Clinical Study Protocol

NCT Number: NCT03215030

Title: A Phase 1/2 Open-label Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of Modakafusp Alfa (TAK-573) as a Single Agent in Patients With Relapsed Refractory Multiple Myeloma

Study Number: TAK-573-1501

Document Version and Date: Amendment 10 v2, 03 April 2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

A Phase 1/2 Open-label Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of Modakafusp Alfa (TAK-573) as a Single Agent in Patients With Relapsed Refractory Multiple Myeloma

A Safety and Preliminary Efficacy, Pharmacokinetics, and Immunogenicity Study

Sponsor:	Takeda Development Center Americas, Inc 95 Hayden Avenue Lexington, MA 02421 USA		
Study Number:	TAK-573-1501		
IND Number:	130,756		
Abbreviated EudraCT Number:	2021-006038		
Compound:	Modakafusp Alfa (TAK-573)		
Amendment Date:	03 April 2024	**Amendment Number:**	10 v2

Amendment History:

Date	Amendment Number	Region
03 April 2024	Amendment 10 v2	Global
26 February 2024	Amendment 10 v1 (not implemented)	Global
02 August 2023	Amendment 9	Global
10 February 2023	Amendment 8 CH v1	Local China
12 July 2022	Amendment 8 NO v1	Local Norway
23 June 2022	Amendment 8 GB v1	Local United Kingdom
01 March 2022	Amendment 8	Global
25 October 2021	Amendment 7 (not implemented)	Global
16 October 2020	Amendment 6	Global
03 July 2019	Amendment 5	Global
22 October 2018	Amendment 4	Global
29 June 2018	Amendment 3	Global
07 November 2017	Amendment 2	Global
05 April 2017	Amendment 1	Global
14 December 2016	Initial protocol	Global

1.0 ADMINISTRATIVE

1.1 Contacts

A separate study contact list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines are provided to the site.

Contact Type/Role	United States Contact
Serious adverse event and pregnancy reporting	See Section 10.0

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual study participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories, as applicable can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

[redacted], MD (or designee) Date [redacted], [redacted]	[redacted], MD (or designee) Date [redacted], Clinical Study Lead

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator (Appendix D).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix E of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 10 v2 Summary of Changes

Protocol Amendment 10 v2 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 10 v2. The primary reason for this amendment was to implement new dose modification guidelines in cases of bleeding treatment-emergent adverse events (TEAEs) as an urgent safety measure to mitigate the risk of fatal hemorrhagic events in response to the observation of a suspected unexpected serious adverse reaction (SUSAR) in this study.

New dose modification guidelines have been added to this protocol.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

A summary of changes for all prior protocol amendments is found in Appendix J.

Protocol Amendment 10 v2			
Summary of Changes Since the Last Implemented Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	8.4.3 Criteria for Treatment Interruption and Dose Reductions	Specified that "Patients experiencing AEs attributed to modakafusp alfa may continue study treatment with the same dose, may have modakafusp alfa treatment held, dose reduced, discontinued, or may be permanently discontinued from the study." Specified that "Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE at the same dose level or at a reduced dose, depending on the nature and severity of the AE and whether it is the first occurrence or is recurrent unless otherwise specified in the protocol" Addition of Table 8.e with the dose modifications for modakafusp alfa bleeding TEAEs for Parts 1, 2, and 3. Updates to the table captions for Table 8.a, Table 8.b, and Table 8.c to indicate guidance for management of bleeding TEAEs and IRRs. Subheadings for the management of dose modifications were added by study part: Parts 1 and 2; Part 3; and Parts 1, 2, and 3.	Updated to mitigate the risk of fatal hemorrhagic events.
2.	8.4.4 Criteria for Discontinuing Modakafusp Alfa	Removal of text related to bleeding TEAEs that was present in prior versions of the protocol. This section was previously labeled as "Part 3", as numbered. This has been removed and this section has been re-named accordingly.	Updated to align with changes made in this protocol amendment.

Protocol Amendment 10 v2			
Summary of Changes Since the Last Implemented Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
3.	8.6.3 Other Permitted Concomitant Medications and Procedures	Added "Platelet transfusion should not be applied only for the purpose of meeting the treatment criterion of platelet count to start a new cycle."	Updated to align with changes made in this protocol amendment.
4.	8.7.1.2 Handling of Low Platelet Counts	Addition of mention to reference Table 8.e with the dose modifications for modakafusp alfa bleeding TEAEs	Updated to mitigate the risk of fatal hemorrhagic events.

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA	**Compound:** Modakafusp alfa (TAK-573)
Title of Protocol: A Phase 1/2 Open-label Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of Modakafusp Alfa as a Single Agent in Patients With Relapsed Refractory Multiple Myeloma	
Study Number: TAK-573-1501	**Phase:** 1/2

Study Design

This is a multicenter, open-label, phase 1/2 study designed to determine the safety, tolerability, and efficacy of modakafusp alfa as an intravenous (IV) single agent and in combination with dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM).

Phase 1 will provide a preliminary assessment of modakafusp alfa antitumor activity against RRMM with one or more single agent schedules.

Phase 2, which includes the Part 2 expansion cohorts and the Part 3 extension cohorts, will provide a more robust estimate of the safety profile, antimyeloma activity, PK, and pharmacodynamics in order to determine whether the maximum tolerated dose (MTD)/optimal biologic dose (OBD) is appropriate for future studies. The Part 2 expansion cohorts will include at least one combination cohort of modakafusp alfa with dexamethasone using the same dose and schedule of modakafusp alfa. The Part 3 extension component is designed to identify the optimal dose level of modakafusp alfa. In Part 3, patients will be randomized 1:1 to receive modakafusp alfa 120 or 240 mg once every 4 weeks (Q4W), stratified by their cytogenetics risk (high risk [del17, t(4;14) and/or t(14;16)] vs standard risk) and myeloma type (IgA vs other).

Part 1 Dose Escalation

The primary objective of Part 1 of the study was to determine the safety and tolerability of one or more schedules of single-agent modakafusp alfa in patients with RRMM.

Part 1 followed a 3 + 3 dose escalation design to evaluate up to 4 different schedules of administration of modakafusp alfa with the objective of determining, with one or more schedules, either an MTD based on the observation of DLTs, or an OBD.

Four single-agent schedules were evaluated during Part 1:

- Schedule A (initial): Modakafusp alfa infusion was given at weekly intervals in a 28-day cycle for 2 cycles followed by 1 infusion every 2 weeks (twice per cycle) in Cycles 3 to 6, and once every 4 weeks from Cycle 7 until treatment discontinuation.
- Schedule B: Modakafusp alfa infusions were administered on a 28-day (4-week) cycle once every 2 weeks until treatment discontinuation criterion is met.
- Schedule C: Modakafusp alfa infusions were administered on a 21-day (3-week) cycle once every 3 weeks until a treatment discontinuation criterion was met.
- Schedule D: Modakafusp alfa infusions were administered on a 28-day (4-week) cycle once every 4 weeks until a treatment discontinuation criterion was met.

Part 2 Expansion Cohorts

The primary objective of Part 2 of the study is to provide a preliminary evaluation of the clinical activity of one or more schedules of modakafusp alfa given as a single agent in patients with RRMM. Additional cohort(s) in combination with dexamethasone will be carried out with one or more selected schedule(s) to be determined once the modakafusp alfa MTD or OBD is established. The dexamethasone is to be given as a single oral dose of 40 mg/day weekly. Patients over 75 years of age will receive a reduced dose of dexamethasone (20 mg, same

schedule). The aim of this approach is to obtain preliminary information on the effect of standard doses of dexamethasone on modakafusp alfa safety, efficacy, and pharmacodynamic endpoints. The MTD for single-agent modakafusp alfa was established as 3 mg/kg on a Q4W schedule.

Part 3 Extension Cohorts:

The MTD at Q4W dosing was exceeded at 6 mg/kg in June 2021 with 2 DLTs (Grade 3 infusion-related reaction [IRR] and a greater than 2 week delay in start of cycle 2 due to thrombocytopenia and neutropenia).

Based on this, and preliminary efficacy seen in patients in the initial Part 2 expansion cohort receiving 1.5 mg/kg Q4W, the protocol is amended to add the Part 3 extension of the study that includes 2 dose levels to identify the optimal dose, defined as having the more favorable risk-benefit profile based on the totality of data from both arms as well as Parts 1 and 2.

Fixed dosing is considered an appropriate dosing approach for further clinical development based on collective PK and clinical findings and the benefits of fixed dosing due to its lower risk of dosing errors and substantial reduction of drug wastage. Accordingly, the 2 doses of 1.5 and 3 mg/kg Q4W will be translated into 2 fixed doses of 120 and 240 mg Q4W based on the median bodyweight of approximately 80 kg (from Parts 1 and 2 of Study TAK-573-1501) for the Part 3 evaluation.

Part 3 China Continuation Cohort

After global patient enrollment is completed in Part 3, enrollment will continue for the China continuation cohort until about 15% of the total sample size is reached at the selected dose (eg, 18 patients based on 118 patients treated at the selected dose[s]).

PK, Immunogenicity, and Biomarker Assessments

Blood samples for PK testing and immunogenicity will be collected at regular time points. Intensive PK samples will be collected in up to 8 Chinese patients enrolled in China per dose to assess the modakafusp alfa PK profile in Chinese patients. Longitudinal peripheral blood samples will be collected for CD38 receptor occupancy/density (applicable to Parts 1 and 2 only), RNA sequencing, immunoprofiling, T-cell and B-cell receptor sequencing, and serum biomarkers.

Within Part 1 dose escalation and Part 2 expansion cohorts, bone marrow aspirates are collected at screening and at another 2 time points while on treatment and at progressive disease (PD) for CD38 receptor occupancy/density, RNA sequencing, immunoprofiling, and T-cell and B-cell receptor sequencing. An additional bone marrow aspirate will be collected if the patient is suspected of being in complete response (CR) for assessment of minimal residual disease (MRD). Within Part 3 Extension cohorts, bone marrow aspirates are collected at screening, suspected CR, and every 6 months thereafter for assessment of MRD, RNA sequencing, immunoprofiling, and DNA sequencing.

Not all collections are applicable to all cohorts or patients within a cohort.

Primary Objectives

Part 1 Dose Escalation: To determine the safety and tolerability of single-agent modakafusp alfa in patients with RRMM.

Part 2 Expansion Cohorts: To provide a preliminary evaluation of the clinical activity of modakafusp alfa as a single agent and in combination with dexamethasone in patients with RRMM.

Part 3 Extension Cohorts: To determine the objective response rate (ORR) as assessed by IRC according to International Myeloma Working Group (IMWG) criteria (Appendix F) of modakafusp alfa in patients who have MM defined by the IMWG criteria with evidence of PD and are in need of additional myeloma therapy as determined by the investigator, have previously received at least 3 lines of myeloma therapy, and are refractory to at least 1 IMiD (ie, lenalidomide or pomalidomide [thalidomide excluded]), at least 1 PI (ie, bortezomib, ixazomib, or carfilzomib), and refractory to at least 1 anti-CD38 antibody and who have demonstrated PD with the last therapy.

Secondary Objectives

Part 1 Dose Escalation:

- To determine the MTD/OBD of modakafusp alfa with 1 or more schedules of administration.
- To characterize the PK profile of modakafusp alfa.
- To evaluate the immunogenicity of modakafusp alfa.
- To provide a preliminary evaluation of the clinical activity of modakafusp alfa.

Part 2 Expansion:

- To further evaluate safety and to determine the suitability of MTD/OBD of modakafusp alfa as a single agent and in combination with dexamethasone for further trials as the recommended dose and schedule.
- To further characterize the PK profile of modakafusp alfa as a single agent and in combination with dexamethasone.
- To further characterize the immunogenicity of modakafusp alfa as a single agent and in combination with dexamethasone.

Part 3 Extension:

- To determine ORR by investigator assessment, duration of response (DOR), clinical benefit rate (CBR), duration of clinical benefit, disease control rate (DCR), duration of disease control, progression-free survival (PFS), time to progression (TTP), and overall survival (OS).
- To assess MRD negativity in patients achieving CR.
- To further characterize safety and tolerability of modakafusp therapy.
- To collect PK data to contribute to population PK and exposure-response analyses.
- To further characterize the immunogenicity of modakafusp alfa.
- To assess health care utilization.
- To evaluate patient-reported disease symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity).
- To characterize the PK profile of modakafusp alfa in Chinese patients.

