1 postbaseline immunogenicity assessment. Immunogenicity analysis will be primarily based on the immunogenicity-evaluable population.

## 6.0 STATISTICAL ANALYSIS

### 6.1 General Considerations

All statistical analyses will be conducted using SAS® Version 9.4 or later.

For categorical variables, the count and proportions of each possible category value will be tabulated. The denominator for the proportion will be based on the number of subjects in the

populations. For continuous variables, the mean, median, standard deviation, minimum, and maximum values will be presented for all patients in the relevant population.

All 95% confidence intervals will be reported as 2-sided. No formal statistical comparisons will be performed between dose levels.

Baseline values are defined as the last observed value before the first dose of any study drug.

### 6.1.1 Study Definitions

#### *6.1.1.1 Definition of Study Days*

Study Day 1 is defined as the date on which the patient is administered the first dose of any study drug.

Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and (Day - 1) being the day prior to Study Day 1.

#### *6.1.1.2 Definition of Study Cycle*

The starting date of a new cycle is the date on which the dose of modakafusp alfa is administrated.

#### *6.1.1.3 Definition of Study Visit Window*

All data will be categorized on the basis of the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF). The analysis of PK data will be based on the actual elapsed time post dose.

### 6.1.2 Analysis Approach for Continuous Variables

Continuous variables will be summarized by dose level by phase using summary statistics including mean, standard deviation, median, first and third quartiles.

### 6.1.3 Analysis Approach for Binary Variables and Categorical Variables

For binary and categorical variables, frequency and percentage will be provided by dose level by phase. The 2-sided 95% CI will be calculated based on Clopper-Pearson method (exact method) (Clopper, C., Pearson, E.S, 1934). No formal statistical comparisons will be performed between dose levels.

### 6.1.4 Analysis Approach for Time-to-Event Variables

Time to event endpoints will be estimated using the Kaplan-Meier (K-M) method (Kaplan, E.L, Meier, P., 1958). The K-M curves, the 25$^{th}$, 50$^{th}$ (median) and 75$^{th}$ percentiles, alone with associated 2-sided 95% CIs based on Brookmeyer and Crowley method (Brookmeyer, R., Crowley, J., 1982). The K-M probability estimates with 95% CIs at appropriate times will be presented if data permits. The number of patients with events and the number of patients

censored will be summarized. No formal statistical comparisons will be performed between dose levels.

## 6.2 Disposition of Subjects

Study information, including the date first subject signed informed consent form (ICF) for each phase, date of first subject dosed (for phase 1 dose escalation portion), date of last subject dosed (for phase 1 dose escalation portion), date of first subject randomized (for phase 2a dose finding portion), date of last subject randomized (for phase 2a dose finding portion), date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint(s), data cut-off date for analysis, MedDRA version, NCI CTCAE version, WHO Drug version, and SAS version will be presented in listings.

Screen failures as well as reasons will be summarized.

Patient disposition will be summarized using counts and percentage of patients based on all enrolled patients. The disposition will include the following categories:

- Treatment status (never treated (only applicable for phase 2a portion), ongoing, discontinued treatment)
  - Reasons for discontinuation of treatment
- Study status (discontinued from study, ongoing in study)
  - Reason for discontinuation of study
- Participating in PFS follow-up
- Participating in OS follow-up

The number and percentage of subjects in each population will be summarized.

A table and listing of significant protocol deviations will be presented.

## 6.3 Demographic and Other Baseline Characteristics

### 6.3.1 Demographics

All demographics will be summarized based on the safety population using descriptive statistics. Demographic data to be evaluated will include, but not limited to, age, sex, race, ethnicity, height, and weight.

### 6.3.2 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the most recent version of MedDRA available at the time of coding. Concurrent medical conditions are the ones ongoing or started on or after the day informed consent is signed. Medical history and concurrent medical conditions will be summarized separately based on safety population by System Organ Class (SOC) and Preferred Term (PT) using counts and percentages.

If both start date and stop date are missing, medical condition will be assumed to start before informed consent and continue after treatment discontinuation. If only start date is missing, then

medical condition will be assumed to start before informed consent. If stop date is missing, then medical condition will be assumed to continue after treatment discontinuation.

