Statistical Analysis Plan

NCT Number: NCT05556616

Title: A Phase 1b Open-label Study to Evaluate the Safety and Tolerability of Intravenous Modakafusp Alfa as Part of Combination Therapy in Adult Patients With Multiple Myeloma

Study Number: TAK-573-1502

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STATISTICAL ANALYSIS PLAN

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Phase: Phase 1b

Version: 1.0

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N/A	N/A	N/A

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LIST OF IN-TEXT TABLES AND FIGURES

ABBREVIATIONS

ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
ASCT	Autologous stem cell transplant
C1D1	Cycle 1 day 1
CBR	Clinical benefit rate
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
IRR	Infusion-related reaction
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MRD	Minimal/measurable residual disease
MTD	Maximum tolerated dose
NAb	Neutralizing antibody
NDMM	Newly diagnosed multiple myeloma
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term (MedDRA)
QTcF	QT interval with Fridericia correction method
RP2D	Recommended phase 2 dose
RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event
sCR	Stringent CR
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTNT	Time to next treatment
TTP	Time to progression
TTR	Time to response
VGPR	Very good partial response

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

The primary objectives of the study are:

Group 1: Newly Diagnosed Multiple Myeloma (NDMM) Maintenance

- To determine the safety and tolerability of modakafusp alfa and lenalidomide combination therapy as maintenance in adult patients with NDMM after autologous stem cell transplant (ASCT).
- To determine the recommended phase 2 dose (RP2D) of the combination therapy with modakafusp alfa.

Group 2: Relapsed Refractory Multiple myeloma (RRMM) Doublet Combinations (Doublets)

- To determine the safety and tolerability of modakafusp alfa as part of 2-drug combination therapy in adult patients with RRMM.
- To determine the RP2D of the combination therapy with modakafusp alfa (recommended doses of the doublet combinations).

Group 3: RRMM Triplet Combinations (Triplets)

- To determine the safety and tolerability of modakafusp alfa as part of 3-drug combination therapy in adult patients with RRMM.
- To determine the RP2D of the combination therapy with modakafusp alfa (recommended doses of the triplet combinations).

1.1.2 Secondary Objectives

The secondary objectives of the study are:

Group 1: NDMM Maintenance

- To evaluate the preliminary efficacy of modakafusp alfa and lenalidomide combination therapy as maintenance in adult patients with NDMM after ASCT.
- To evaluate the rate and duration of minimal/measurable residual disease (MRD) negativity.
- To collect PK data to support population PK and exposure-response analysis of modakafusp alfa when given in combination therapy.
- To characterize the immunogenicity profile of modakafusp alfa when given in combination therapy.

Group 2: RRMM Doublets

- To evaluate the preliminary efficacy of modakafusp alfa as part of 2-drug combination therapy in adult patients with RRMM.
- To collect PK data for modakafusp alfa to support population PK and exposure-response analysis of modakafusp alfa when given in combination therapy.
- To collect PK data of daratumumab to support population PK and exposure-response analysis of daratumumab when given in modakafusp alfa/daratumumab combination therapy.
- To characterize the immunogenicity profile of modakafusp alfa when given in combination therapy.

Group 3: RRMM Triplets

- To evaluate the preliminary efficacy of modakafusp alfa as part of 3-drug combination therapy in adult patients with RRMM.
- To evaluate the rate and duration of MRD negativity in patients achieving complete response (CR).
- To collect PK data to support population PK and exposure-response analysis of modakafusp alfa when given in combination therapy.
- To characterize the immunogenicity profile of modakafusp alfa when given in combination therapy.

1.1.3 [redacted]

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoints

The primary endpoints of the study for Groups 1, 2, and 3 (NDMM Maintenance, RRMM doublets, and RRMM triplets) are:

- Occurrence of dose-limiting toxicities (DLTs) in Cycle 1.
- Frequency and severity of treatment-emergent adverse events (TEAEs).

1.2.2 Secondary Endpoints

Secondary endpoints are:

Group 1: NDMM Maintenance

- Progression free survival (PFS).
- Overall response rate (ORR) (local assessment).
- Duration of response (DOR).
- MRD negative rate at a sensitivity of 10^{-5} in patients 6 months, 1 year, and 2 years after treatment in the MRD analysis set.
- Duration of MRD negativity at a sensitivity of 10^{-5} for patients achieving MRD negativity.
- Antidrug antibody (ADA) incidence and characteristics (eg, titer and specificity) and neutralizing antibody (NAb).

Group 2: RRMM Doublets

- Overall survival (OS).
- ORR.
- PFS.
- Time to progression (TTP).
- Time to next treatment (TTNT).
- DOR.
- Disease control rate (DCR).
- Clinical benefit rate (CBR).
- Time to response (TTR).
- ADA incidence and characteristics (eg, titer and specificity) and NAb.

Group 3: RRMM Triplets

- OS.

- ORR.
- PFS.
- TTP.
- TTNT.
- DOR.
- DCR.
- CBR.
- TTR.
- Rate of MRD negative status at a sensitivity of 10^{-5} in patients achieving CR.
- Duration of MRD negativity at a sensitivity of 10^{-5} for patients achieving MRD negativity.
- ADA incidence and characteristics (eg, titer and specificity) and NAb.

1.2.3 [redacted]

[redacted]

1.3 Estimands

Not applicable.