Exploratory Objectives

Part 1 Dose Escalation:

- To explore potential biomarkers to test their correlation with clinical efficacy and safety parameters.

Part 2 Expansion:

- To explore potential biomarkers to test their correlation with clinical efficacy and safety parameters.

Part 3 Extension:

- To explore predictive biomarkers of response and resistance.
- To characterize MRD negativity at a higher sensitivity in patients achieving CR.
- To evaluate generic health-related quality of life/health status as measured by the EuroQoL-5-Dimensions-5 Levels (EQ-5D-5L) instrument.

Subject Population: Subjects aged 18 years or older with relapsed/refractory MM.

Number of Patients	**Number of Sites**
Part 1 Escalation: 36 to 51 evaluable patients. Part 2 Expansion: Approximately 100 patients: 4 planned expansion cohorts will each include a total of 25 patients. Part 3 Extension: Approximately 236 patients (~118 per arm). After global patient enrollment is completed in Part 3, enrollment will continue for the China continuation cohort until about 15% of the total sample size is reached at the	Approximately 100 investigational centers globally.

selected dose (eg, 18 patients based on 118 patients treated at the selected dose[s]).	
Dose Levels Phase 1 Dose Escalation: Modakafusp alfa infusions will be escalated as follows: 0.001, 0.01, 0.1, 0.75, 1.5, 3, 6, 9, and 14 mg/kg. Evaluation of intermediate doses is permissible following discussions between the sponsor and the investigators. Part 2 Expansion Cohorts with Dexamethasone: Modakafusp alfa infusion at MTD/OBD as determined in the Part 1 dose escalation. Dexamethasone 40 mg (20 mg if age >75 years). Part 3 Extension: Modakafusp alfa 120 mg and 240 mg Q4W.	**Route of Administration:** Modakafusp alfa: Intravenous (IV). Dexamethasone: Oral (PO)
Duration of Treatment Modakafusp alfa for up to 1 year (Parts 1 and 2); however, patients with clinical benefit can continue treatment beyond 1 year with explicit sponsor approval. Patients in Part 3 may continue treatment until disease progression. If the investigator considers that treatment after PD is in the patient's best interest, it can be approved after consultation with the sponsor.	**Period of Evaluation** Patient participation includes up to 21 days of screening, 1 year of treatment (Parts 1 and 2) or until disease progression (Part 3), and 1 month posttreatment follow-up (end-of-treatment [EOT] visit). Patients who discontinue for reasons other than 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 from the EOT visit until death, study termination, or patient withdrawal. The estimated time frame for study completion is approximately 90 months.
Main Criteria for Inclusion Patients with evidence of disease progression during/after the most recent line of therapy who are in need of additional myeloma therapy as determined by the investigator and have previously received ≥3 prior lines of therapy. Patients in the Part 2 expansion and Part 3 extension cohorts must have measurable disease defined as one of the following: serum M-protein ≥500 mg/dL (≥0.5 g/dL); urine M-protein ≥200 mg/24 hours; serum free light chain (FLC) assay, with involved FLC level ≥10 mg/dL (≥100 mg/L). During dose escalation only, patients not meeting these criteria should, at least, have measurable bone marrow plasmacytosis (≥10%) and/or plasmacytoma (≥1 cm in diameter) detected by physical examination or imaging. Patients must have adequate organ function as determined by the following laboratory values: absolute neutrophil count (ANC) ≥1000/mm^3 (≥1.0×10^9/L); platelets ≥75,000/mm^3 (≥75×10^9/L); hemoglobin ≥75 g/L; creatinine clearance ≥30 mL/min (Cockcroft-Gault); total bilirubin ≤2.0 × upper limit of normal (ULN); and alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤3.0 × ULN. Part 1: Until the MTD/OBD is defined, patients who have received daratumumab (or other investigational anti-CD38 antibody) for at least 5 months (steady state) require a 90-day wash-out period before receiving modakafusp alfa. For patients who have received less than 5 months of daratumumab or who have received another anti-CD38 monoclonal antibody, the necessary wash-out period needs to be discussed and approved by the sponsor. Once MTD/OBD has been confirmed, these patients can be enrolled in the trial (Parts 2 and 3)	

Part 2 and Part 3: No washout from daratumumab or isatuximab is required.

Part 3: In addition to the above criteria, patients must have MM defined by the IMWG criteria with evidence of disease progression and:

- Are in need of additional myeloma therapy as determined by the investigator.
- Have previously received at least 3 lines of myeloma therapy.
- Are refractory to at least 1 IMiD (ie, lenalidomide or pomalidomide [thalidomide excluded]), at least 1 PI (ie, bortezomib, ixazomib, or carfilzomib), and refractory to at least 1 anti-CD38 antibody (ie, daratumumab or isatuximab) and who have demonstrated disease progression during or after the last therapy (see *NOTE below). Patients who are primary refractory to all prior therapies, meaning they never achieved at least a minimal response (MR) with any previous treatment line, are not eligible.

  *NOTE: Refractory is defined as <25% reduction in M-protein or progression of disease during treatment or within 60 days after cessation of treatment.

Main Criteria for Exclusion

Patients who have had a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in modakafusp alfa formulation; a significant history of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes); monoclonal gammopathy of unknown significance; smoldering myeloma; solitary plasmacytoma; amyloidosis; Waldenström macroglobulinemia or immunoglobulin M myeloma; lymphoplasmacytic lymphoma; or any significant results from physical examinations or clinical laboratory results per the investigator.

Part 3 Extension**:**

In addition to the above criteria, patients must not have plasma cell leukemia or have had primary refractory MM, current central nervous system involvement of MM, myelodysplastic syndrome, myeloproliferative syndrome, or have had a second malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, cervical carcinoma in situ, resected colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapy.

Endpoints

Part 1 Primary Endpoints**:**

- The number of patients with TEAEs overall and per dose level.
- Patients with DLTs at each dose level.
- Patients with Grade ≥3 TEAEs.
- Patients with serious adverse events (SAEs).
- Patients who discontinue because of TEAEs.
- Patients with dose modifications (delays, interruptions, dose reductions).
- Clinically significant laboratory values.
- Clinically significant vital sign measurements.

Part 1 Secondary Endpoints:

- DLT-like events (TEAEs meeting DLT definition that occur after phase 1 Cycle 1) frequencies and other TEAEs occurring over the course of extended treatment with modakafusp alfa, including information about dose modification, treatment discontinuation, and clinically significant laboratory values and vital signs.
- Summary statistics by dose level and cycle day for the following PK parameters:
  - 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_{∞}).
  - 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 (λ_z).
  - Apparent serum modakafusp alfa terminal elimination phase half-life ($t_{1/2z}$).

  - Total clearance after intravenous administration (CL).
  - Volume of distribution at steady state (Vss).
- Antimodakafusp-alfa antibody incidence and characteristics (eg, titer and specificity), neutralizing antibody (NAb).
- For patients with measurable disease only: ORR, defined as the proportion of patients who achieved a partial response (PR) or better during the study; stringent complete response (sCR), CR, very good partial response (VGPR) (as defined by IMWG Uniform Response Criteria in (Appendix F).
- PR as defined by IMWG Uniform Response Criteria (Appendix F).
- CBR (includes patients with a response of sCR, CR, VGPR, PR, or minimal response).
- Disease control rate (DCR; includes patients with a response of sCR, CR, VGPR, PR, minimal response, or stable disease).
- For patients with measurable disease only: median DOR, with DoR defined as the time from the date of first documentation of response of PR or better to the time of disease progression or death, whichever occurs first.
- Progression-free survival (PFS), defined as the time from the date of first dose until the sooner of the date of progressive disease (PD), defined by IMWG criteria (Appendix F), or the date of death due to any cause.
- For patients with measurable disease only: time to response, defined as the time from first dose to the date of first documentation of response (PR or better).

Part 1 Exploratory Endpoints**:**

- CD38 expression on MM cells and other immune cells in bone marrow aspirate and its correlation with clinical outcome.
- Pharmacodynamic biomarkers including, but not limited to, neopterin, complement, cytokines/chemokines, and gene expression and their correlation with clinical outcome.
- Pharmacodynamic analysis of the presence and changes of immune cells from whole blood and bone marrow and their correlation with clinical outcome.
- Effects of modakafusp alfa administration on the electrocardiographic QT/QT interval corrected with Fridericia correction method (QTc).

Part 2 Expansion Primary Endpoint:

- ORR, defined as the proportion of patients who achieved a PR or better during study; sCR, CR, VGPR, and PR as defined by IMWG Uniform Response Criteria (Appendix F).

Part 2 Expansion Secondary Endpoints:

- DOR.
- CBR.
- DCR.
- PFS, defined as the time from the date of first dose until the sooner of the date of PD, defined by IMWG criteria, or the date of death due to any cause.
- OS, defined as the date from first dose to the date of death due to any cause.
- Time to response, defined as the time from first dose to the date of first documentation of response (PR or better).
- DLT-like (TEAEs meeting DLT definition that occur after Part 1 Cycle 1) frequencies and other TEAEs occurring over the course of extended treatment with modakafusp alfa, including information about dose modification, treatment discontinuation, and clinically significant laboratory values and vital signs.
- Summary statistics by dose level and cycle day for the following PK parameters: C_{max}, AUC_{∞}, AUC_{last}, λ_z, t_{max}, CL, V_{ss}, and $t_{1/2z}$.
- Antimodakafusp alfa-antibody incidence and characteristics (eg, titer and specificity), NAb.

Part 2 Expansion Exploratory Endpoints:

- CD38 expression on MM cells and other immune cells in bone marrow aspirate and its correlation with clinical outcome.
- Pharmacodynamic biomarkers including, but not limited to, neopterin, cytokines/chemokines, and gene expression and their correlation with clinical outcome.
- Pharmacodynamic analysis of the presence and changes of immune cells from whole blood and bone marrow and their correlation with clinical outcome.
- Effects of modakafusp alfa administration on the electrocardiographic QT/QT interval corrected with Fridericia correction method (QTc).

Part 3 Extension Primary Endpoint:

- ORR (PR or better) assessed by the IRC according to modified IMWG criteria (Appendix F).

Part 3 Extension Secondary Endpoints**:**

- ORR by investigator assessment.
- DOR.
- CBR (response of sCR, CR, VGPR, PR, or minimal response) by IRC and investigator assessment.
- DCR (response of sCR, CR, VGPR, PR, minimal response, or stable disease) by IRC and investigator assessment.
- Duration of clinical benefit.
- Duration of disease control.
- PFS (time from the date of first dose until the sooner of the date of PD, defined by IMWG criteria [Appendix F]), or the date of death due to any cause by IRC and investigator assessment.
- TTP by IRC and investigator assessment.
- OS (date from first dose to the date of death due to any cause).
- 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} in patients achieving CR.
- AEs, SAEs, laboratory assessments, supportive care use.
- Eastern Cooperative Oncology Group status.
- Antimodakafusp alfa-antibody incidence and characteristics (eg, titer and specificity), NAb.
- Length of hospital stay, types of hospital stay, and other health care resource utilization data as defined in Section 9.3.13.
- No worsening of disease symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity) from baseline at approximately 12 weeks across doses of modakafusp alfa as measured by the patient-reported outcome (PRO) instrument European Organisation for Research and Treatment of Cancer MM Module Quality of Life Questionnaire (EORTC QLQ-MY20).
- Summary statistics by dose level and cycle day for the following PK parameters in Chinese patients with intensive PK schedule: C_{max}, AUC_{∞}, AUC_{last}, λ_z, t_{max}, CL, V_{ss}, and $t_{1/2z}$.

Part 3 Extension Exploratory Endpoints:

- CD38 expression on MM cells and other immune cells within the bone marrow and its correlation with clinical outcome.
- Evaluation of somatic mutations and polymorphisms and their associations with response and/or acquired resistance.
- Evaluation of anti-interferon antibodies at baseline and correlation with response.
- Rate of MRD negative status at a sensitivity of 10^{-6} in patients achieving CR.
- Duration of MRD negativity (10^{-6}) in patients who achieve MRD negative status at CR.
- Evaluation of generic health-related quality of life/health status, measured by the EQ-5D-5L instrument.