### 6.3.3 Baseline Characteristics

Baseline characteristics will be summarized using descriptive statistics based on the safety population. The characteristics include the following:

Disease characteristics:

- Years since initial diagnosis [ (date of first dose – date of diagnosis) / 365.25)].
- Type of Myeloma
  - IgG, IgA, IgD, IgM, Biclonal (if known, otherwise summarize with Light chain below).
  - Light Chain Kappa, Light Chain Lambda, Light chain Biclonal, Light Chain unknown.
- Measurable disease
  - Measurable by both SPEP (baseline serum M-protein ≥0.5 g/dL) and UPEP (baseline urine M-protein ≥200 mg/24 hr)
  - Measurable by SPEP only
  - Measurable by UPEP only
  - Measurable by FLC only (met all three criteria below):
    1. Involved either Kappa or Lambda free light chain level at baseline ≥10 mg/dL;
    2. and FLC ratio (Kappa FLC/Lambda FLC) is abnormal (serum FLC ratio >1.65 or <0.26)
    3. and not measurable by SPEP or UPEP
- International Staging System (ISS) at study entry.
- Revised ISS (R-ISS) at study entry.
- Evidence of Lytic Bone Disease at initial diagnosis.
- Evidence of Extramedullary Disease at initial diagnosis.
- Eastern Cooperative Oncology Group (ECOG) performance status.

Baseline disease characteristics– laboratory values

- $\beta_2$-microglobulin category (<2.5, 2.5-5.5, >5.5 mg/L).
- Serum albumin category (<3.5, ≥3.5 mg/dL).
- Serum creatinine category (≤2, >2 mg/dL).
- Calculated creatinine clearance category (<30, 30 - <60, 60 - <90, ≥90 mL/min).
  Creatinine clearance will be calculated using the Cockcroft-Gault formulas as follows:

  For male patients:

$$\text{creatinine clearance} = \frac{(140 - \text{Age[yrs]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

For female patients multiply by 0.85.

- Hemoglobin (g/L).
- Platelet count (10^9/L).
- Absolute neutrophil count (10^9/L).
- Lactate dehydrogenase (LDH) > Upper limit of normal (ULN).

Baseline Bone Marrow Evaluation

- Baseline bone marrow aspirate/biopsy performed and adequate for interpretation.
- Percent plasma cells in bone marrow (if both biopsy and aspirate were performed use larger value; unable to detect is considered as zero).

Cytogenetics

- Cytogenetic testing performed.

The number and percentage of patients with each type of chromosomal aberration or abnormality will be presented including but not limited to the following:

- high risk cytogenetics [del 17, t(4;14) or t(14;16)].
- expanded high risk cytogenetics [del 17, t(4;14), (14;16), or 1q21 amplification/gain].
- del 17.
- t(4:14).
- t(14:16).
- 1q21 amplification/gain.

(percentages are based on the number of patients with cytogenetic testing performed)

Extramedullary Disease Assessment (imaging)

- Imaging lytic lesions (yes, no, indeterminate).
- Imaging extramedullary plasmacytomas (yes, no, indeterminate).
- Location of plasmacytomas.
- Number of plasmacytomas (1, 2, ≥3).
- Skeletal survey results (normal, abnormal not clinically significant, abnormal clinically significant, and not done).
- Skeletal survey lytic lesions (yes, no, indeterminate).

Prior therapy

- Prior radiation (yes, no).
- Prior surgery (yes, no).
- Prior bone marrow transplant or stem cell transplant.

  - Type of stem cell transplant (autologous, allogeneic, syngeneic, unknown).
- Prior systemic therapy (yes, no).
- Lines of prior therapy (descriptive statistics and categorical summary: 1, 2, 3, 4, 5, 6, >6).
- Lines of prior therapy initiated within 12 months of first dose of modakafusp alfa (categorical summary).
- Type of prior therapy may include (if data permits) but not limited to:
  - Anti-CD38 monoclonal antibody (i.e. Daratumumab, Isatuximab).
  - CAR-T.
  - Anti-BCMA.
  - T-Cell engager.
  - IMiD.
  - Proteasome inhibitor (PI).
  - Anti-SLAMF7 (i.e. Elotuzumab).
- Type of last line of prior therapy.
- Best response to any prior anti-CD38.
- Best response to last line of prior therapy
- Refractory to prior therapy may include but not limited to:
  - Refractory to BCMA agents.
  - Refractory to anti-CD38.
  - Refractory to IMiD.
  - Refractory to PI.
  - Refractory to IMiD and PI.
  - Refractory to IMiD, PI, and anti-CD38.
  - Refractory to last line of prior therapy.

Refractory to therapy is defined as: best response of the treatment is stable disease or disease progression on treatment or date of progression is no more than 60 days from the end date of the last agent (start date to be imputed where only year or month/year are entered).

## 6.4 Medication History and Concomitant Medications

Medication history and concomitant medications will be coded using the latest World Health Organization (WHO) Drug Dictionary.

If both start date and stop date are missing, medication will be assumed to start before the first dosing date of the study drug and continue after treatment discontinuation. If only start date is missing, then medication will be assumed to start before the first dosing date of the study drug. If

only stop date is missing, then medication will be assumed to continue after treatment discontinuation.

### 6.4.1 Prior Therapy

Prior medication is defined as the anticancer medication stopped before the date of first dose of any study drug. Prior medication will be coded by preferred term using the latest World Health Organization (WHO) Drug Dictionary.

The safety population will be used for the analysis of prior therapy.