2.0 STUDY DESIGN

This is a global multicenter, open-label, phase 1b study designed to evaluate the safety and tolerability of modakafusp alfa in combination therapy and determine the RP2D of the combination therapy with modakafusp alfa in adult patients with MM. The study will be conducted using 3 groups based on MM status; the combinations to be evaluated within each group are as follows:

Group 1: NDMM Maintenance

Arm 1: Modakafusp alfa + lenalidomide after ASCT as maintenance therapy in NDMM post-ASCT

Group 2: RRMM Doublets

Arm 2: Modakafusp alfa + pomalidomide (MP) in RRMM

Arm 3: Modakafusp alfa + bortezomib (MV) in RRMM

Arm 4: Modakafusp alfa + carfilzomib (MK) in RRMM

Arm 5: Modakafusp alfa + daratumumab (MD) in RRMM

Group 3: RRMM Triplets

Arm A: Modakafusp alfa + pomalidomide + bortezomib (MPV) in RRMM

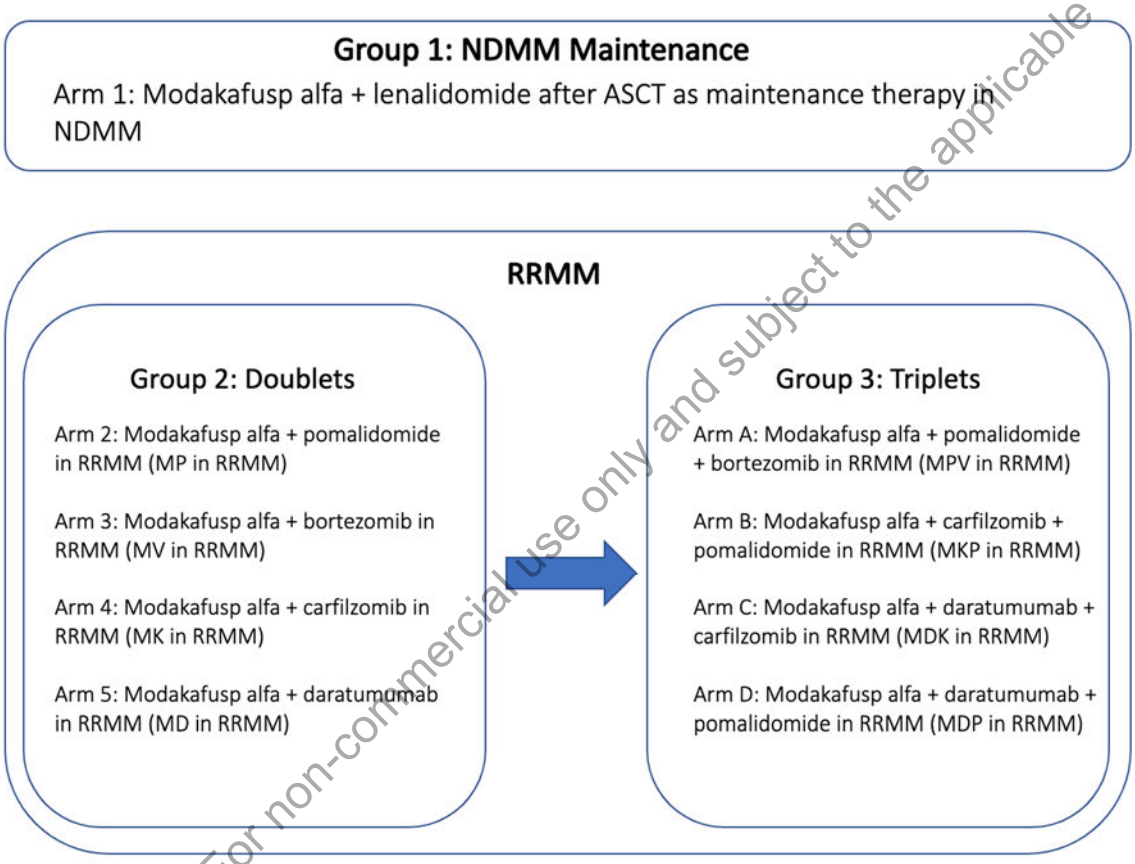
Arm B: Modakafusp alfa + carfilzomib + pomalidomide (MKP) in RRMM

Arm C: Modakafusp alfa + daratumumab + carfilzomib (MDK) in RRMM

Arm D: Modakafusp alfa + daratumumab + pomalidomide (MDP) in RRMM

The overall study schema is shown in **Error! Reference source not found.**.

Figure 2.a Study Schema



➔ After the doublet RP2D is determined in RRMM doublets, dose escalation of modakafusp alfa in triplet combinations will begin.

ASCT: autologous stem cell transplant; MD: modakafusp alfa and daratumumab; MDK: modakafusp alfa, daratumumab, and carfilzomib (Kyprolis®); MDP: modakafusp alfa, daratumumab, and pomalidomide; MK: modakafusp alfa and carfilzomib (Kyprolis®); MKP: modakafusp alfa, carfilzomib (Kyprolis®), and pomalidomide; MP: modakafusp alfa and pomalidomide; MPV: modakafusp alfa, pomalidomide, and bortezomib (Velcade®); MV: modakafusp alfa and bortezomib (Velcade®); NDMM: newly diagnosed multiple myeloma; RRMM: relapsed or refractory multiple myeloma.

Patient participation will include a screening phase, a treatment phase, and a follow-up phase. The screening phase will be up to approximately 21 days before Cycle 1 Day 1.