Statistical Considerations

The MTD/OBD will be estimated by a standard 3 + 3 method using data collected in the dose escalation phase. Adverse events (AEs) will be summarized by treatment group and overall. Categorical variables such as ORR, CBR, and DCR will be tabulated by treatment group and overall. Time-to-event variables such as DOR and PFS will be analyzed using Kaplan-Meier survival curves, and Kaplan-Meier medians (if estimable) will be provided. PK parameters will be summarized as appropriate. An OBD is a dose level that is below or coincides with the MTD for which there is evidence of antimyeloma activity plus data supporting of significant pharmacodynamic effects in one or more biomarkers. An OBD for one or more schedules can be selected before or after identifying MTD.

The Part 2 Expansion portion will evaluate the clinical activity of one or more schedules of modakafusp alfa given as a single agent in patients with relapsed/refractory MM. Additional cohort(s) in combination with dexamethasone will evaluate one or more selected schedule(s), which will be determined once the modakafusp alfa MTD or OBD is established.

Part 3 Extension

The Part 3 extension cohorts will identify the optimal dose level for modakafusp alfa. Patients will be randomized 1:1 to receive either 120 mg or 240 mg Q4W and stratified by their cytogenetics risk (high risk [del17, t(4;14) and/or t(14;16)] vs standard risk) and myeloma type and myeloma type (IgA vs other). Cytogenetic results from samples taken within 5 weeks prior to first dose are acceptable for stratification. All patients should also have a sample from screening sent for central analysis. If a previous result is not available and the patient is known to have high-risk disease [ie, del17, t(4;14) and/or t(14;16)] from prior cytogenetic testing, regardless of timing, they should be stratified as high risk for the purpose of enrollment.

The primary endpoint of Part 3 is the ORR, defined as the percentage of patients with a confirmed PR or better (ie, PR, VGPR, CR, and sCR) according to the IMWG Response Criteria (Appendix F) assessed by the independent review committee (IRC). The primary endpoint, ORR assessed by IRC, will be evaluated for all treated patients within each treatment arm based on the 95% exact confidence interval (CI) of the observed ORR at the primary analysis. No formal statistical analysis will be performed to compare the 2 treatment arms. Prespecified subgroup analyses based on stratification factors will be performed as data permits.

Two interim analyses for futility are planned for the study when approximately 15 and 48 of the planned 118 patients per arm have been randomized and treated for at least 3 cycles or discontinued treatment prematurely. The futility stopping boundary is determined based on the predictive probability of success (Lee and Liu 2008) at the primary analysis. The treatment arm will be dropped for futility if the predictive probability of success at the primary analysis is found to be smaller than 10% based on the data from the interim analysis.

Two-sided exact 95% binominal CIs will be computed for all binary secondary endpoints, including ORR as assessed by the investigator, DCR, and CBR as assessed by the IRC and the investigator. Kaplan-Meier methods, including medians and CIs, will be used to estimate PFS as assessed by the IRC and the investigator, DOR as assessed by the IRC and the investigator, OS, and other time to event endpoints.

Sample Size Justification

Part 1 of the study will follow a standard 3 + 3 dose escalation design. MTD/OBD will be defined for each schedule currently under evaluation (B [Q2W], C [Q3W] and D [Q4W]). A maximum of 9 dose levels are planned (from 0.001 mg/kg to 14 mg/kg). For Part 1, the number of evaluable patients is planned to be 36 to 51.

Part 2 Expansion:

The study will enroll up to 25 patients in each Part 2 cohort to further characterize safety of the OBD/MTD and obtain preliminary clinical efficacy data. An OBD/MTD dose will be considered clinically relevant if at least 11 out of 25 response-evaluable patients have a confirmed PR or better. With a vague beta prior with shape parameters 0.428 and 1 for ORR, 11 responders out of 25 gives a greater than 90% posterior probability of true ORR being greater than 30%. The design has reasonable operating characteristics. With a true ORR of 30%, the probability of declaring success is 7%. On the other hand, with a true ORR of 50% the probability of declaring success is 70%.

Part 3 Extension:

A total sample size of approximately 236 patients (118 patients per arm) will allow the study to have over 90% power to rule out an uninteresting response rate of 20% if the true rate is 35% with a 1-sided alpha of 0.025. Patients who were randomized but did not receive any study treatment will be replaced. However, all patients who received at least one dose of study treatment will be included in the analysis and will not be replaced if they drop out after receiving study treatment.

After global patient enrollment is completed in Part 3, enrollment will continue for the China continuation cohort until about 15% of the total sample size is reached at the selected dose(s) (eg, 18 patients based on 118 patients treated at the selected dose[s]).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities (Appendix D). The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 Committees in Part 3 Dose Extension

No committees will be used in Parts 1 and 2. The following committees will be used for Part 3.

3.3.1 Independent Review Committee

An independent review committee (IRC) will review all disease evaluation data to independently assess disease response, and the assessments will be used for analysis of endpoints as described in Section 13.1. Details regarding the committee and its procedures will be described in the IRC charter. Data from the IRC will not be provided to the investigator during the conduct of the study.

3.3.2 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will review safety data and the interim analysis data for futility as detailed in the IDMC charter. The charter of the IDMC will specify that this committee is charged with providing periodic reports to the Sponsor that contain recommendations that include, but are not limited to, (a) continuation of the study, (b) continuation with modification, and (c) termination of the study.

3.4 List of Abbreviations

Abbreviation	Term
λ_z	terminal disposition phase rate constant
ADA	antidrug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
anti-HBs	antibodies to hepatitis B surface antigen
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC_{∞}	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
BMA	bone marrow aspirate
C1D1	Cycle 1 Day 1
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CL	total clearance after intravenous administration
C_{max}	maximum observed serum concentration
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Multiple Myeloma Module Quality of Life Questionnaire
EOT	end of treatment
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
FDA	[United States] Food and Drug Administration
FIH	first-in-human
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor

Abbreviation	Term
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HRQOL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IFN	interferon
IFN-α	interferon-alpha
IFN-α 2b	interferon alpha 2b
Ig	immunoglobulin
IL	interleukin
IMiD	immunomodulatory imide drug
IMWG	International Myeloma Working Group
IRB	institutional review board
IRC	independent review committee
IRR	infusion-related reaction
IV	intravenous(ly)
IVIG	IV immunoglobulins
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
Modakafusp alfa	TAK-573
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAb	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drugs
OBD	optimal biological dose
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease; disease progression

Abbreviation	Term
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PO	orally
PoS	probability of success
PPOS	posterior probability of success
PR	partial response
PRO	patient-reported outcome
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks
QD	*quaque die* (once daily)
QTcF	QT interval with Fridericia correction method
RBC	red blood cells
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SCT	stem cell transplant
SD	stable disease
SOC	System Organ Class
SOE	schedule of events
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal disposition phase half-life
TAK-573	modakafusp alfa
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of maximum observed serum modakafusp alfa concentration
TMDD	target-mediated drug disposition
TTP	time to progression
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
Vc	central volume of distribution
Vd	volume of distribution
VGPR	very good partial response
V_{ss}	volume of distribution at steady state

4.0 INTRODUCTION

4.1 Multiple Myeloma

Multiple myeloma (MM) is a plasma cell-derived malignancy characterized by bone lesions, hypercalcemia, anemia, and renal insufficiency. The 5-year survival rate of patients diagnosed with MM is approximately 45% (Siegel et al. 2013). MM persists as a mostly incurable disease because of its highly complex and diverse cytogenetic and molecular abnormalities (Chapman et al. 2011). There has been an improvement in the outcome for MM patients in the last decade with the discovery, development, and approval of proteasome inhibitors (PI) (eg, bortezomib) and immunomodulatory imide drugs (IMiDs); however, patients who become refractory or are ineligible to receive bortezomib and IMiDs have a dismal prognosis (Kumar et al. 2012).

Daratumumab, a CD38 antibody, is currently approved in many countries for the treatment of MM. (Poh 2016). Daratumumab was studied in patients who had received at least 3 prior lines of therapy, including a PI and an IMiD, or who were double-refractory to these agents. An objective response rate (ORR) of 29% was documented, including a 3% rate of complete response (CR)/stringent complete response (sCR). The main toxicity associated with daratumumab was infusion-related reactions (IRRs), which could be severe in some patients. Other common adverse drug reactions (ADRs) were fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection ((Darzalex (daratumumab) injection 2015)daratumumab United States (US) Package Insert (2015). However, not all patients respond to daratumumab, and many patients eventually develop PD (Nijhof et al. 2016). Response to daratumumab therapy is significantly associated with CD38 expression levels on the tumor cells, and pretreatment levels of CD38 expression on MM cells were significantly higher in patients who achieved at least a partial response (PR) compared with patients who did not achieve a PR. In addition, CD38 expression in these patients was reduced in both bone marrow–localized and circulating MM cells following the first daratumumab infusion, and increased again following daratumumab discontinuation (Nijhof et al. 2016). There is still a need for development of novel targeted therapies that act specifically on the biology of the tumor cells, overcoming limitations related to the CD38 expression level.

4.2 Modakafusp Alfa Targets

The tumor cell surface–expressed antigen CD38 is uniformly and highly expressed on MM cells (Lin et al. 2004; Santonocito et al. 2004) and at lower levels on various lymphoid and myeloid cells and some solid organs (Deaglio et al. 2008). Being highly expressed on the myeloma cell surface and showing lower expression on normal cells makes CD38 an appropriate target for delivering drugs (cytokines, radioisotopes (Green et al. 2014), and toxins (Bolognesi et al. 2005; Goldmacher et al. 1994) to receptor-expressing cells. A promising moiety to be conjugated to an anti-CD38 monoclonal antibody (mAb) is the cytokine interferon-alpha (IFN-α), which is currently used by clinicians as a potential maintenance treatment option for MM following primary treatment and autologous and allogeneic stem cell transplant (SCT). IFN-α has direct inhibitory effects on some tumors and is a potent stimulator of both the innate and adaptive immune systems. Systemic toxicity of IFN-α, however, precludes the use of the cytokine at

therapeutically effective doses for the majority of patients. By reducing the binding affinity of IFN-α (KD) for its receptor, interferon alpha receptor, modakafusp alfa (previously known as TAK-573) is expected to reduce binding of-IFN-α to nontargeted, CD38-negative cells. In contrast, binding of modakafusp alfa with high affinity via its CD38 targeting moieties is expected to increase the local concentration attenuated IFNα on these CD38+ target cells, thereby inducing desired on-target IFN pathway activation. In addition, IFN-α pathway activation induces up-regulation of CD38 messenger RNA and protein levels in malignant cells of patients with B cell chronic lymphocytic leukemia (Bauvois et al. 1999), suggesting that modakafusp alfa may be able to increase CD38 target expression in MM and other CD38+ immune cells, thus overcoming the limitations seen with anti-CD38-depleting antibodies such as daratumumab. Modakafusp alfa increases CD38 expression on MM cells in vitro, which further supports this hypothesis (Report TPA-38-051).

CD38 is a multifunctional ectoenzyme involved in cell adhesion and transmembrane signaling. It is over expressed in hematologic tumors, where it is believed to play a role in tumor cell migration and metastasis. CD38 has been reported to be highly expressed in 80% of MM patient-derived tumor cells (Lin et al. 2004). CD38 is an approximately 45kDa transmembrane glycoprotein expressed by immature hematopoietic cells, down regulated in mature cells, and re-expressed at higher levels by activated lymphocytes such as T cells, B cells, dendritic cells, and natural killer (NK) cells (Funaro et al. 1990). Early bone marrow cells, which are crucial for long-term (sustained) marrow recovery, do not express CD38 but committed progenitor bone marrow cells, B cells in germinal centers, terminally differentiated plasma cells, and activated tonsils are CD38+ (Chillemi et al. 2013). Deaglio et al (Deaglio et al. 2008) reviewed the main tissues and cells where CD38 is present, as summarized in Table 4.a. CD38 is also found in a soluble form in normal and pathological fluids.