### 6.4.2 Concomitant Medications

Concomitant medication is defined as the medication ongoing at the time of the first dose of any study drug or medications started on or after the first dose of any study drug. Concomitant medications will be coded using the latest WHO Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO standardized medication name.

The safety population will be used for the analysis of concomitant medications.

## 6.5 Study Drug Exposure and Compliance

The exposure to study drugs (modakafusp alfa and daratumumab) will be characterized based on safety population by summaries and descriptive statistics of duration of treatment in weeks, number of treated cycles (1, 2, 3, 4, 5, 6, 7-12, 13-18, 19-24, >24 and summary statistics), and relative dose intensity (<50%, 50% - <80%, 80% - <100%, 100%, >100%, and summary statistics).

The algorithm/calculation details will be documented in the analysis dataset specifications.

**Action on Study Drug**

The reason for treatment discontinuation and dose modification (e.g. dose increased, dose reduced, interrupted, withdrawn, delayed, infusion rate increased, infusion rate reduced, drug infusion interrupted) of the study drug will be summarized based on safety population.

## 6.6 Efficacy Analysis

All efficacy endpoints are based on investigator's assessment, if applicable.

### 6.6.1 Primary Endpoint Analysis

The primary efficacy endpoint for phase 2a is investigator-assessed ORR.

#### *6.6.1.1 Derivation of Endpoint(s)*

ORR is defined as the proportion of patients who achieved a confirmed response of PR or better per IMWG criteria.

#### *6.6.1.2 Main Analytical Approach*

Investigator-assessed ORR will be analyzed as the primary endpoint and calculated based on the safety population.

ORR at the primary analysis will be analyzed based on the confirmed responses, details of which is described as follows.

Confirmation of Response:

To confirm a response of sCR, CR, VGPR, PR, or MR, it requires 2 consecutive adequate assessments made at any time before the initiation of subsequent anti-cancer therapy. There is no requirement on the time interval between the two visits.

Below are some exceptions:

1. One or two consecutive occurrences of "not done" (ND) or "not evaluable" (NE) between responses can be skipped when confirming a response. For example,

   PR → NE → PR: PR is considered to be confirmed in this case.

   CR → ND → CR: CR is considered to be confirmed in this case.

2. Bone marrow assessments do not need to be confirmed.

Confirmation of PD:

It also requires 2 consecutive adequate assessments made at any time before the initiation of subsequent anti-cancer therapy to confirm PD. If only one PD value is recorded in the middle of responses better than PD, it will not be counted as a confirmed PD and therefore not an event for DOR, TTP, and PFS analyses. For example, the following case is not a confirmed PD:

**BL → SD → PD → SD → SD → Subsequent anti-cancer therapy/End**

Below are some exceptions:

- If only one PD is recorded as the last available assessment, then
  1) If this PD is due to imaging (plasmacytomas or bone lesion), then it can be considered as a confirmed PD.
  2) If this PD is the last available assessment prior to the subsequent anti-cancer therapy or is the reason for End of Treatment (EOT), then it can be considered as a confirmed PD.
  3) Otherwise, the PD is considered as unconfirmed.

**Best Overall Response**

Best overall response (BOR) is defined as the best response recorded after the first dose of study drug. The number and percentage of patients as well as corresponding 95% exact CIs with BOR in the following response categories will be summarized by dose level: sCR, CR, VGPR, PR, MR, SD, PD, and NE/ND. A list of investigator-assessed response at each visit will be provided.

Only the assessments from the start of treatment up to the earlier of confirmed disease progression or the start of subsequent anti-cancer therapy will be considered. Only subsequent systemic anti-cancer drugs are considered as anti-cancer therapy (radiotherapy and surgeries are not considered as systemic anti-cancer therapy for the purpose of this analysis). However, assessment after the treatment discontinuation will be considered. Subjects with only assessments of "Not Evaluable" or missing response will be treated as non-responders, i.e., they will be included in the denominator when calculating the percentage.

### *6.6.1.3 Sensitivity Analysis*

The primary analysis of ORR will be based on the safety population. Sensitivity analyses for ORR include, but not limited to:

1. ORR assessed by investigator will be analyzed using the ITT population.
2. ORR assessed by investigator will be analyzed using the per protocol population if patients excluded due to major protocol deviation are deemed to have significant impact on the analysis of primary endpoints.
3. ORR assessed by investigator will be analyzed using the response-evaluable population.