Patients will be evaluated approximately 30 days after the last dose of modakafusp alfa (EOT visit) or right before the start of subsequent systemic anticancer therapy to permit the detection of any delayed TEAEs. The follow-up phase of the study begins once a patient discontinues study treatment and completes the EOT visit; study follow-up continues until the study ends or the patient completes OS follow-up.

Patients who discontinue for reasons other than progressive disease (PD) will continue PFS follow-up every 4 weeks from the EOT visit until the occurrence of PD, death, the start of subsequent systemic antineoplastic therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first. OS follow-up continues every 12 weeks until death, study termination, or patient withdrawal.

The BOIN design (Liu & Yuan, 2015) will be implemented for dose escalation/de-escalation (Figure 2.b). Patients will be enrolled and treated in cohort sizes of approximately 3. The starting dose will need to treat at least 3 evaluable patients.

Group 1: NDMM Maintenance

The target toxicity rate for maximum tolerated dose (MTD) is set to be $\phi = 0.25$. For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.25 \mid \text{data}) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level j. When the lowest dose is eliminated, the study will be stopped for safety. It is estimated that approximately 12 DLT-evaluable patients will be enrolled.

The BOIN design will be implemented following the steps described below:

1. Patients in the first cohort are treated at a starting dose with at least 3 evaluable patients.
2. A dose is assigned to the next cohort of patients according to the rule below:
   - If the observed DLT rate at the current dose is $\leq \lambda_e = 0.197$, escalate the dose to the next higher level.
   - If the observed DLT rate at the current dose is $> \lambda_d = 0.298$, de-escalate the dose to the next lower dose level.
   - Otherwise, stay at the current dose.
3. Repeat step 2 until the maximum sample size of 12 is reached or stop the study if the number of evaluable patients treated at the current dose reaches 6 and the decision is made to stay at the current dose.

Group 2: RRMM Doublets

The BOIN design will be implemented in the same way as Group 1. It is estimated that approximately 48 DLT-evaluable patients will be enrolled for RRMM doublet combinations, with approximately 12 for each of Arms 2-5.

Group 3: RRMM Triplets

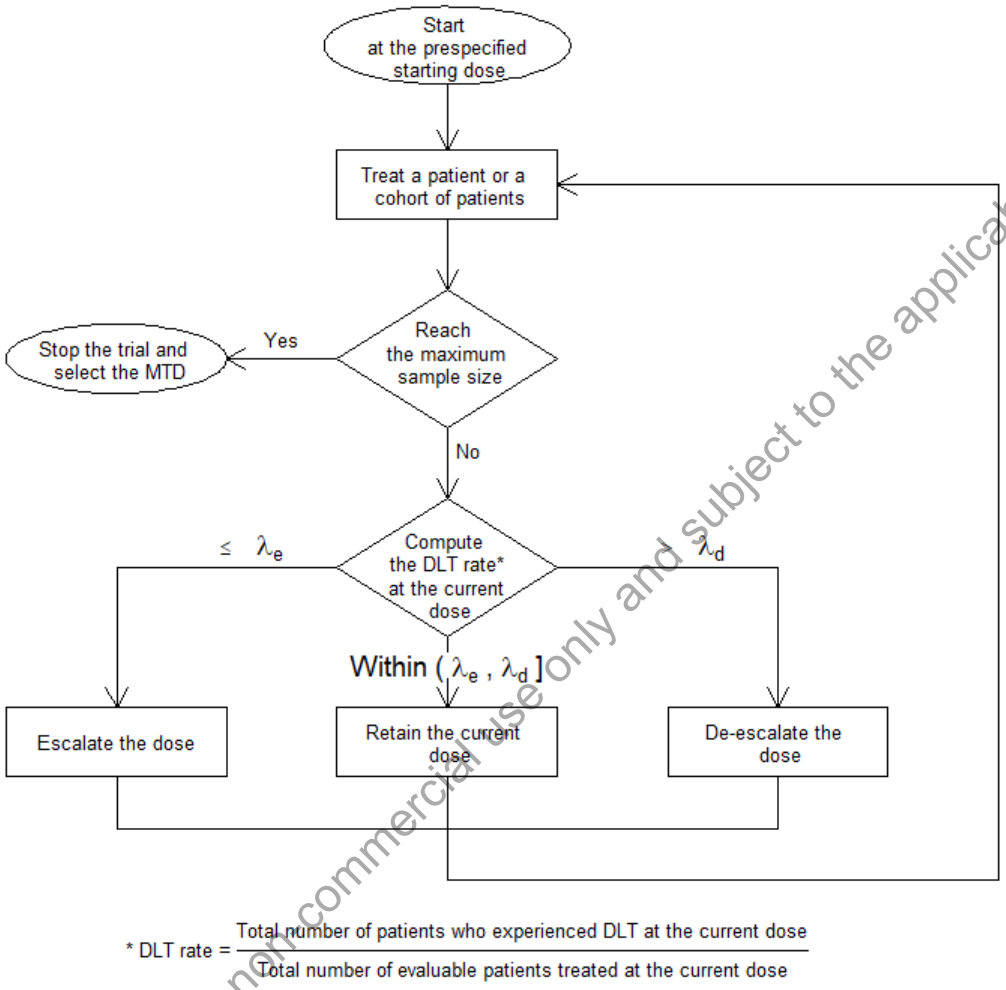
After the doublet RP2D is determined in Group 2, dose escalation of modakafusp alfa in Group 3 will begin. The target toxicity rate for MTD is set to be $\phi = 0.33$.