Table 4.a Reported Distribution of Human CD38

Tissue	Cellular Distribution	Putative Function
Bone marrow	hematologic precursors plasma cells	Homing and apoptosis; marker of precursor cell commitment
Thymus	Throughout thymic development	Unknown
Spleen/lymph nodes	Germinal center B cells	Rescue from apoptosis
Blood	T, B, NK, and monocyte subsets; platelets and erythrocytes; hematologic precursors plasma cells	Interaction with endothelium
Gut	Intra-epithelial and lamina propria lymphocytes	Mucosal immunity
Brain	Purkinje cells; neurofibrillary tangles	Memory process
Prostate	Epithelial cells	Unknown
Pancreas	β cells	Insulin secretion
Bone	Osteoclasts	Bone resorptions
Eye	Retinal cells	Vision process
Muscle	Sarcolemma of smooth and striated muscle	Muscle contraction

Source: (Deaglio et al. 2008).
NK: natural killer.

4.3 Modakafusp Alfa

Modakafusp alfa is a recombinant humanized immunoglobulin (Ig) G4 anti-CD38 monoclonal antibody fused to attenuated interferon alpha 2b (IFN-α 2b). Modakafusp alfa is produced by recombinant DNA technology in a mammalian cell expression and is purified by a process that includes specific viral inactivation and removal steps. The CD38 antibody portion of modakafusp alfa directs the attenuated IFN-α portion to CD38+ cells, thus achieving a high local concentration on IFNα2b at the surface of these target cells. On CD38- cells the attenuation results in approximately 130,000-fold reduced potency compared with IFNα2b.

Modakafusp alfa has a high binding affinity (dissociation constant [K_D]) for human and cynomolgus CD38, with a K_D of 168 pM and 1.25 nM, respectively (Report TPA-38-009). Modakafusp alfa can potently inhibit proliferation of CD38+ MM cells (half-maximal inhibitory concentration 19.9 pM), whereas potency on CD38- cells is approximately 2500-fold lower. The antibody portion of modakafusp alfa is an IgG_4 isotype (unlike the IgG_1 isotype of daratumumab) and is therefore unlikely to induce antibody-dependent cell mediated cytotoxicity of normal CD38+ cells. Modakafusp alfa does not modulate the adenosine diphosphate-ribosyl cyclase activity of CD38, unlike daratumumab (Report TPA-38-045). Interferon-α2b (Intron A) by comparison has similar potency to modakafusp alfa on CD38+ cells (IC50 12.3 pM) but on CD38- cells is approximately 130,000-fold more potent than modakafusp alfa (EC50 ~0.37 pM).

4.4 Findings From Nonclinical and Toxicology Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies are provided in the following sections. More-detailed information is provided in the Investigator's Brochure (IB).

4.4.1 Nonclinical Studies

Modakafusp alfa effectively induces apoptosis in high-expressing CD38+ human myeloma cells as demonstrated in a caspase activation assay (half-maximal effective concentration 23 pM); no apoptotic effects are observed with normal human peripheral blood mononuclear cells (PBMCs). Modakafusp alfa elicited a low level of cytokine release (tumor necrosis factor alpha, interleukin [IL] 6, IL-8, IFN-γ, and IL-2) from human PBMCs in vitro, less than or comparable to palivizumab (IgG_1 against the syncytial respiratory virus) and is, therefore, unlikely to induce cytokine storm in the clinic.

Modakafusp alfa is active in multiple human myeloma xenograft models and induces complete regressions at tolerated doses. A single dose of 10 mg/kg modakafusp alfa in the NCI-H929 human myeloma xenograft model resulted in complete regressions in all treated animals. In comparative xenograft studies using the H929 model, modakafusp alfa had more robust antitumor activity than established myeloma therapies including bortezomib, lenalidomide, and daratumumab. Furthermore, under conditions of suboptimal dosing of modakafusp alfa, strong synergy has been observed with other standard treatment agents such as bortezomib and lenalidomide.

4.4.2 Toxicology Studies

A series of toxicological studies in cynomolgus monkeys was conducted to support the phase 1/2 clinical trial TAK-573-1501. Please refer to the IB for additional information.

As described in International Conference on Harmonisation (ICH) Guidance S6 (R1), the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals. ICH Guidance S9, Nonclinical Evaluation for Anticancer Pharmaceuticals, also states that genotoxicity studies are not considered essential to support clinical trials for therapeutics intended to treat patients with advanced cancer. Therefore, genotoxicity studies have not been conducted with modakafusp alfa.

4.5 Known and Potential Benefits and Risks of Modakafusp Alfa

4.5.1 Nonclinical Safety Summary

On the basis of nonclinical studies and clinical experience with related antidrug antibodies (ADAs), the following ADRs may be associated with modakafusp alfa administration: IRRs (pyrexia, chills, nausea, vomiting, flushing, dyspnea, cough, headache, dizziness, rash, and hypertension), cytokine release syndrome, changes in blood cell counts, elevations in liver enzymes, and ADA-mediated hypersensitivity reactions. Additional information regarding benefits and risks to patients can be found in the IB.

4.5.2 Clinical Safety

The most common treatment-emergent adverse events (TEAEs) reported have been hematologic, which have been mitigated by dosing Q4W to allow count recovery after observing inadequate recovery at more frequent dosing.

Patients receiving modakafusp alfa have experienced IRRs. Premedications and treatment should be provided as described in Section 8.7.1.1.

Neuropsychiatric events have been reported in modakafusp alfa clinical studies.

Dose modifications should be applied per the guidelines in Section 8.4.

For more detailed information on the adverse events (AEs) associated with modakafusp alfa, as well as the identified and potential risks, please refer to the most recent IB.

Clinical safety will be monitored per the assessments described in the Schedule of Events.

4.6 Rationale for the Proposed Study

This is a first-in-human (FIH) study of the anticancer product modakafusp alfa. The drug is a fusion protein that binds CD38 with high affinity and the IFN receptor with low affinity. Therefore, it is expected that its effect will be restricted predominantly to CD38-positive cells. The study is designed with a slow dose escalation design with a starting dose defined with the minimum anticipated biological effect level (MABEL) approach (Section 4.6.1). Due to CD38 targeting and the solid evidence of anti-myeloma activity in xenograft models, multiple myeloma is selected as the initial indication to test the safety and efficacy of modakafusp alfa. The trial also aims to collect translational research information in support of the nonclinical hypothesis of the activation of the innate immunity through the Type I interferon pathway.

The trial is currently enrolling at different dose levels and schedules with modakafusp alfa as a single agent. After Protocol Amendment 5 was implemented, the trial also included one combination arm with dexamethasone.

Corticosteroids have been a mainstay of MM treatment for decades (Alexanian et al. 1992). They are highly active against the disease and are considered standard of care treatment in many combination regimens. For example, dexamethasone is combined seemingly by default with cytotoxic chemotherapies predating the novel agent era as well as relatively newer agents with novel mechanisms of action such as PIs and immunomodulators. At the same time, corticosteroids have immunosuppressive effects as illustrated by their longstanding use as anti-inflammatory agents and in the treatment of autoimmune disease (Coutinho and Chapman 2011). Recent advances applying immunotherapy in the oncology setting have raised the question of whether steroid therapy may reduce the efficacy of immunotherapy (Arbour et al. 2018; Giles et al. 2018). Given that modakafusp alfa affects the immune pathway via IFNα2b signaling, it is hypothesized that investigating the effect of corticosteroids in the setting of modakafusp alfa therapy will provide a platform to further understand the safety, efficacy, and biology of modakafusp alfa in MM.

4.6.1 Rationale for the Part 1 Starting Dose of Modakafusp Alfa

In view of the marked decrease in modakafusp alfa plasma concentrations observed in repeated dosing in the nonhuman primate toxicology studies, a MABEL calculation was used to provide a framework for determining the FIH starting dose.

The calculation of the MABEL was based on projection of CD38 occupancy that would be maximally achievable at peak concentrations of modakafusp alfa following intravenous (IV) dosing (Saber et al. 2016). Although modakafusp alfa was initially (prior to Amendment 5) administered over a 4-hour ramped infusion (Section 8.1), in the absence of clinical PK data on modakafusp alfa, the calculation conservatively assumed dilution of the entire dose instantaneously in total plasma volume (2.8 L for a 70 kg patient). As such, a dose of 0.001 mg/kg (70 µg for a 70 kg patient) would be expected to achieve a maximum serum concentration of modakafusp alfa of no greater than 25 ng/mL (134 pM based on a molecular weight of 186 KDa). On the basis of the in vitro estimate of the CD38 target K_D of 168 pM (determined by a surface plasmon resonance assay), this translates to a projected receptor occupancy of <44% at the proposed starting dose of 0.001 mg/kg.

4.6.2 Rationale for Part 3

The rationale for conducting Part 3 of Study TAK-573-1501 is based on the totality of the data from Part 1 (dose escalation) and Part 2 (dose expansion) of Study TAK-573-1501.

Part 1 of Study TAK-573-1501 involved extensive dose exploration with 10 modakafusp alfa dose levels ranging from 0.001 mg/kg to 6.0 mg/kg on 4 different dosing schedules. The optimal schedule for modakafusp alfa was determined to be every 4 weeks (Q4W) based on the recovery time of hematological toxicities. The maximum tolerated dose (MTD) at this schedule was established as 3 mg/kg as 6 mg/kg exceeded the MTD with 2 dose-limiting toxicities (DLTs) (Grade 3 IRR and a greater than 2-week delay in start of cycle 2 due to thrombocytopenia and neutropenia). No DLTs were seen at 3 mg/kg. Preliminary efficacy activity was also seen in dose-escalation with 1 PR and 2 minimal responses (MRs) in 5 patients at 1.5 mg/kg on the Q4W schedule and 1 PR and 1 CR (patient ongoing at Cycle 21) in 7 patients at 3 mg/kg on the Q4W schedule.

Part 2 of Study TAK-573-1501 included a dose-expansion cohort of 25 patients treated at 1.5 mg/kg Q4W. A response rate of 44% was seen. The median duration of response has not yet been reached.

Toxicities were primarily hematologic, with thrombocytopenia and neutropenia observed at rates of 73% (17% Grade 4) and 70% (30% Grade 4) respectively. IRRs have been observed at a rate of 30%. Toxicities have been managed with dose delays and supportive care and have rarely resulted in study drug discontinuation or dose reduction.

In addition, the dose- and exposure-response relationship based on the preliminary pharmacodynamics (M-protein and free light chain), efficacy, and safety data indicate that 1.5 and 3 mg/kg Q4W dosing are within the optimal biological dose range.

Based on the preliminary risk/benefit profile seen in the dose escalation and expansion cohorts and the increased efficacy signals seen with increasing doses up to and including the MTD of 3 mg/kg Q4W, a randomized noncomparative trial of modakafusp alfa 120 mg or 240 mg Q4W (fixed dosing equivalents of 1.5 and 3 mg/kg) was designed to identify the dose with an optimal benefit/risk profile for patients with this incurable disease.

4.6.2.1 Rationale for Fixed Dosing

At the initiation of clinical development of modakafusp alfa, early phase 1 clinical studies empirically used a body weight-based (in mg/kg) dosing approach that has been traditionally used in the development of cytotoxic anticancer agents. The appropriateness of the conventional body weight-based approach for dosing therapeutic mAb has been critically questioned in the recent scientific literature (Bai et al. 2012; Mould 2015; Wang et al. 2009). Because of its in vivo properties, including linear catabolic degradation and saturable target-mediated elimination pathways, the PKs of a therapeutic mAb can be affected by multiple potential factors, including target cell trafficking, target antigen expression levels per cell/tissue, serum protein levels, and disease status in addition to patient demographics such as age, body size, and sex. Thus, the impact of body weight may only explain a small portion of the overall interindividual variability of the PK parameters of mAb, especially in cases where the contribution of the target-mediated elimination pathway exceeds that of the linear catabolic elimination pathway (Bai et al. 2012; Mould 2015; Wang et al. 2009).

Following a single-dose administration, the increase of modakafusp alfa exposure was greater than dose-proportional in the dose range of 0.1 to 3 mg/kg and approximately dose-proportional in the dose range of 3 to 6 mg/kg. Both visual inspection of the serum PK profiles and the apparent nonlinear PK across dose groups indicated saturable target-mediated elimination for modakafusp alfa. Despite the body weight-based dosing, between-subject exposure variability was moderate (30%-100%) to high (>100%).