For the primary endpoint ORR, subgroup analysis will be performed in the following selected subgroups and presented using forest plot within each treatment arm. Additional subgroups of clinical interest may also be considered if data permits, but not required by this SAP.

| Subgroups | Categories |
|---|---|
| Age group (at screening) | 18 to <65; 65 to < 75; ≥ 75 |
| Gender | Male; female |
| Race | White; Black; Asian; Other |
| Type of myeloma | IgA; IgG; light chain only |
| Cytogenetics risk | High risk [defined as 17p-, t(4;14) and/or t(14;16)]; complementary standard risk (non-high risk) |
| R-ISS | I/II; III |
| ISS | I/II; III |

| | |
|---|---|
| Extramedullary disease | Yes; no |
| Prior treatment | Naïve to anti-CD38; sensitive (non-refractory) to anti-CD38 |
| Number of prior lines of therapy | 1; 2/3 |
| Transplant status | Transplanted; Non-transplanted |

If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to the database lock.

### 6.6.2 Secondary Endpoints Analysis

#### *6.6.2.1 Phase 1 dose escalation*

For the phase 1 dose escalation, secondary efficacy endpoints include ORR, DOR, PFS, OS, MRD[-] CR rate, MRD[-] rate, and duration of MRD negativity.

**ORR**

ORR is defined in Section 6.6.1.1.

The analysis of ORR will be based on the response-evaluable population.

ORR will be summarized by frequencies, percentages, and 2-sided 95% exact binomial CIs.

**DOR**

DOR is defined as the time from the date of first documentation of a confirmed PR or better to the date of first documentation of confirmed progressive disease or death due to any cause, whichever occurs first. Responders without documentation of confirmed progressive disease or death will be censored at the date of last adequate disease assessment. The censoring rule for DOR is the same as for PFS. Please refer to Table 1 in Section 6.6.2.2 for the detailed censoring rules.

DOR (months) = (earliest date of progression or death or censor – date of confirmed response + 1)/30.4375

The analysis of DOR will only include confirmed responders (PR or better) based on the safety population.

DOR will be summarized using KM method. The K-M curves, the 25$^{th}$, 50$^{th}$ (median) and 75$^{th}$ percentiles, alone with associated 2-sided 95% CIs based on Brookmeyer and Crowley method, and the K-M probability estimates with 95% CIs at 3, 6, 9 and 12 months (or later time points if applicable) will be presented. The number of patients with events along with the type of events (death or progressive disease) and the number of patients censored will be summarized.

## PFS

PFS is defined as the time from the date of the first dose administration of any study drug to the first documentation of confirmed progressive disease or death due to any cause, whichever occurs first. Patients without documentation of confirmed progressive disease or death will be censored at the date of last adequate disease assessment prior to the date of initiation of subsequent anti-cancer therapy. Patients with no post baseline response assessment will be censored on day 1 unless patient died without extended loss-to-follow-up time. Determination of dates of PFS event and date for censoring is summarized in Table 1 as follows.

**Table 1: PFS Event and Censoring Method**

| Scenarios | Event date/censoring date | Event status |
|---|---|---|
| No (or inadequate) baseline tumor assessments[1] | Date of the first dose | Censored |
| No post-baseline assessments | Date of the first dose | Censored |
| Confirmed progression documented without extended loss-to-follow-up time (two or more missed cycles) | Date of assessment of the earliest date of the confirmed progression | PFS Event |
| No confirmed progression or death | Date of last adequate disease assessment[2] | Censored |
| Subsequent anti-cancer therapy started (before documented confirmed progression or death)[3] | Date of last adequate disease assessment[2] (prior to the initiation of the subsequent anti-cancer therapy) | Censored |
| Death without extended loss-to-follow-up time | Death date | PFS Event |
| Death or progression after an extended loss-to-follow-up time (two or more missed cycles) | Date of last adequate disease assessment[2] (prior to missed assessments) | Censored |

1. Adequate baseline assessment is defined as at baseline, a patient has at least one of the following measurements:
   a) Serum M-protein ≥ 0.5g/dL (≥500 mg/dL) or
   b) Urine M-protein ≥200 mg/24 hours or
   c) Serum FLC assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
2. An adequate disease assessment is defined as an assessment where the investigator determined response is sCR, CR, VGPR, PR, MR, or SD prior to a subsequent anti-cancer therapy. An unconfirmed PD assessment is also considered as an adequate assessment.
3. If PD or death and the subsequent anti-cancer therapy occur on the same day, it is assumed that the progression or death was documented first (e.g., event status is an event, and the date of event is the date of progression or death). If the subsequent anti-cancer therapy is initiated prior to any adequate assessment, censoring date should be the date of the first dose.

PFS (months) = (earliest date of progression or death or censor – date of first dose + 1)/30.4375.

The analysis of PFS will be based on the safety population.

PFS will be summarized using KM method. The K-M curves, the 25$^{th}$, 50$^{th}$ (median) and 75$^{th}$ percentiles, alone with associated 2-sided 95% CIs based on Brookmeyer and Crowley method, and the K-M probability estimates with 95% CIs at 3, 6, 9 and 12 months (or later time points if applicable) will be presented. The number of patients with events along with the type of events (death or progressive disease) and the number of patients censored will be summarized. The PFS follow-up time will be summarized and reported using the inverse KM methods.