For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.33 \mid \text{data}) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level j. When the lowest dose is eliminated, stop the study for safety. It is estimated that approximately 60 DLT-evaluable patients will be enrolled, with approximately 15 for each of 4 arms A-D.

The escalation/de-escalation will be conducted in steps as follows:

4. Patients in the first cohort are treated at the starting dose level with at least 3 evaluable patients.
5. Assign a dose to the next cohort of patients according to the rule below:
   - If the observed DLT rate at the current dose is $\leq \lambda_e = 0.260$, escalate the dose to the next higher level.
   - If the observed DLT rate at the current dose is $> \lambda_d = 0.395$, de-escalate the dose to the next lower dose level.
   - Otherwise, stay at the current dose.
6. Repeat step 2 until the maximum sample size of 15 is reached or stop the study if the number of evaluable patients treated at the current dose reaches 9 and the decision is to stay at the current dose.

Figure 2.b Flowchart for Study Conduct Using the BOIN design



BOIN: Bayesian Optimal Interval; DLT: dose-limiting toxicity; MTD: maximum tolerated dose; λ_d: DLT rate de-escalation boundary; λ_e: DLT rate escalation boundary.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

The BOIN design will be implemented for dose escalation/de-escalation. The target toxicity rate for MTD is set to be $\phi = 0.25$ for NDMM maintenance (Group 1) and RRMM doublets (Group 2) and $\phi = 0.33$ for RRMM triplets (Group 3). Approximately 120 patients will be enrolled into the following groups:

- Group 1 (NDMM maintenance; Arm 1) A total of approximately 12 patients will be enrolled.

- Group 2 (RRMM doublets): A total of approximately 48 patients will be enrolled (12 for each of 4 cohorts: Arms 2 to 5).
- Group 3 (RRMM triplets): Approximately 60 patients will be enrolled (15 for each of 4 cohorts: Arms A to D).

The operating characteristics of the BOIN design evaluated with 1000 simulations assuming various distributions of toxicity across dose levels are presented in Appendix 9.4.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set will include all patients who have received at least 1 dose, even if incomplete, of any study drug.

5.2 PK Analysis Set

Patients from the safety analysis set with sufficient dosing and PK data to reliably report 1 or more PK concentration will be used for PK analyses.

5.3 DLT-Evaluable Analysis Set

The DLT-evaluable analysis set will include patients who experienced a DLT in Cycle 1 in the treatment phase of the study or have completed Cycle 1 procedures and have received Cycle 1 dose of modakafusp alfa and at least 75% of the planned dose of the combination partners. The DLT-evaluable population will be used to determine the RP2D/MTD.

5.4 Response-Evaluable Analysis Set

The response-evaluable analysis set is a subset of the safety analysis set including patients with measurable disease at baseline and at least 1 post-baseline efficacy evaluation.

5.5 Immunogenicity-Evaluable Analysis Set

Analysis will be based on available data from patients with a baseline assessment and at least 1 post-baseline immunogenicity assessment.

5.6 MRD Analysis Set

The MRD-evaluable analysis set for Group 1 (NDMM Maintenance) will be all patients who are MRD+ upon study entry, as determined by the required central analysis for MRD at screening. The MRD-evaluable analysis set for Group 3 (RRMM Triplets) will be a subset of the safety analysis set including all patients who are in CR and have at least 1 evaluable post-baseline MRD assessment.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Where applicable, variables will be summarized descriptively by study visit. For categorical variables, the count and proportions of each possible category value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated for all patients in the relevant analysis set. Means and medians will be presented to 1 more decimal place than the recorded data. The SDs will be presented to 2 more decimal places than the recorded data. CIs will be presented using the same number of decimal places as the parameter estimate.

6.2 Disposition of Subjects

Reasons for screen failures will be generated in a summary table.

Subjects disposition including subjects in each of the study populations, subjects who have completed the study, subjects who are off treatment, the primary reasons for discontinued treatment, subjects who are ongoing (if applicable at the time of database lock/data cut-off), subjects participating in PFS follow-up, subjects who discontinued from the study, as well as primary reasons discontinued from the study, will be generated in a summary table by safety analysis set.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Demographics will be summarized using safety analysis set. Demographics variables include age at the date of informed consent, race, ethnicity, sex, height, and weight.

6.3.2 Medical History and Concurrent Medical Conditions

Medical History and concurrent medical conditions will be summarized using safety analysis set. Medical history and concurrent medical conditions will be coded using the latest MedDRA dictionary. Concurrent medical conditions are the ones ongoing or started on or after the day informed consent was signed. Medical history and concurrent medical conditions will be summarized separately by safety analysis set.

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 safety analysis set.

Variables include disease characteristics, imaging assessments, laboratory assessments, baseline bone marrow assessment, cytogenetics, and prior therapy.

6.4 Medication History and Concomitant Medications

Medication history and concomitant medications will be coded using the latest 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 Medications

Medication history is defined as the medication stopped before the first dosing date of the study drug. Medication history will be summarized using safety analysis set.

6.4.2 Concomitant Medications

Concomitant medication is defined as the medication ongoing or started on or after the first dosing date of the study drug. Concurrent medications will be summarized using safety analysis set by WHO standardized medication name.