A preliminary population PK analysis was performed using emerging data from the 2 ongoing phase 1/2 studies (Study TAK-573-1501 in MM patients and Study TAK-573-1001 in patients with solid tumors). A quasi-equilibrium bispecific mAb 2-compartment population PK model with both linear total clearance after IV administration (CL) and saturable target-mediated drug disposition (TMDD) represented a semi-mechanistic structural model to account for target engagement with both IFNα and CD38 receptors and was shown to adequately describe the modakafusp alfa PK. The effect of body weight on the central volume of distribution (Vc) parameter for modakafusp alfa was characterized using a power model with the exponent estimated to be 0.664 on Vc. The relationship between body weight and CL, CLd, and Vp was not statistically significant. The impact of body weight on TMDD parameters including target capacity (Rtot) for CD38 was explored graphically and was not warranted.

The model-based simulation was conducted to assess the impact of body weight on the PK of modakafusp alfa. Boxplots of the simulated exposures with the 2 dosing approaches, for the overall population, are shown in Figure 4.a. Comparison of the 2 dosing approaches was conducted based on the simulated exposures following Cycle 1 single dose administration to

minimize the confounding impact of the potential time-varying factors (eg, ADA) on the assessment of body weight effect on PK. Figure 4.a illustrates the comparable PK variability and exposure for the overall patient population between the fixed dose and weight-based dosing approaches. In addition, the projected exposures (ie, maximum observed serum concentration [C_{max}] area under the serum concentration-time curve concentration [AUC]) at the proposed fixed doses (120 and 240 mg) are generally below the exposures for a patient administered 6 mg/kg who exhibited a DLT and model-predicted exposure for 6 mg/kg.

Figure 4.a **Boxplot Comparison of Model-Predicted Single-Dose C_{max} (3 mg/kg vs 240 mg) and AUC (1.5 mg/kg vs 120 mg and 3 mg/kg vs 240 mg) for Fixed Dose and Weight-Based Dosing for Modakafusp Alfa for Overall Population**

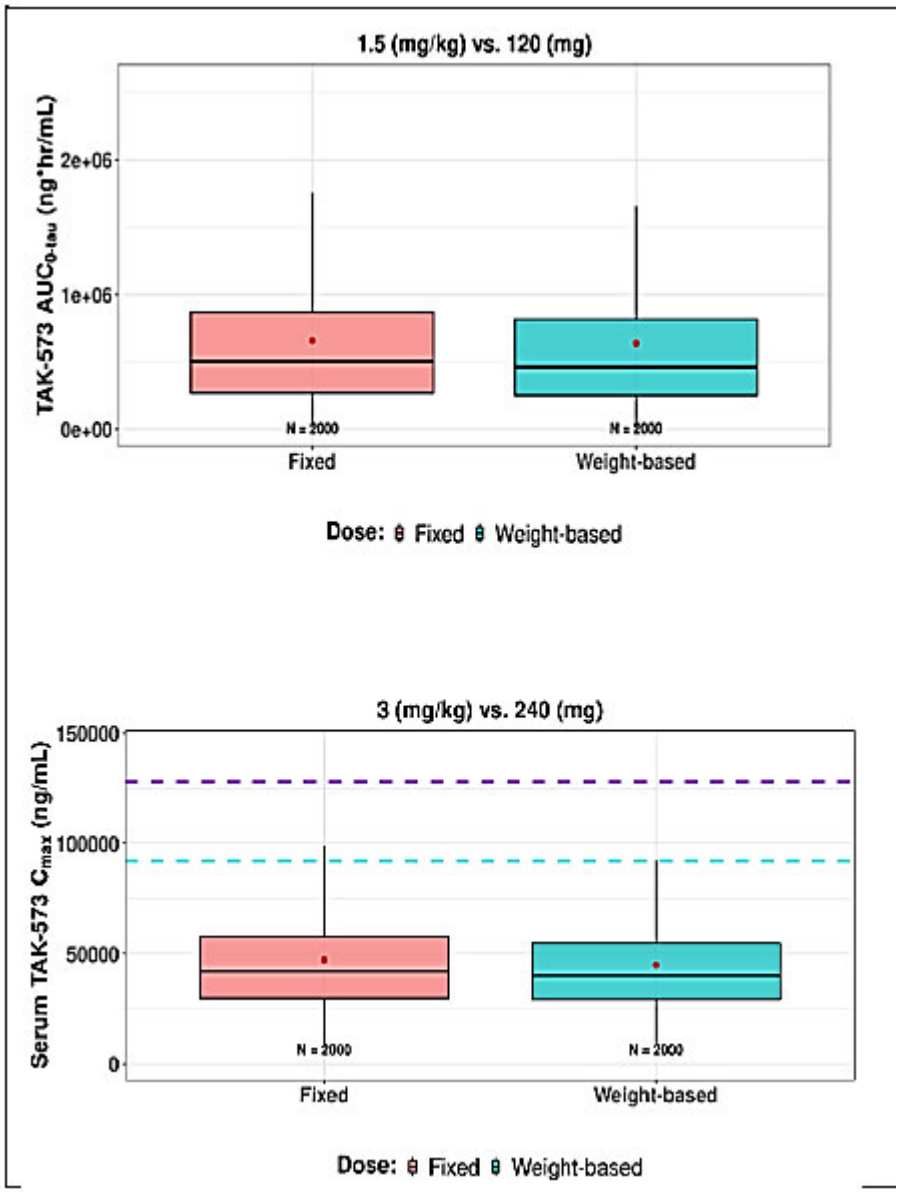
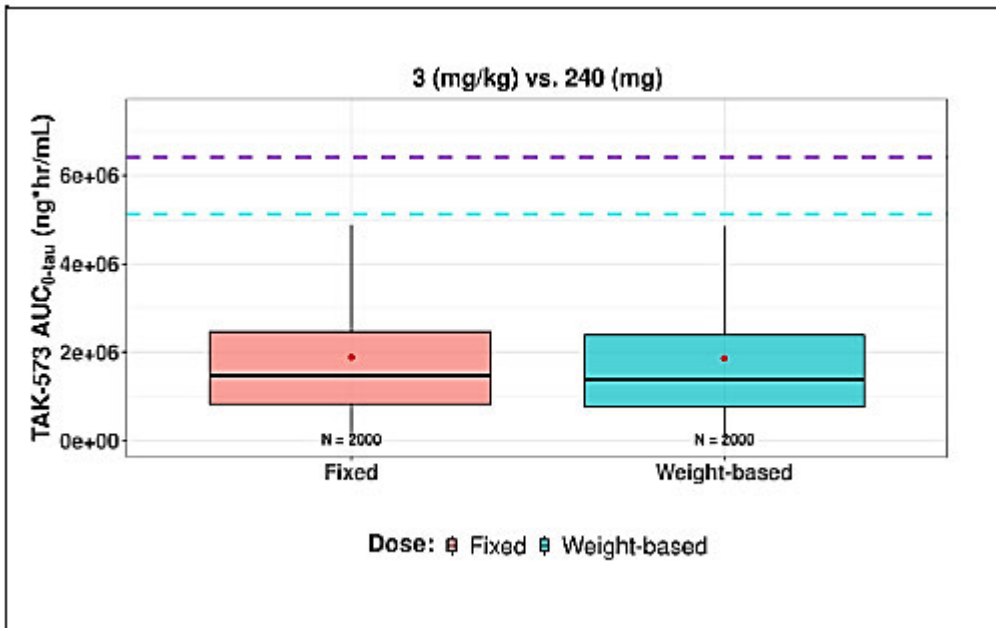


Figure 4.a Boxplot Comparison of Model-Predicted Single-Dose C_{max} (3 mg/kg vs 240 mg) and AUC (1.5 mg/kg vs 120 mg and 3 mg/kg vs 240 mg) for Fixed Dose and Weight-Based Dosing for Modakafusp Alfa for Overall Population



AUC: area under the serum concentration-time curve; $AUC_{0\text{-}tau}$ BW: body weight; C_{max}: maximum observed serum concentration; DLT: dose-limiting toxicity; Q4W: once every 4 weeks.

Red dots are means. The purple line denotes the exposure based on the noncompartmental analysis of the observed data for a patient of the 6 mg/kg Q4W dose group who exhibited DLT (delayed platelet count recovery). The cyan line denotes the mean simulated exposure for 6 mg/kg dose group.

Overall, the data and preliminary population PK analysis suggest that there is a low impact of body weight on the PK of modakafusp alfa (ie, no appreciable impact of body weight on CL and a weight exponent of 0.664 on Vc only), likely because the contribution of the TMDD pathway exceeds that of the linear catabolic elimination pathway. Additionally, exploratory population PK-PD modeling of serum m-protein and free light-chain, which are 2 potential outcome biomarkers for efficacy, have been conducted. These preliminary population PK-PD analyses are not presented here, but no apparent effect of body weight on any PK-PD parameters was observed. Although the final population PK model included weight effect on Vc, the impact of body weight was not expected to be clinically meaningful, based on the totality of the PK (eg, moderate to high PK variability despite of fixed-dosing in phase 1 and clinical data, including the magnitude of the PD variability in the PK-PD models for efficacy. Based on these collective findings and the benefits of fixed dosing due to its convenience, better compliance, less risk for dosing errors, and reduced drug wastage, fixed dosing is considered an appropriate dosing approach for further clinical development. Accordingly, the 2 modakafusp alfa body

weight–based doses of 1.5 and 3 mg/kg Q4W will be translated into 2 fixed doses of 120 and 240 mg Q4W based on the median bodyweight of approximately 80 kg (from Parts 1 and 2 of Study TAK-573-1501) for the Part 3 evaluation.

4.6.3 Changes to Modakafusp Alfa Infusion

The initial administration over 4 hours with premedications and postmedication was based on the administration schema of the only commercialized anti-CD38, daratumumab. Daratumumab is an IgG1 monoclonal antibody with intact antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and immune-mediated tumor cell lysis through complement dependent cytotoxicity. Modakafusp alfa belongs to the IgG4 class which does not have immune-effector properties.

Amendment 05 allowed optional administration of premedications and shortened the infusion time of modakafusp alfa to 1 hour. As of Amendment 6, based on the experience with infusion reactions in patients not receiving premedications per the guidance set forth in Amendment 05, it was strongly recommended that all patients receive premedications prior to modakafusp alfa dosing and any decision to stop premedications would have to be discussed with and agreed upon by the sponsor. In addition, patients receiving modakafusp alfa doses ≥6 mg/kg are treated with additional premedication and the dose is delivered over a longer infusion time.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Part 1 Dose Escalation Objectives

5.1.1 Part 1 Primary Objective

To determine the safety and tolerability of single agent modakafusp alfa in patients with relapsed/refractory MM.

5.1.2 Part 1 Secondary Objectives

- To determine the MTD/ optimal biological dose (OBD) of modakafusp alfa with 1 or more schedules of administration.
- To characterize the PK profile of modakafusp alfa.
- To evaluate the immunogenicity of modakafusp alfa.
- To provide a preliminary evaluation of the clinical activity of modakafusp alfa.

5.1.3 Part 1 Exploratory Objectives

- To explore potential biomarkers to test their correlation with clinical efficacy and safety parameters.

5.2 Part 2 Dose Expansion Objectives

5.2.1 Part 2 Primary Objective

To provide a preliminary evaluation of the clinical activity of modakafusp alfa as a single agent and in combination with dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM).

5.2.2 Part 2 Secondary Objectives

- To further evaluate efficacy and safety and to determine the suitability of the modakafusp alfa MTD/OBD as a single agent and in combination with dexamethasone for further trials as the recommended dose and schedule.
- To further characterize the PK profile of modakafusp alfa as a single agent and in combination with dexamethasone.
- To further characterize the immunogenicity of modakafusp alfa as a single agent and in combination with dexamethasone.

5.2.3 Part 2 Exploratory Objectives

- To explore potential biomarkers to test their correlation with clinical efficacy and safety parameters.