## OS

OS is defined as the time from the date of first dose administration of any study drug to the date of death from any cause. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

OS (months) = (date of death or censor – date of first dose + 1)/30.4375.

The analysis of OS will be based on the safety population.

OS will be summarized using KM method. The K-M curves, the 25$^{th}$, 50$^{th}$ (median) and 75$^{th}$ percentiles, alone with associated 2-sided 95% CIs based on Brookmeyer and Crowley method, and the K-M probability estimates with 95% CIs at 3, 6, 9 and 12 months (or later time points if applicable) will be presented. The number of patients with events and the number of patients censored will be summarized. The OS follow-up time will be summarized and reported using the inverse KM method.

## MRD[-] CR Rate

MRD[-] CR rate is defined as the proportion of patients who have achieved confirmed CR assessed by the investigator and MRD[-] status using a threshold of $10^{-5}$.

The analysis of MRD[-] CR rate will be based on the response-evaluable population.

MRD[-] CR rate will be summarized by frequencies, percentages, and 2-sided 95% exact binomial CIs.

## MRD[-] Rate

MRD[-] rate is defined as the proportion of patients who have achieved MRD[-] status using a threshold of $10^{-5}$.

The analysis of MRD[-] rate will be based on the response-evaluable population.

MRD[-] rate will be summarized by frequencies, percentages, and 2-sided 95% exact binomial CIs.

**Duration of MRD negativity**

Duration of MRD negativity is defined as the time from the date of first documentation of MRD negativity to the first documentation of MRD positivity or confirmed progressive disease, or death due to any cause, whichever occurs first. Patients without documentation of MRD positivity or confirmed progressive disease will be censored at the date last known to be MRD negative.

Duration of MRD negativity (months) = (earliest date of MRD positivity or progression or death or censor – date of MRD negativity + 1)/30.4375.

The analysis of duration of MRD negativity will include only patients who have achieved MRD negativity with a threshold of $10^{-5}$ based on the safety population.

If data permits, duration of MRD negativity will be summarized using KM method. Otherwise, a listing will be generated.

#### *6.6.2.2 Phase 2a dose finding*

Secondary efficacy endpoints include DOR, CBR, DCB, DCR, duration of disease control, TTP, TTR, TTNT, PFS, OS, MRD[-] CR rate, MRD[-] rate, and duration of MRD negativity.

**DOR**

DOR is defined in Section 6.6.2.1 and will be analyzed in the same way.

**CBR**

CBR is defined as the proportion of patients with a confirmed response of sCR, CR, VGPR, PR, or minimal response per IMWG criteria.

The analysis of CBR will be based on the safety population.

CBR will be summarized by frequencies, percentages, and 2-sided 95% exact binomial CIs.

**DCB**

DCB is defined as the time from the date of first documentation of a minimal response or better to the date of first documentation of confirmed progressive disease or death due to any cause, whichever occurs first. Patients without documentation of confirmed progressive disease or death will be censored at the censoring time point for PFS as specified in Table 1.

DCB (months) = (earliest date of PD or death or censor – date of first minimal response or better + 1)/30.4375.

The analysis of DCB is based on a subset of safety population that only includes patients who have achieved a minimal response or better.

DCB will be summarized using KM method. The 25th, 50th (median) and 75th percentiles, alone with associated 2-sided 95% CIs based on Brookmeyer and Crowley method.

## DCR

DCR is defined as the proportion of patients with a confirmed response of sCR, CR, VGPR, PR, minimal response, or SD per IMWG criteria.

The analysis will be based on the safety population.

DCR will be summarized by frequencies, percentages, and 2-sided 95% exact binomial CIs.

## Duration of disease control

Duration of disease control is defined as the time from date of first documentation of SD or better to the date of first documentation of confirmed progressive disease or death due to any cause. Patients without documentation of confirmed PD or death will be censored following the same censoring rule for PFS as specified in Table 1.

Duration of disease control (months) = (earliest date of PD or death or censor – date of first SD or better + 1)/30.4375.

The analysis of duration of disease control will include only patients who have achieved SD or better based on the safety population.

Duration of disease control will be summarized using KM method. The 25th, 50th (median) and 75th percentiles, alone with associated 2-sided 95% CIs based on Brookmeyer and Crowley method.

## TTP

TTP is defined as the time the date of randomization to the first documentation of confirmed PD per IMWG criteria, or death due to PD.

TTP (months) = (earliest date of progression or death due to PD or censor – date of randomization + 1)/30.4375.

The analysis of TTP will be based on the ITT population.

TTP will be summarized using KM method. The K-M curves, the 25th, 50th (median) and 75th percentiles, alone with associated 2-sided 95% CIs based on Brookmeyer and Crowley method, and the K-M probability estimates with 95% CIs at 3, 6, 9 and 12 months (or later time points if applicable) will be presented. The number of patients with events and the number of patients censored will be summarized. Sensitivity analysis based on the safety population will also be provided.