6.5 Efficacy Analysis

Efficacy endpoints will be derived for all patients enrolled into the study and listed as appropriate. Efficacy analyses will be summarized by treatment arms.

6.5.1 Primary Endpoints Analysis

No primary efficacy endpoints are included.

6.5.2 Secondary Endpoints Analysis

<u>Group 1: NDMM Maintenance</u>

Secondary endpoints include PFS, ORR, DOR, MRD negative rate, duration of MRD negativity, and MRD negative rate at 6 months, 1 year, and 2 years after treatment.

<u>Group 2: RRMM Doublets</u>

Secondary endpoints include OS, PFS, ORR, DOR, TTP, TTNT, DCR, CBR, and TTR.

<u>Group 3: RRMM Triplets</u>

Secondary endpoints include OS, PFS, ORR, DOR, TTP, TTNT, DCR, CBR, TTR, and MRD negative rate in patient achieving CR.

6.5.2.1 Derivation of Endpoints

Group 1: NDMM Maintenance

PFS is defined as the time from the date of the first dose administration to the date of first documentation of confirmed PD or death due to any cause, whichever occurs first. PD will be determined by IMWG criteria. Patients without documentation of PD or death will be censored at the date of last response assessment.

ORR is defined as the proportion of patients who achieved a partial response (PR) or better (determined by the investigator) during the study based on IMWG criteria.

DOR is defined as time from the date of first documentation of a confirmed PR or better to the date of first documentation of PD or death due to any cause. Responders without documentation of PD or death will be censored at the date of last adequate response assessment that is stable disease or better. The DOR will be calculated only for those patients with a confirmed PR or better.

MRD negative rate at a sensitivity of 10^{-5} is defined as the proportion of patients who have achieved MRD negative status.

Duration of MRD negativity is defined as the duration from the start of MRD negative status to the time of reappearance of detectable MRD (MRD positive), PD, or death. Patients who achieve MRD negative status, but have no documentation of reappearance of detectable MRD, PD, or death will be censored at the date of last assessment that is MRD negative.

Group 2: RRMM Doublets

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

PFS, ORR, and DOR are defined same as in Group 1.

TTP is defined as the time from the date of the first dose administration to the date of the first documentation of PD as defined by IMWG criteria. Patients without documentation of progression will be censored at the date of last response assessment.

TTNT is defined as the time from the date of first dose administration to the date of the first dose initiation of the next line of antineoplastic therapy, for any reason. Patients who have not started the next-line therapy will be censored at the date last known to be alive before subsequent anticancer therapy.

DCR is defined as the proportion of patients with a response of stringent complete response (sCR), CR, very good partial response (VGPR), PR, minimal response, or stable disease based on investigator's disease assessment per IMWG criteria.

CBR is defined as the proportion of patients who had a response of sCR, CR, VGPR, PR, or minimal response based on investigator's disease assessment per IMWG criteria.

TTR is defined as the time from the date of the first dose administration to the date of the first documentation of objective response as defined by IMWG criteria.

Group 3: RRMM Triplets

The definitions are defined same as in Group 1 and Group 2.

6.5.2.2 Main Analytical Approach

Group 1: NDMM Maintenance

- PFS will be analyzed using the safety analysis set.

  The PFS in months [(earliest date of progression or death or censor – date of first dose + 1)/30.4375], and the status (death, PR, or censored) will be presented in listing. Refer to Table 6.a for detailed censoring rules.

  The Kaplan-Meier method will be used to estimate the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% CIs based on Brookmeyer and Crowley method.

- ORR will be analyzed using the response-evaluable analysis set.

  The frequencies, percentages, and the exact two-sided 95% CIs will be summarized.

- DOR will be analyzed for the responders only (PR or better).

  DOR in months [(date of progression/death or censor – date of confirmed response + 1)/30.4375], and the status (death, PD, or censored) will be presented in listing. Refer to Table 6.a for detailed censoring rules.

  The Kaplan-Meier method will be used to estimate the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% CIs based on Brookmeyer and Crowley method.

- MRD negativity rate at a sensitivity of 10^{-5} will be analyzed based on MRD-evaluable analysis set. The denominator would be all patients who are MRD+ based on the central analysis during screening who have a subsequent on-treatment MRD evaluation. The number and percentage of subjects who have achieved MRD negativity rate at a sensitivity of 10^{-5} will be presented in listing by dose level. The corresponding exact 95% CI for MRD negativity (10^{-5}) rate will also be provided. The rate of maintaining MRD negativity (10^{-5}) will be reported in patients who achieve CR and MRD negativity (10^{-5}).

- Duration of MRD negativity at a sensitivity of 10^{-5} will be analyzed for patients who reach MRD negative status only. The Kaplan-Meier method will be used to estimate the 25^{th}, 50^{th} (median), and 75^{th} percentiles, along with associated 2-sided 95% Cis based on Brookmeyer and Crowley method.

Table 6.a Progression and Censoring Date for PFS and DOR Analyses

Scenarios	Event date/censoring date	Event status
No (or inadequate) baseline tumor assessments	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	Event
No confirmed progression or death	Date of last adequate assessment of response	Censored
Subsequent anti-cancer therapy started (before documented confirmed progression or death)*	Date of last adequate assessment of response[2] (prior to the initiation of the subsequent anti-cancer therapy)	Censored
Death without extended loss-to-follow-up time	Death date	Event
Death or progression after an extended loss-to-follow-up time (two or more missed cycles)[4]	Date of last adequate assessment of response[2] (prior to missed assessments)	Censored

*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.