5.3 Part 3 Dose Extension Objectives

5.3.1 Part 3 Primary Objective

To determine the ORR as assessed by IRC according to International Myeloma Working Group (IMWG) criteria (Appendix F) of modakafusp alfa in patients who have MM defined by the IMWG criteria with evidence of disease progression and are in need of additional myeloma therapy as determined by the investigator, have previously received at least 3 lines of myeloma therapy, and are refractory to at least 1 IMiD (ie, lenalidomide or pomalidomide [thalidomide excluded]), at least 1 PI (ie, bortezomib, ixazomib, or carfilzomib), and refractory to at least 1 anti-CD38 antibody and who have demonstrated disease progression during or after the last therapy.

5.3.2 Part 3 Secondary Objectives

- To determine ORR by investigator assessment, duration of response (DOR), clinical benefit rate (CBR), duration of clinical benefit, disease control rate (DCR), duration of disease control, progression-free survival (PFS), time to progression (TTP), and overall survival (OS).
- To assess minimal residual disease (MRD) negativity in patients achieving CR.
- To further characterize safety and tolerability of modakafusp therapy.

- To collect PK data to evaluate population PK and exposure-response (safety/efficacy) analysis.
- To characterize the PK profile of modakafusp alfa in Chinese patients.
- To further characterize the immunogenicity of modakafusp alfa.
- To assess healthcare resource utilization.
- To evaluate patient-reported disease symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity).

5.3.3 Part 3 Exploratory Objectives

- To explore predictive biomarkers of response and resistance.
- To characterize MRD negativity at a higher sensitivity in patients achieving CR.
- To evaluate generic health-related quality of life (HRQOL)/health status, measured by the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) instrument.

5.4 Endpoints

5.4.1 Part 1 Dose Escalation Endpoints

5.4.1.1 Part 1 Primary Endpoints

- The number of patients with TEAEs overall and per dose level.
- Patients with DLTs at each dose level.
- Patients with Grade ≥3 TEAEs.
- Patients with SAEs.
- Patients who discontinue because of TEAEs.
- Patients with dose modifications (delays, interruptions, dose reductions).
- Clinically significant laboratory values.
- Clinically significant vital sign measurements.

5.4.1.2 Part 1 Secondary Endpoints

- DLT-like (TEAEs meeting DLT definition that occur after phase 1 Cycle 1) frequencies and other TEAEs occurring over the course of extended treatment with modakafusp alfa, including information about dose modification, treatment discontinuation, and clinically significant laboratory values and vital signs.

- Summary statistics by dose level and cycle day for the following PK parameters:
  - Single-dose C_{max}.
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the serum concentration-time curve from time 0 to infinity (AUC_{∞}).
  - 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 (λ_z).
  - Apparent serum modakafusp alfa terminal elimination phase half-life ($t_{1/2z}$).
  - CL.
  - Volume of distribution at steady state (V_{ss}).
- Anti-modakafusp alfa-antibody incidence and characteristics (eg, titer and specificity), Nab.
- Preliminary evaluation of antitumor activity of modakafusp alfa:
  - For patients with measurable disease only: ORR, defined as the proportion of patients who achieved a PR or better during the study; sCR, CR, very good partial response (VGPR), and PR as defined by IMWG Uniform Response Criteria (Appendix F), CBR (includes patients with a response of sCR, CR, VGPR, PR, or minimal response); DCR (includes patients with a response of sCR, CR, VGPR, PR, minimal response, or stable disease).
  - For patients with measurable disease only: median DOR, with DoR defined as the time from the date of first documentation of response PR or better to the time of disease progression or death, whichever occurs first.
  - For patients with measurable disease only: time to response, defined as the time from first dose to the date of first documentation of response (PR or better).
  - Progression-free survival (PFS), defined as the time from the date of first dose until the sooner of the date of PD, defined by IMWG criteria (Appendix F), or the date of death due to any cause.

5.4.1.3 Part 1 Exploratory Endpoints

- CD38 expression on MM cells and other immune cells in bone marrow aspirate (BMA) and its correlation with clinical outcome.
- Pharmacodynamic biomarkers including, but not limited to, neopterin, complement, cytokines/chemokines, and gene expression and their correlation with clinical outcome.
- Pharmacodynamic analysis of the presence and changes of immune cells from whole blood and bone marrow and their correlation with clinical outcome.

- Effects of modakafusp alfa administration on the electrocardiographic QT/QT interval with Fridericia correction method (QTcF).

5.4.2 Part 2 Expansion Endpoints

5.4.2.1 Part 2 Primary Endpoints

- ORR, defined as the proportion of patients who achieved a PR or better during study; sCR, CR, VGPR, and PR as defined by IMWG Uniform Response Criteria (Appendix F).

5.4.2.2 Part 2 Secondary Endpoints

- DOR.
- CBR.
- DCR.
- PFS, defined as the time from the date of first dose until the sooner of the date of PD, defined by IMWG criteria (Appendix F), or the date of death due to any cause.
- OS, defined as the date from first dose to the date of death due to any cause.
- Time to response, defined as the time from first dose to the date of first documentation of response (PR or better).
- DLT-like events (TEAEs meeting DLT definition that occur after Part 1 Cycle 1) frequencies and other TEAEs occurring over the course of extended treatment with modakafusp alfa, including information about dose modification, treatment discontinuation, and clinically significant laboratory values and vital signs.
- Summary statistics by dose level and cycle day for the following PK parameters: C_{max}, AUC_{∞}, AUC_{last}, λ_z, t_{max}, CL, V_{ss}, and $t_{1/2z}$.
- Anti-modakafusp alfa antibody incidence and characteristics (eg, titer and specificity), NAb.

5.4.2.3 Part 2 Exploratory Endpoints

- CD38 expression on MM cells and other immune cells in BMA and its correlation with clinical outcome.
- Pharmacodynamic biomarkers including, but not limited to, neopterin, cytokines/chemokines, and gene expression and their correlation with clinical outcome.
- Pharmacodynamic analysis of the presence and changes of immune cells from whole blood and bone marrow and their correlation with clinical outcome.
- Effects of modakafusp alfa administration on the electrocardiographic QT/QT interval with Fridericia correction method (QTcF).

5.4.3 Part 3 Extension Endpoints

5.4.3.1 Part 3 Primary Endpoint

- ORR (PR or better) assessed by IRC according to modified IMWG criteria (Appendix F).

5.4.3.2 Part 3 Secondary Endpoints

- ORR by investigator assessment.
- DOR.
- CBR (response of sCR, CR, VGPR, PR, or minimal response) by IRC and investigator assessment.
- Duration of clinical benefit.
- DCR (CBR + stable disease [SD]) by IRC and investigator assessment.
- Duration of disease control.
- PFS (time from the date of first dose until the sooner of the date of PD, defined by IMWG criteria [(Appendix F)] or the date of death due to any cause by IRC and investigator assessment.
- TTP by IRC and investigator assessment.
- OS (date from first dose to the date of death due to any cause).
- 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} in patients achieving CR.
- AEs, SAEs, laboratory assessments, supportive care use.
- Eastern Cooperative Oncology Group (ECOG) status.
- ADA incidence and characteristics (eg, titer and specificity) and NAb.
- Length of hospital stay, types of hospital stay, and other healthcare resource utilization data as defined in Section 9.3.13.
- No worsening of disease symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity) from baseline at 12 weeks across doses of modakafusp alfa as measured by the patient-reported outcome (PRO) instrument European Organisation for Research and Treatment of Cancer QLQ Questionnaire Multiple Myeloma Module (EORTC QLQ-MY20).
- Summary statistics by dose level and cycle day for the following PK parameters in Chinese patients with intensive PK schedule: C_{max}, AUC_{∞}, AUC_{last}, λ_z, t_{max}, CL, V_{ss}, and $t_{1/2z}$.

5.4.3.3 Part 3 Exploratory Endpoints

- CD38 expression on MM cells and other immune cells within the bone marrow and its correlation with clinical outcome.
- Evaluation of somatic mutations and polymorphisms and their associations with response and/or acquired resistance.
- Evaluation of anti-interferon antibodies at baseline and correlation with response.
- Rate of MRD negative status at a sensitivity of 10^{-6} in patients achieving CR.
- Duration of MRD negativity (10^{-6}) in patients who achieve MRD negative status at CR.
- Evaluation of generic HRQOL/health status as measured by the EQ-5D-5L instrument.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a multicenter, open-label, phase 1/2 study designed to determine the safety and tolerability of modakafusp alfa as a single agent and in combination with dexamethasone in patients with relapsed/refractory MM. The study will be conducted in 3 parts.

Part 1 Dose Escalation: Single-agent modakafusp alfa with 1 or more schedules of administration.

Part 2 Dose Expansion: At least 1 cohort of modakafusp alfa combined with dexamethasone using the dose and schedule determined in Part 1.

Treatment cycle duration is 28 days (21 days for Schedule C). For Parts 1 and 2, modakafusp alfa with or without dexamethasone will be administered for up to 12 cycles or until disease progression, unacceptable toxicity, or any other discontinuation criterion is met (Section 9.4). Patients with demonstrated clinical benefit may continue treatment beyond 12 cycles with the agreement of the sponsor.

Part 3 Dose Extension: Single-agent modakafusp alfa with 1:1 randomization to receive modakafusp alfa 120 or 240 mg. Patients will be stratified by their cytogenetics risk (high risk [del17, t(4;14) and/or t(14;16)] vs standard risk) and myeloma type (IgA vs other). Cytogenetic results from samples taken within 5 weeks prior to first dose are acceptable for stratification. All patients should also have a sample from screening sent for central analysis. If a previous result is not available and the patient is known to have high-risk disease [ie, del17, t(4;14) and/or t(14;16)] from prior cytogenetic testing, regardless of timing, they should be stratified as high risk for the purpose of enrollment.

For Part 3, treatment can continue until any criterion described in Section 9.4 is met. **Response assessments in Part 3 will be made on the basis of central laboratory data**.

Patient participation includes a screening phase, a treatment phase, and a follow-up phase (Section 9.3). The screening phase will be up to 21 days before Cycle 1 Day 1 (C1D1). Please

refer to the guidance in the Site Operations Manual if a patient needs to be rescreened. The follow-up phase begins once a patient discontinues study treatment and completes the end-of-treatment (EOT) visit; study follow-up continues until the study ends or the patient completes OS follow-up (Section 9.5). The total duration of patient participation is described in Section 6.3.

Part 1 Dose Escalation

The primary objective of Part 1 of the study was to determine the safety and tolerability of one or more schedules of single-agent modakafusp alfa in patients with RRMM.

Part 1 followed a 3 + 3 dose escalation design to evaluate up to 4 different schedules of administration of modakafusp alfa with the objective of determining, with one or more schedules, either an MTD based on the observation of DLTs, or an OBD.

Four single-agent schedules were evaluated during Part 1:

- Schedule A (initial): Modakafusp alfa infusion is given at weekly intervals in a 28-day cycle for 2 cycles followed by 1 infusion every 2 weeks (twice per cycle) in Cycles 3 to 6, and once every 4 weeks from Cycle 7 until treatment discontinuation.
- Schedule B: Modakafusp alfa infusions will be administered on a 28-day (4-week) cycle once every 2 weeks until treatment discontinuation criterion is met.
- Schedule C: Modakafusp alfa infusions will be administered on a 21-day (3-week) cycle once every 3 weeks until treatment discontinuation criterion is met.
- Schedule D: Modakafusp alfa infusions will be administered on a 28-day (4-week) cycle once every 4 weeks until treatment discontinuation criterion is met.

The overall study schematic is displayed in Figure 6.a.

Part 2 Dose Expansion

The primary objective of Part 2 of the study is to provide a preliminary evaluation of the clinical activity of one or more schedules of modakafusp alfa given as a single agent in patients with RRMM. Additional cohort(s) of modakafusp alfa (using the same dose used in a single-agent cohort) in combination with dexamethasone will be implemented, with the selected schedule(s) to be determined once the modakafusp alfa MTD or OBD is established. Treatment allocation will be randomly assigned. Dexamethasone will be given as a once weekly oral dose of 40 mg. Patients over 75 years of age will receive a reduced dose of dexamethasone (20 mg, same schedule). The aim of this approach is to obtain preliminary information on the effect of standard doses of dexamethasone on modakafusp alfa safety, efficacy, and pharmacodynamic endpoints.