## TTR

TTR is defined as the time from the date of first dose administration of any study drug to the date of first documentation of confirmed PR or better.

The analysis of TTR will include only responders (PR or better) based on the safety population.

TTR will be summarized using descriptive statistics with mean and 95% CI.

## TTNT

TTNT is defined as the time from the date of first dose administration of any study drug to the date of the first dose initiation of the next line of anticancer therapy for any reason or death from any cause, whichever occurs first. Patients who neither started the next-line therapy nor die will be censored at the date last known to be alive before subsequent anticancer therapy. Patients who do not have any post-baseline follow-up assessments and who have not died will be censored at the date of first dose administration.

TTNT (months) = (earliest date of next line or death or censor – date of first dose + 1)/30.4375.

The analysis of TTNT will be based on the safety population.

TTNT will be summarized using KM method. The K-M curves, the 25$^{th}$, 50$^{th}$ (median) and 75$^{th}$ percentiles, alone with associated 2-sided 95% CIs based on Brookmeyer and Crowley method, and the K-M probability estimates with 95% CIs at 3, 6, 9 and 12 months (or later time points if applicable) will be presented. The number of patients with events along with the type of events (death or next line of anticancer therapy) and the number of patients censored will be summarized.

## PFS

PFS is defined as the time from the date of randomization to the date of confirmed disease progression or death due to any cause, whichever occurs first.

Censoring rule would follow Table 1 except for replacing "the date of first dose" with "the date of randomization".

PFS (months) = (earliest date of progression or death or censor – date of randomization + 1)/30.4375.

PFS would be analyzed in the same way as described in Section 6.6.2.1 based on the ITT population. Sensitivity analysis based on the safety population may also be provided.

## OS

OS is defined as the time from the date of randomization to the date of death due to any cause.

OS (months) = (date of death or censor – date of randomization + 1)/30.4375.

OS would be analyzed in the same way as described in Section 6.6.2.1 based on the ITT population. Sensitivity analysis based on the safety population will also be provided.

**MRD[-] CR rate**

MRD[-] CR rate is defined in Section 6.6.2.1 and will be analyzed in the same way based on the safety population.

**MRD[-] rate**

MRD[-] rate is defined in Section 6.6.2.1 and will be analyzed in the same way based on the safety population.

**Duration of MRD negativity**

Duration of MRD negativity is defined in Section 6.6.2.1 and will be analyzed in the same way based on the safety population.

### 6.6.3 Exploratory Endpoints Analysis

[redacted]

### 6.6.4 Subgroup Analyses

Please see Section 6.6.1.3.

## 6.7 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and type of AEs, and by changes from baseline in patients' vital signs, weights, ECOG performance status, ECG results, and clinical laboratory results.

All safety analyses will be performed using the safety population. Unless otherwise specified, all safety analyses will be reported according to actual study treatment received.

### 6.7.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 or later (based on the version at time of database lock) with the severity graded by the NCI CTCAE Version 5.0 or later (based on the version at time of database lock). Treatment-emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug.

Treatment-emergent AEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT) by dose level. For summary tabulations the following hematologic abnormalities coded to MedDRA preferred terms in the Investigations SOC will be pooled with the appropriate clinical terms in the Blood and lymphatic system disorders SOC:

| **MedDRA Preferred Term (Investigation SOC)** | **Mapped to (Blood and lymphatic system disorders SOC)** |
|---|---|
| Neutrophil count decreased | Neutropenia |
| Platelet count decreased | Thrombocytopenia |
| Hemoglobin decreased | Anemia |
| While blood cell count decreased | Leukopenia |
| Lymphocyte count decreased | Lymphopenia |

Summary tabulations will include the following categories by SOC/PT unless otherwise specified:

- Treatment-emergent AEs (by PT as well).
- Drug-related treatment-emergent AEs.

- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.
- Grade 3 and Grade 4 treatment-emergent AEs (based on maximum severity, by PT as well).
- Grade 5 treatment-emergent AEs.
- Grade 5 drug-related treatment-emergent AEs.
- The most commonly reported treatment-emergent AEs (i.e., those events reported by >= 10% of all patients, by PT only).
- Serious treatment-emergent adverse events (SAEs) (based on maximum severity).
- Drug-related treatment-emergent SAEs.
- Grade 3 or higher treatment-emergent SAEs.
- Grade 3 or higher drug-related treatment-emergent SAEs.
- Grade 3 and Grade 4 treatment-emergent SAEs (based on maximum severity).
- Grade 3 and Grade 4 drug-related treatment-emergent SAEs (based on maximum severity).
- Treatment-emergent AEs resulting in discontinuation of study drug.
- Treatment-emergent AEs resulting in study drug modifications (including discontinuation, delay, reduction, and interruption).
- Treatment-emergent AEs resulting in dose delays.
- Treatment-emergent AEs resulting in dose reductions.
- Treatment-emergent AEs resulting in infusion rate reductions
- Treatment-emergent AEs resulting in drug interruptions.
- Treatment-emergent AEs resulting in drug infusion interruptions.
- Treatment-emergent AESI – all Grades (by PT as well).
- Treatment-emergent AESIs Grade 3 or Grade 4.
- Treatment-emergent AESIs Grade 5.
- Serious treatment-emergent AESIs.