Group 2: RRMM Doublets

- OS will be analyzed using the safety analysis set.

  The OS in months [(death or censored – date of first dose + 1)/30.4375], and the status (death or censored) and the status (death, or censored) will be presented in listing by dose level.

  The Kaplan-Meier method will be used to estimate the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% CIs based on Brookmeyer and Crowley method.

- PFS will be analyzed the same way as in Group 1.
- ORR will be analyzed the same way as in Group 1.
- DOR will be analyzed the same way as in Group 1.

- TTP will be analyzed using the safety analysis set.

  The Kaplan-Meier method will be used to estimate the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% CIs based on Brookmeyer and Crowley method by dose level. A Kaplan-Meier plot of TTP time will be provided. Refer to Table 6.b for detailed censoring rules.

- TTNT will be analyzed using the safety analysis set.

  The Kaplan-Meier method will be used to estimate the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% CIs based on Brookmeyer and Crowley method by dose level. A Kaplan-Meier plot of TTNT time will be provided.

- DCR will be analyzed using the response-evaluable analysis set.

  The frequencies, percentages, and the exact two-sided 95% CIs will be summarized.

- CBR will be analyzed using the response-evaluable analysis set.

  The frequencies, percentages, and the exact two-sided 95% CIs will be summarized.

- TTR will be analyzed as a continuous variable for the responders only (PR or better).

  Mean, median, standard deviation, minimum, maximum, 25th, and 75th percentiles will be summarized.

Table 6.b Progression and Censoring Date for TTP Analyses

Scenarios	Event date/censoring date	Event status
No (or inadequate) baseline tumor assessments	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	Event
No confirmed progression or death	Date of last adequate assessment of response	Censored
Subsequent anti-cancer therapy started (before documented confirmed progression or death)*	Date of last adequate assessment of response (on or prior to the initiation of the subsequent anti-cancer therapy)	Censored
Death due to progression without extended loss-to-	Death date	Event

follow-up time		
Death from causes other than progression without extended loss-to-follow-up time	Date of last adequate assessment of response[2] prior to death	Censored
Death or progression after an extended loss-to-follow-up time (two or more missed cycles)	Date of last adequate assessment of response[2] (prior to missed assessments)	Censored

*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.

Group 3: RRMM Triplets

The main analytical approach will be the same as in Group 1 and Group 2 except for MRD negativity rate in patients achieving CR, the denominator would be the number of patients in CR that have an evaluable MRD test.

6.6 Safety Analysis

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

6.6.1 DLTs

DLT will be analyzed in the DLT-evaluable analysis set. A by-patient listing of DLTs as identified by the investigator that occur during cycle 1 will be presented by dose schedule and dose levels. 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.

6.6.2 Adverse Events

Adverse events (AEs) will be analyzed using safety analysis set.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or later (based on version at time of database lock).

Treatment-emergent AE is defined as any AE that occurs after administration of the first dose of any study treatment through 30 days after the last dose of any study treatment. Treatment-emergent AEs will be summarized by MedDRA system organ class (SOC), and preferred term (PT). 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

TEAEs will also be summarized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 or later.

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 after 30 days after the last dose of study drug but are assessed as related to treatment. The following tables will be presented with the number and percentage of subjects by MedDRA SOC and PT. All summaries will be by group and dose levels. Patients with multiple occurrences of same AEs of the same PT and SOC will be counted once for each PT or SOC. Patients with multiple occurrences of same AEs will have only the maximum intensity of that AE event counted once for each PT or SOC. These tables will be ordered in descending order of overall SOC incidence and overall PT incidence within each SOC.

- All DLTs (in the DLT Evaluable Population);
- All treatment-emergent AEs (TEAEs);
- All TEAEs by maximum CTCAE severity grade;
- All TEAEs CTCAE severity Grade 3 or 4;
- All TEAEs CTCAE severity Grade 5;
- Drug-related TEAEs;
- Drug-related TEAEs by maximum CTCAE severity grade;
- Drug-related TEAEs CTCAE severity Grade 3;
- Drug-related TEAEs CTCAE severity Grade 4;
- Drug-related TEAEs CTCAE severity Grade 3 or 4;
- Drug-related TEAEs CTCAE severity Grade 5;
- Serious TEAEs (SAEs) ;
- SAEs by maximum CTCAE severity grade;
- SAEs CTCAE severity Grade 3 or 4;

- SAEs CTCAE severity Grade 5;
- Drug-related SAEs (any related serious TEAEs);
- Drug-related SAEs by maximum CTCAE severity grade;
- Drug-related SAEs and CTCAE severity Grade 3 or 4;
- Drug-related SAEs and CTCAE severity Grade 5;
- TEAEs leading to dose delays;
- TEAEs leading to dose reduction;
- TEAEs leading to infusion rate reduction;
- TEAEs leading to dose interruption;
- TEAEs leading to drug infusion interruptions;
- TEAEs leading to drug discontinuation;
- All TE AESIs, e.g. infusion-related reactions (IRR)
- TE AESIs (IRRs) CTCAE severity Grade 3 or 4;
- TE AESIs (IRRs) CTCAE severity Grade 5;
- All Serious TE AESIs (IRRs);TEAEs leading to on-study death or treatment related death.