Preliminary activity of modakafusp alfa as a single agent and in combination with dexamethasone will be evaluated by measuring the confirmed ORR (PR or better) according to IMWG Uniform Response Criteria (Appendix F). The efficacy of modakafusp alfa will further assessed by assessing DOR, PFS, OS, and time to response.

Figure 6.a Overall Study Schematic Diagram

Treatment Cycle – Schedule A: 28-day Cycles; Q1W Dosing [a]

C1				C2				C3		C4		C5		C6		C7	C8	C9	C10	C11	C12	C13
D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1	D15	D1	D15	D1	D15	D1	D1	D1	D1	D1	D1	D1

Treatment Cycle – Schedule B: 28-day Cycles; Q2W Dosing [a]

C1		C2		C3		C4		C5		C6		C7		C8		C9		C10		C11		C12		C13	
D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15

Treatment Cycle – Schedule C: 21-day Cycles; Q3W Dosing [a]

C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17
D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1

Treatment Cycle – Schedule D: 28-day Cycles; Q4W Dosing [a]

C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13
D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1

C: cycle; D: day; Q1W: once every week; Q2W: once every 2 weeks; Q3W: once every 3 weeks; Q4W: once every 4 weeks.
Cycle = 4 weeks for Schedules A, B and D; 3 weeks for Schedule C.
In Part 3, Schedule D Q4W dosing will be followed by one cohort receiving 120 mg and one cohort receiving 240 mg to determine the optimal dose.
Dose modification guidelines are detailed in Section 8.4, study completion guidelines are detailed in Section 9.4, treatment discontinuation guidelines are detailed in Section 9.4.1, and study withdrawal is detailed in Section 9.4.2.
Dose escalation:
Schedule A = 0.001, 0.01, 0.1, 0.75, 1.5, 3, 6, 9, 14 mg/kg. Intermediate dose levels are permissible with agreement between investigators and sponsor.
Schedule B, C and D = opening of the first cohort and starting dose level will be decided by the investigators and sponsor. For each of these levels, the starting dose will not be above the highest dose previously tested with a more intensive schedule.
[a] In Part 2, only, at least one cohort(s) will combine modakafusp alfa with dexamethasone in parallel with a Part 2 single-agent cohort using the same modakafusp alfa schedule. Dexamethasone is administered once weekly (starting on C1D1) at 40 mg (20 mg for patients >75 years of age) until a discontinuation criterion is met.

Part 3 Dose Extension

Part 3 will determine the confirmed ORR per IRC assessment, evaluate other efficacy endpoints, assess MRD negativity in patients achieving CR, further characterize the safety, tolerability, and immunogenicity of modakafusp alfa therapy, collect PK data, and assess healthcare resource utilization.

The modakafusp alfa doses of 1.5 and 3 mg/kg Q4W will be translated into 2 fixed doses of 120 and 240 mg based on the median bodyweight of approximately 80 kg (from Parts 1 and 2 of Study TAK-573-1501) for the Part 3 evaluation.

Two interim analyses for futility are planned for the study when approximately 15 and 48 patients of the planned 118 patients per arm are enrolled and treated for at least 3 cycles or have discontinued treatment prematurely (Figure 6.b).

The sponsor will only proceed with enrolling additional patients into a treatment arm where the futility boundary is not crossed; more specifically:

Scenario 1: If the futility boundary is not crossed in one arm (eg, the 120 mg arm) but is crossed in the second treatment arm (eg, the 240 mg arm), patient enrollment will continue only in the arm that did not cross the futility boundary (eg, the 120 mg arm).

Scenario 2: If the futility boundary is not crossed in the 120 mg treatment arm and is not crossed in the 240 mg treatment arm, patient enrollment will continue for both arms to identify the optimal dose, defined as having the more favorable risk-benefit profile based on the totality of data from both arms and Parts 1 and 2.

Scenario 3: If the futility boundary is crossed in the 120 mg treatment arm and is crossed in the 240 mg treatment arm, the study will be terminated.

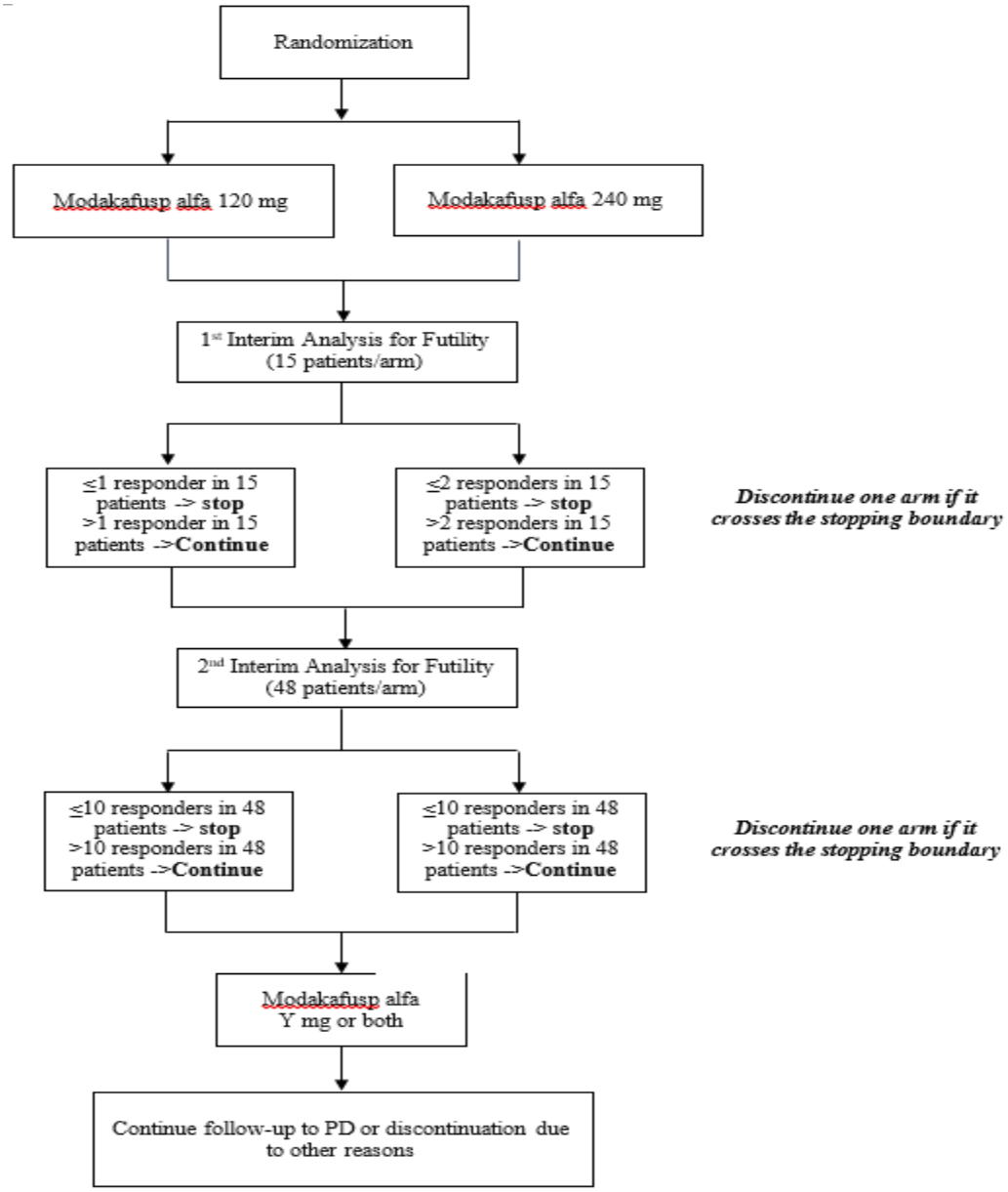
In addition, the sponsor may decide to discontinue 1 arm if there is early detection of an unfavorable risk-benefit profile based on the interim data analysis data.

Study procedures and assessments, with their time points, are shown in Appendix A, Appendix B, and Appendix C.

Part 3 China Continuation Cohort

After global patient enrollment is completed in Part 3, enrollment will continue for the China continuation cohort until about 15% of the total sample size is reached at the selected dose(s) (eg, 18 patients based on 118 patients treated at the selected dose[s]).

Figure 6.b Part 3 Study Schematic



PD: progressive disease; Q4W: once every 4 weeks.
Dosing is Q4W in both cohorts.

6.2 Number of Patients

For Part 1, the number of evaluable patients is planned to be 36 to 51.

For Part 2, a total of approximately 25 patients will be enrolled in each expansion cohort. The planned expansion cohorts include 3 modakafusp alfa single-agent cohorts plus at least one combination cohort of modakafusp alfa with dexamethasone using the same dose and schedule of modakafusp alfa used in a single-agent expansion cohort (approximately 100 patients).

For Part 3, approximately 236 patients (118 per dose cohort) will be enrolled.

After global patient enrollment is completed in Part 3, enrollment will continue for the China continuation cohort until about 15% of the total sample size is reached at the selected dose(s) (eg, 18 patients based on 118 patients treated at the selected dose[s]).

Details on the definition of evaluable patients and sample size are given in Section 13.0.

The study is planned to be conducted globally at approximately 100 investigational centers.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may receive modakafusp alfa until they experience PD, unacceptable toxicity, or any other discontinuation criterion is met (Section 9.4). In Parts 1 and 2, the maximum scheduled duration of treatment will be 1 year; however, patients with clinical benefit can continue treatment beyond 1 year with explicit sponsor approval. Patients in the modakafusp alfa plus dexamethasone cohort can continue receiving single-agent modakafusp alfa if the investigator considers that there are clinical reasons (for example safety) supporting the removal of dexamethasone from the treatment.

Patients may be treated in Part 3 until progression or other discontinuation criteria are met. If the investigator considers that treatment after PD is in the patient's best interest, it can be approved after consultation with the sponsor.

Patients will be evaluated 30 days (EOT visit) after the last dose of modakafusp alfa or right before the start of subsequent systemic anticancer therapy to permit the detection of any delayed TEAEs.

Patient participation includes up to 21 days of screening, 1 year of treatment (Parts 1 and 2) or until disease progression (Part 3), and 1 month posttreatment follow-up (EOT visit). Patients who discontinue for reasons other than 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 (Section 9.4), or until 6 months after the discontinuation of study treatment, whichever occurs first. OS follow-up continues every 12 weeks from the EOT visit until death, study termination, or patient withdrawal.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final analysis for the clinical study report will be conducted after all patients enrolled in the study have completed OS follow-up, have withdrawn from the study, or have transitioned to posttrial access (Section 6.3.5).

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosure information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Part 1		
Primary: Percentage of patients with TEAEs	TEAEs, DLTs, SAEs, Grade ≥3 TEAEs, dose modification, discontinuations, and clinically significant laboratory values and vital signs.	Up to ~90 months.
Secondary: DLT-like TEAEs	TEAEs meeting DLT definition that occur after phase 1 Cycle 1) frequencies and other TEAEs occurring over the course of extended treatment with modakafusp alfa, including information about dose modification, treatment discontinuation, and clinically significant laboratory values and vital signs.	Up to ~90 months.
Secondary: Summary PK statistics	See Section 9.3.11.	Up to ~90 months.
Secondary: ORR, sCR, CR, VGPR, and PR	See Section 9.3.10.	Up to ~90 months.
Secondary: CBR and DCR	See Section 9.3.10.	Up to ~90 months.
Secondary: PFS	See Section 9.3.10.	Up to ~90 months.
Secondary: Duration of response, time to response	See Section 9.3.10.	Up to ~90 months.
Secondary: Anti–modakafusp alfa antibody incidence and characteristics, NAb	See Section 13.1.7.	Up to ~90 months.
Part 2 Expansion		
Primary: ORR	See Section 9.3.10.	Up to ~90 months.
Primary: DOR, time to response		Up to ~90 months.
Primary: PFS	See Section 9.3.10.	Up to ~90 months.
Primary: OS	See Section 9.3.10.	Up to ~90 months.
Primary: Time to response	See Section 9.3.10.	Up to ~90 months.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Secondary: DLT-like TEAEs	TEAEs meeting DLT definition that occur after Part 1 Cycle 1 and TEAEs occurring over the course of extended treatment with modakafusp alfa including information about dose modification, treatment discontinuation, clinically significant laboratory values, and vital signs.	Up to ~90 months.
Secondary: Summary PK statistics	See Section 9.3.11.2.	Up to ~90 months.
Part 3 Extension		
Primary: ORR as assessed by the IRC	See Section 9.3.10.	Up to ~90 months.
Secondary: ORR as assessed by the investigator	See Section 9.3.10.	Up to ~90 months.
Secondary: CBR, DCR, DOR by IRC and investigator assessment	See Section 9.3.10.	Up to ~90 months.
Secondary: PFS, TTP by IRC and investigator assessment	See Section 9.3.10.	Up to ~90 months.
Secondary: Duration of clinical benefit and disease control	See Section 9.3.10.	Up to ~90 months.
Secondary: OS	See Section 9.3.10.	Up to ~90 months.
Secondary: Summary PK statistics in Chinese patients	See Section 9.3.11.2.	Up to ~90 months.
Secondary: Antimodakafusp alfa antibody incidence and characteristics and NAb	See Section 9.3.11.5.	Up to ~90 months.
Secondary: Rate and duration of MRD negativity in patients achieving CR	See Section 9.3.11.3.	Up to ~90 months.
Secondary: AEs, SAEs, laboratory assessments, supportive care use	See Section 9.3.9.	Up to ~90 months.
Secondary: HRU measures	See Section 9.3.13.	Up to ~90 months.
Secondary: HRQOL measures	See Section 9.3.12.	