All summaries will be by dose levels by phases (phase 1 escalation and phase 2a dose finding) for patients in the safety population.

Patients with the same AE more than once will have that event counted only once within each SOC, and once within each preferred term. Patients with the same AE more than once will have only the maximum intensity of that event counted once within each SOC, and once within each preferred term.

Most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by preferred term only. Patients with multiple occurrences of the same AE will have that event counted only once within each preferred term.

An overall summary treatment-emergent AE table will include numbers and percentages of patients who had any treatment-emergent AE, drug-related treatment-emergent AE, Grade 3 or higher treatment-emergent AE, grade 3 or higher drug-related treatment-emergent AE, serious treatment-emergent AE, drug-related serious treatment-emergent AE, serious treatment-emergent AE leading to study drug discontinuation, treatment-emergent AE resulting in study drug discontinuation, and on-study deaths. On-study death is defined as deaths that occur between the first dose of study drug and up to 30 days after the last dose of study drug and deaths that occur more than 30 days after the last dose of study drug but are assessed as study drug-related.

A by-patient listing of DLTs as identified by the investigator that occur during Cycle 1 of treatment will be presented by dose levels for all patients enrolled during the phase 1 dose escalation portion of this study. Patients will be grouped by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower or higher dose level.

A by-patient listing of all deaths regardless of whether on study or not will also be presented. In this listing, on-study deaths will be flagged.

### 6.7.2 Adverse Events of Special Interest

AE of special interest from a scientific and medical perspective (AESI) will be reported by SOC and preferred terms. In this study, infusion-related reactions (IRR) are considered as AESIs. The IRR signs and symptoms will be counted with other AEs in the treatment-emergent AE tables with other AEs, and also reported separately in AESI tables.

### 6.7.3 Clinical Laboratory Evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used. Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will be presented. Scheduled laboratory along with unscheduled lab test results will be listed. Unscheduled laboratory test results will be included in the laboratory shift tables.

Lab parameters to be analyzed are as follows:

- Hematology: Hematocrit, Hemoglobin, Platelet count, Leukocytes with differential, Neutrophils (ANC).

- Chemistry: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen, calcium, bicarbonate ($HCO_3$) or carbon dioxide ($CO_2$), creatinine, standard C-reactive protein, chloride, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, urate, thyroid function test.

Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE Version 5.0. Shift tables will be constructed for laboratory parameters either using CTCAE grade or based on low/medium/high compared to normal ranges on patients who have both baseline and at least one post-baseline assessment. Individual platelet and ANC profiles will be generated for each dose level. Mean values over time for platelets and ANC will be produced.

### 6.7.4 Vital Signs

For dose escalation cohorts, descriptive statistics for vital sign results (diastolic and systolic blood pressure, respiratory rate, pulse rate, oxygen saturation and body weight) will be summarized by dose levels as follows:

- Baseline value (C1D1 or screening if C1D1 is not available).
- Minimum post-baseline value.
- Change to Minimum post-baseline value.
- Maximum post-baseline value.
- Change to Maximum post-baseline value.

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value.

### 6.7.5 12-Lead ECGs

ECG data (ventricular rate, RR interval, PR interval, QT interval, and QTcF interval) will be summarized by dose levels as follows:

- Baseline value (C1D1 or screening if C1D1 is not available).
- Minimum post-baseline value.
- Change to Minimum post-baseline value.
- Maximum post-baseline value.
- Change to Maximum post-baseline value.

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value.

In addition, a categorical analysis of QTcF intervals will be performed for each time point. The number and percentage of patients in each QTcF interval (<450 msec, 450-480 msec, >480-

<500 msec, and ⩾500msec) will be summarized at baseline and each of the subsequent time points. Categories of changes from baseline (⩾30 msec and ⩾60 msec) will be summarized as well.

### 6.7.6 Other Observations Related to Safety

Shifts from baseline to the worst post-baseline ECOG score will be tabulated.

## 6.8 Pharmacokinetic, [redacted], and Biomarker Analyses

### 6.8.1 Pharmacokinetic Analysis

#### *6.8.1.1 Serum Modakafusp alfa Concentrations*

Blood samples will be collected at prespecified time points as described in the study protocol for the measurement of serum modakafusp alfa and daratumumab concentrations. Individual serum concentration data will be listed by patient, dose level, study day, and sampling time. Both nominal (scheduled) and actual sampling times will be presented in the listings.