The following summary tables will display the number and percentage of patients by PT only and will be ordered in descending order of PT:

- All TEAEs;
- Drug-related TEAEs;
- SAEs (any serious TEAEs);
- Drug-related SAEs (any related serious TEAEs);
- All TE AESIs, e.g. infusion-related reactions (IRR)
- The most commonly reported TEAEs (i.e. those events reported by >= 10% of all patients)

6.6.3 Clinical Laboratory Evaluations

All laboratory values (e.g. hematology, chemistry, urinalysis, etc) 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 by dose level. Scheduled laboratory along with unscheduled lab test results will be listed.

Lab parameters to be analyzed are as follows:

Table 6.c Clinical Laboratory Tests

Hematology	Chemistry		Urinalysis	Other
Hematocrit	Albumin	Standard C-reactive protein	Bilirubin	Serology Hepatitis B (HBsAg, HBcAb, HBsAb)
Hemoglobin	Alkaline phosphatase	Chloride	Glucose	Serology Hepatitis C (HCV Ab)
Platelet count	Alanine aminotransferase	Glucose (nonfasting)	Ketones	Serology HIV
Leukocytes with differential	Aspartate aminotransferase	Lactate dehydrogenase	Leukocytes	Serum β_2 macroglobulin
Neutrophils (ANC)	Bilirubin (total)	Magnesium	Nitrites	Thyroid function test (TSH, T4, T3)
Plasma cells and blasts	Blood urea nitrogen	Phosphate	Occult blood	
	Calcium	Potassium	pH	
	Bicarbonate (HCO_3^-) or carbon dioxide (CO^2)	Sodium	Protein	
	Creatinine	Urate	Specific gravity	
			Turbidity and color	
			Urobilinogen	

Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE Version 5.0 or later. 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 schedule/dose level.

6.6.4 Vital Signs

Vital sign results (temperature, pulse, respiratory rate, oxygen saturation, diastolic blood pressure, systolic blood pressure) will be summarized by schedules and 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.

For blood pressure values collected during the infusion, the number and percentage of patients with changes from pre-infusion blood pressure values will be summarized in the following categories:

- Increase of diastolic blood pressure of at least 10 mm Hg during any infusion.
- Decrease of diastolic blood pressure of at least 10 mm Hg during any infusion.
- Increase of systolic blood pressure of at least 20 mm Hg during any infusion.
- Decrease of systolic blood pressure of at least 20 mm Hg during any infusion.

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

6.6.5 12-Lead ECGs

ECG data (ventricular rate, RR interval, PR interval, QT interval, and QTcF interval) will be summarized by schedules and 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.

6.6.6 ECOG

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

6.6.7 Extent of Exposure and Compliance

The exposure to study drugs (modakafusp alfa and combinations agents) characterized by summaries and descriptive statistics of duration of treatment in weeks [(Date of last study drug exposure – date of first study drug dose + 1)/7], number of treated cycles (1, 2, 3, 4, 5, 6, 7-12, >12), and relative dose intensity will be summarized using the safety analysis set.

- A treated cycle is defined as a cycle in which any amount of study drug for at least one of the dosing days in the cycle;
- Cumulative dose is defined as the sum of all doses of the study drug administered to a subject during the treatment period. For example, cumulative dose of modakafusp alfa is defined as the sum of all doses of modakafusp alfa administered to a subject during the treatment period; Cumulative dose of each agent is defined as the sum of all doses of the agent administered to a subject during the treatment period.
- Relative dose intensity = (actual dose per week / planned dose per week) × 100. The actual dose per week adjusts for delays in the start of a cycle and assumes the last cycle is fixed at the intended duration.
    - Actual dose per week: cumulative dose / treatment interval in weeks;
    - Planned dose per week: starting dose on C1D1 / treatment interval in weeks.

Action on Study Drug

The reason for dose modification (e.g. dose increased, dose reduced, interrupted, withdrawn, delayed, rate increased, rate reduced, drug infusion interrupted) of study drugs (modakafusp alfa and combination agents) will be summarized by cycles for the safety analysis set.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic/Pharmacodynamic Analyses

The pharmacokinetic and pharmacodynamic analyses will be performed using PK analysis set and described in a separate analysis plan.

6.7.2 Immunogenicity Analysis

The immunogenicity analysis will be performed using immunogenicity-evaluable analysis set. The immunogenicity of modakafusp alfa will be assessed by determining anti–modakafusp alfa antibody (ADA) incidence and characteristics and by determining neutralizing antibody (NAb) incidence. All ADA and NAb data will be listed. Proportion of subjects with positive ADA (rate, titer at each timepoint, and domain specificity) or Nab against modakafusp alfa will be summarized. [redacted] 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. Summaries will be provided separately by dose level. [redacted]. ADA titer distribution over time will be presented through a box-plot on a logarithmic scale.

6.7.3 Interim Analyses

Not applicable.

6.8 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

Liu, S., & Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. *J R Stat Soc Ser C Appl Stat*, 64(3):507-523.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Data Handling Conventions

9.2.1 Definition of Baseline

Baseline is defined as the last non-missing evaluation prior to or on the date that the first dose of the study drug is taken.

9.2.2 Definition of Visit Windows

A window of ±2 days will be permitted from the study visit schedule.

9.2.3 Date Imputation Rules

Incomplete Dates in the Screening Period

1. If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
2. If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the first of January will be used.
3. If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used.

Incomplete Adverse Event Onset Date

Assumption: For on-study Adverse Events.

If *year* is missing (or completely missing): set to the date of first dose.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

If *year* > year of first dose: set *month* and *day* to January 1st.