Serum modakafusp alfa and daratumumab concentrations will be summarized by nominal time post dose, grouped by dose level, nominal infusion duration, and study day by phases (escalation and dose finding). Summary statistics will be reported at nominal sampling times; means will be reported if the number of observations above the lower limit of quantitation (NALQ) is ⩾50% of the number of patients. The summary statistics will consist of: N, NALQ, arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, geometric CV, median, min, and max. The SD and CV will be reported on at least 3 non-missing values. Modakafusp alfa concentrations that are below the limit of quantitation (BLQ) will be set to zero for calculation of summary statistics, except for geometric means, where BLQ values will be considered missing.

Concentration data that are considered anomalous may be excluded from the concentration summaries and plots. Evidence or explanations will be provided in the clinical study report to justify the exclusion of concentration data.

Mean and individual modakafusp alfa and daratumumab serum concentration data will be plotted over nominal sampling time, grouped by dose level, nominal infusion duration, and study day on both linear and semi-logarithmic scales. Mean and individual serum concentrations will be plotted over time (labeled with cycle number), grouped by dose level on a linear scale by phases (escalation and dose finding). Visual inspection of the serum concentration-time plots will be used to make inferences regarding the attainment of PK steady-state by cycle. BLQ values will be plotted as zero on a linear scale and treated as missing on a semi-logarithmic scale.

*6.8.1.2 Serum PK Parameters (Phase 1 Dose Escalation)*

The serum PK concentration-time course data will be used to calculate standard PK parameters using noncompartmental methods with Phoenix WinNonlin.

Actual sampling times will be used for the calculation of PK parameters. In the event that actual collection times are either unreliable or missing, nominal collection times will be used. For the calculation of PK parameters, serum concentrations of modakafusp alfa that are BLQ will be treated as zero prior to $t_{max}$, missing between $t_{max}$ and the time of the last measurable concentration, and the concentration-time curve will be considered to have terminated at the time of the last measurable concentration. If measurable concentrations are near the lower limit of quantification (LLOQ) or imbedded between BLQ concentrations, these values may be excluded at the discretion of the Clinical Pharmacologist. Concentration data that are considered anomalous may not be used in the calculation of PK parameters; evidence or explanations will be provided in the clinical study report to justify the exclusion of data. In addition, patients with several missing samples around the expected $T_{max}$ and patients for whom AUC estimation was considered not be reliable due to several missing samples (50% or more of the data are missing) may be excluded from the PK parameter (Cmax and/or AUC) calculation and PK parameter summary.

The following PK parameters for modakafusp alfa will be determined, as permitted by data:

- $C_{max}$.
- $t_{max}$.
- $AUC_{\infty}$.
- $AUC_{last}$.
- $\lambda_z$.
- $t_{1/2z}$.
- CL.
- $V_{ss}$.
- Accumulation ratio based on $AUC_{last}$.

The following PK parameters for daratumumab will be determined, as permitted by data:

- $C_{max}$.
- $t_{max}$.
- $C_{trough}$ (for daratumumab)
- $AUC_{\infty}$.
- $AUC_{last}$.

Individual PK parameters will be presented in listings, PK parameters for Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 2 Day 15, as appropriate, will be summarized and grouped by dose level, and study day by phases (escalation and dose finding). The SD and CV will be reported on at least 3 non-missing values. Except for $t_{max}$, the summary statistics will consist of: N, mean, SD, CV, geometric mean, geometric CV, median, min, and max. The summary statistics for $t_{max}$ will consist of: N, median, min, and max.

The PK data collected in this study (phase 1 dose escalation and phase 2 dose finding) are intended to contribute to future population PK analyses of modakafusp alfa. These population PK analyses may include data collected in other modakafusp alfa clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will not be reported in the clinical study report.

### 6.8.2 [redacted]

[redacted]

### 6.8.3 Immunogenicity Analysis

The immunogenicity of modakafusp alfa will be assessed by determining anti–modakafusp alfa antibody (ADA) incidence and characteristics (eg, titer and specificity) and by determining neutralizing antibody (NAb) incidence. All ADA and NAb data will be listed. Percent of patients with positive ADA or NAb, percent of patients with positive ADA by domain specificity, and summary statistics of ADA titer at each timepoint will be summarized by dose levels by study phases (escalation and dose finding). Percent of patients with positive ADA and NAb at baseline and positive ADA (final result and by domain specificity) and NAb at any post-baseline time point during the study will be summarized. Additional summary of the ADA kinetics including transient- vs. persistent-ADA, preexisting ADA, treatment-induced, or treatment-boosted ADA will be summarized, as applicable. ADA titer distribution over time will be presented through a boxplot on a logarithmic scale. [redacted]

[redacted]

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