If *month* and *year* are present and *day* is missing:

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

If *month* < month of first dose: set *day* to last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.
For all other cases: set to date of first dose.

Incomplete Adverse Event Resolution Date

Assumption: For on-study Adverse Events.

If *day* is missing but *month* and *year* are non-missing, impute as the earliest of:
- Last day of the *month*
- Data cutoff date
- Death date

If *day* and *month* are missing, impute as the earliest of:
- December 31st
- Data cutoff date
- Death date

If date is completely missing (i.e. AE is ongoing), impute as earliest of:
- Data cutoff date
- Treatment discontinuation date (i.e. last dose date) + 30 days
- Death date

Incomplete Concomitant Medication Start Date/Prior Therapy Start Date/Progression Date during Prior Therapy

If *year* is missing (or completely missing): do not impute.
If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):
Set *month* and day to January 1st.
If *year* and *month* are present and *day* is missing:
Set *day* to 1st day of month.

Incomplete Concomitant Medication End Date

If *year* is missing (or completely missing): do not impute.
If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):
Set *month* and day to December 31st.
If *year* and *month* are present and *day* is missing:
Set *day* to last day of the month.

Incomplete Subsequent Anti-Cancer Therapy Start Date

If *year* is missing (or completely missing): set to date of last dose of study treatment + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of the last dose: Set *month* and *day* to January 1st.

If *year* = year of the last dose: Set *month* and *day* to date of last dose of study treatment +1.

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month if the resulting imputed date is greater than date of last dose.

Otherwise set the imputed date to date of last dose + 1.

9.3 Analysis Software

Analyses will be conducted using SAS® Version 9.4 or higher (SAS® Institute, Inc., Cary, North Carolina, United States).

9.4 BOIN Design for Dose Escalation/De-escalation

Group 1: NDMM - Maintenance Therapy

	Dose 1	Dose 2	Dose 3	Average sample size	Correct selection %	Overdose %	% patients at MTD	% patients overdosed	% early stop
Scenario 1									
True DLT rate	0.05	0.10	0.25						
Selection %	3.4	34.1	62.5	11.1	62.5	0	43.3	0	0
% pts treated	10.3	46.3	43.3						
Scenario 2									
True DLT rate	0.10	0.25	0.39						
Selection %	29.9	51.7	18.3	11.5	51.7	18.3	48.3	23.7	0.1
% pts treated	27.9	48.3	23.7						
Scenario 3									
True DLT rate	0.25	0.43	0.62						
Selection %	72.4	23.1	0.8	10.8	72.4	23.9	45.6	54.4	3.7
% pts treated	45.6	45.5	8.9						

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; pts: patients.

Group 2: RRMM - Doublet Combinations

The operating characteristics of Group 2 are the same as those of Group 1.

Group 3: RRMM - Triplet Combinations

Dose 1 as the Starting Dose

	Dose 1	Dose 2	Dose 3	Average sample size	Correct selection %	Overdose %	% patients at MTD	% patients overdosed	% early stop
Scenario 1									
True DLT rate	0.05	0.16	0.33						
Selection %	1.4	35.6	63.0	14.9	63.0	0	36.8	0	0
% pts treated	25.8	37.4	36.8						
Scenario 2									
True DLT rate	0.15	0.33	0.51						
Selection %	24.8	56.8	17.7	14.1	56.8	17.7	41.9	14.8	0.7
% pts treated	43.3	41.9	14.8						
Scenario 3									
True DLT rate	0.33	0.51	0.6						
Selection %	67.0	18.2	2.6	11.4	67.0	20.8	69.6	30.3	12.2
% pts treated	69.6	27.1	3.2						

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; pts: patients.

Dose 2 as the Starting Dose

	Dose 1	Dose 2	Dose 3	Average sample size	Correct selection %	Overdose %	% patients at MTD	% patients overdosed	% early stop
Scenario 1									
True DLT rate	0.05	0.16	0.33						
Selection %	0.8	27.5	71.7	13.5	71.7	0	50.2	0	0
% pts treated	3.6	46.2	50.2						
Scenario 2									
True DLT rate	0.15	0.33	0.51						
Selection %	18.8	60.9	20.0	13.9	60.9	20.0	56.6	23.1	0.3
% pts treated	20.2	56.6	23.1						
Scenario 3									
True DLT rate	0.33	0.51	0.6						
Selection %	59.9	28.3	2.7	13.3	59.9	31.0	46.1	53.9	9.1
% pts treated	46.1	47.2	6.7						

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; pts: patients.

Dose 3 as the Starting Dose

	Dose 1	Dose 2	Dose 3	Average sample size	Correct selection %	Overdose %	% patients at MTD	% patients overdosed	% early stop
Scenario 1									
True DLT rate	0.05	0.16	0.33						
Selection %	0.9	19.6	79.5	11.4	79.5	0	74.2	0	0
% pts treated	1.3	24.5	74.2						
Scenario 2									
True DLT rate	0.15	0.33	0.51						
Selection %	17.2	51.8	30.9	13.4	51.8	30.9	41.0	47.8	0.1
% pts treated	11.2	41.0	47.8						
Scenario 3									
True DLT rate	0.33	0.51	0.6						
Selection %	53.7	28.3	11.0	14.2	53.7	39.3	28.7	71.3	7.0
% pts treated	28.7	36.4	34.9						

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; pts: patients.

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