AE: adverse event; CBR: clinical benefit rate; CR: complete response; DCR: duration of complete response; DLT: dose-limiting toxicity; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; HRQOL: health-related quality of life; HRU: health care resource utilization; IRC: independent review committee; MRD: minimal residual disease; NAb: neutralizing antibody; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetic(s); SAE: serious adverse event; sCR: stringent complete response; TEAE: treatment-emergent adverse event; TTP: time to progression; VGPR: very good partial response.

6.3.4 Total Study Duration

Patients will be followed for 30 days after the last dose of modakafusp alfa or right before the start of subsequent anticancer therapy, whichever occurs first, to permit the detection of any

delayed TEAEs. All patients, including those patients no longer on treatment, will be assessed for PFS and survival. Patients who discontinue the study treatment for any reason other than PD will be followed for PFS every 4 weeks from the EOT visit until PD, start of new systemic anticancer treatment, death, withdrawal of consent for further follow-up, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first. Patients will be followed for OS every 12 weeks from the EOT visit until death, study termination, or patient withdrawal.

Information on any subsequent anticancer therapies will be collected during the PFS/survival follow-up period. For patients who achieve CR but discontinue study treatment while still in remission, PFS information based upon available local data for Parts 1 and 2 and central data for Part 3 will also be collected during the PFS/survival follow-up period.

It is anticipated that this study will last for approximately 90 months.

6.3.5 Posttrial Access

At the end or termination of the study (Section 6.3.2), ongoing patients may continue to receive modakafusp alfa in an extension phase of this study or will be given the opportunity to enroll in a separate open-label rollover study, a single patient Investigational New Drug (IND), or other regulated access to continue receiving modakafusp alfa if, in the opinion of the investigator and confirmed by the sponsor, they have experienced a clinically important benefit from modakafusp alfa received in the study, have no alternative therapeutic option, and would be harmed without continued access.

6.3.5.1 Duration of Posttrial Access

Continued access to modakafusp alfa for participants will be terminated for those individuals who no longer benefit from modakafusp alfa (eg, they have completed the recommended course of therapy or their disease has resolved), the benefit-risk no longer favors the individual, if modakafusp alfa becomes available either commercially or via another access mechanism, or when an alternative appropriate therapy becomes available. Posttrial access may be terminated in a country or geographical region where marketing authorization has been rejected, the development of modakafusp alfa has been suspended or stopped by the sponsor, or the modakafusp alfa can no longer be supplied.

6.4 Randomization in Phase 2 Part 3 Extension

Patients will be randomized in a 1:1 ratio to receive modakafusp alfa fixed doses of 120 mg or 240 mg Q4W. Patients will be stratified by the following 2 factors, each having 2 levels:

1. Cytogenetics risk (high risk [defined as 17p-, t(4;14) and/or t(14;16)] vs standard risk).
2. Myeloma type (IgA vs other).

Randomization procedures should be performed following complete eligibility assessments and prior to the initiation of assigned treatment. This study is unblinded; patients, investigators, and the sponsor will know the identity of each patient's study treatment.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

For Parts 1 and 2:

Each patient must meet all the following inclusion criteria to be enrolled in the study.

1. MM defined by the IMWG criteria with evidence of disease progression and:
   a) Is in need of additional myeloma therapy as determined by the investigator.
   b) Has previously received at least 3 lines of myeloma therapy (eg, containing an IMiD, a PI, an alkylating agent, and/or an anti-CD38 as single agents or in combination).
   c) Is either refractory to, or intolerant of, at least 1 PI and at least 1 IMiD (see NOTE below).

For Part 3:

Each patient must meet all the following inclusion criteria to be enrolled in the study.

1. MM defined by the IMWG criteria with evidence of disease progression and:
   a) Is in need of additional myeloma therapy as determined by the investigator.
   b) Has previously received at least 3 lines of myeloma therapy.
   c) Is refractory to at least 1 IMiD (ie, lenalidomide or pomalidomide [thalidomide excluded]), at least 1 PI (ie, bortezomib, ixazomib, or carfilzomib), and refractory to at least 1 anti-CD38 antibody (ie, daratumumab or isatuximab) and who have demonstrated disease progression during or after the last therapy (see *NOTE below). Patients who were primary refractory to all prior therapies, meaning they never achieved at least a MR with any previous treatment line, are not eligible.

   *NOTE: Refractory is defined as <25% reduction in M-protein or progression of disease during treatment or within 60 days after cessation of treatment.

   A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease (Rajkumar et al. 2011).
2. Aged 18 years or older.
3. For patients in Parts 2 and 3 only: Measurable disease defined as one of the following:
   a) Serum M-protein ≥500 mg/dL (≥5 g/L).
   b) Urine M-protein ≥200 mg/24 hours.

c) Serum free light chain (FLC) assay with involved FLC level ≥10 mg/dL (≥100 mg/L) provided serum FLC ratio is abnormal.

4. During Part 1 only, patients not meeting the above criteria for measurable disease should, at least, have measurable bone marrow plasmacytosis (≥10%) and/or plasmacytoma (≥1 cm in diameter) detected by physical examination or imaging.
5. ECOG performance status of ≤2.
6. Patient has adequate organ function as determined by the following laboratory values.

Absolute neutrophil count [a]	≥1000/mm^3 (≥1.0×10^9/L)
Platelets [a]	≥75,000/mm^3 (≥75×10^9/L)
Hemoglobin	≥75 g/L
Creatinine clearance	≥30 mL/min (Cockcroft-Gault)
Total serum bilirubin	≤2.0×ULN; an exception for patients with Gilbert's syndrome may be granted after discussion with the sponsor.
Liver transaminases (ALT/AST)	≤3.0×ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of the normal range.
[a] Without ongoing growth factor or transfusion support for at least 1 week before Day 1.

7. Female patients who:
   - Are postmenopausal for at least 2 years before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential:
     – Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 7 days after the last dose of study drug, OR
     – Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent through 7 days after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
     – Agree not to donate an egg or eggs (ova) during the study and for 7 days after the last dose of study drug.
8. Male patients, even if surgically sterilized (ie, status post vasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 7 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal,

postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

- Agree not to donate sperm during the study and for 7 days after the last dose of study drug.

9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
10. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period and must be willing to return to the investigational center for the follow-up procedures and assessments specified in this protocol.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study; (exclusions specific to Part 3 appear at end of list):

1. Patient has polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, monoclonal gammopathy of unknown significance, smoldering myeloma, solitary plasmacytoma, amyloidosis, Waldenström macroglobulinemia or IgM myeloma, or lymphoplasmacytic lymphoma.
2. Patients who have received autologous SCT 60 days before first infusion of modakafusp alfa or patients who have received allogeneic SCT 6 months before first infusion.
3. Graft-versus-host disease that is active or requires ongoing systemic immunosuppression.
4. Part 1: Until the MTD/OBD is defined, patients who have received daratumumab (or other investigational anti-CD38 antibody) for at least 5 months (steady state) require a 90-day wash-out period before receiving modakafusp alfa. For patients who have received less than 5 months of daratumumab or who have received another anti-CD38 monoclonal antibody, the necessary wash-out period needs to be discussed and approved by the sponsor. Once the MTD/OBD has been confirmed, these patients can be enrolled in the trial (Parts 2 and 3).

   Parts 2 and 3: No washout from daratumumab or isatuximab is required.
5. Patient has not recovered from adverse reactions to prior myeloma treatment or procedures (chemotherapy, immunotherapy, radiation therapy) to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≤1 or baseline, except for sensory or motor neuropathy which should have recovered to Grade ≤2 or baseline.

6. Patient has received the final dose of any of the following treatments/procedures within the specified minimum intervals before the first dose of modakafusp alfa.

Chemotherapy, including proteasome inhibitors and IMiDs	14 days
Antibody therapy (except anti-CD38 antibody as presented in exclusion criterion #4)	21 days
Corticosteroid therapy for myeloma	7 days
Radiation therapy for localized bone lesions	7 days
Major surgery	21 days

IMiD: immunomodulatory imide drug.

7. Patient has congestive heart failure (New York Heart Association Grade ≥II), cardiac myopathy, active ischemia, or any other uncontrolled cardiac condition such as angina pectoris, clinically significant arrhythmia requiring therapy including anticoagulants, or clinically significant uncontrolled hypertension.
8. Patient has a history of acute myocardial infarction within 5 months from enrollment or has electrocardiogram (ECG) abnormalities during screening that are deemed medically relevant by the investigator.
9. Patient has QT interval corrected by the Fridericia method (QTcF) >480 msec (Grade ≥2).
10. Patient has a concurrent illness that would preclude study conduct and assessment including, but not limited to, uncontrolled medical conditions, uncontrolled and active infection (considered opportunistic, life-threatening, or clinically significant), uncontrolled risk of bleeding, uncontrolled diabetes mellitus, pulmonary disease (including obstructive pulmonary disease, pulmonary fibrosis, and history of symptomatic bronchospasm), alcoholic liver disease, or primary biliary cirrhosis.
11. Patient has a chronic condition requiring the use of systemic corticosteroids >10 mg/day of prednisone or equivalent.
12. Patient has clinical signs of central nervous system involvement of MM.
13. Female patients who are lactating and breastfeeding or have a positive urine or serum pregnancy test during the screening period or a positive urine or serum pregnancy test on Day 1 before first dose of study drug if applicable.
14. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
15. Patient has a known history of human immunodeficiency virus.
16. Parts 1 and 2: Known chronic hepatitis C and/or positive serology (unless due to vaccination or passive immunization due to Ig therapy) for chronic hepatitis B.

    Japan Safety Lead-In and Part 3: Known chronic hepatitis C and/or positive serology for chronic hepatitis B (unless due to vaccination or passive immunization due to Ig therapy), or hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Participants with

resolved infection (that is, participants who are HBsAg negative but positive for antibodies to hepatitis B core antigen and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of HBV DNA levels. Those who are PCR positive will be excluded. Seropositive for hepatitis C (anti-HCV antibody positive or HCV-RNA quantitation positive). *EXCEPTIONS*: Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR; participants with hepatitis C who are seropositive but with a sustained virologic response (defined as absence of viremia at least 12 weeks after completion of antiviral therapy).

17. Patient has a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in modakafusp alfa formulation.
18. The patient is currently participating in another antimyeloma therapeutic clinical study.
19. Previous treatment with modakafusp alfa.

Part 3: In addition to the above criteria, patients must not have plasma cell leukemia or have had primary refractory MM, current central nervous system involvement of MM, myelodysplastic syndrome, myeloproliferative syndrome, or have had a second malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, cervical carcinoma in situ, resected colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapy.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or subinvestigator(s). A starting dose of 0.001 mg/kg (1 μg/kg) has been selected for this FIH study of modakafusp alfa.

Investigational sites will refer to the IB and Pharmacy Manual for the preparation of each dose. Premedications are detailed in Section 8.6.1, and additional precautions and restrictions are described in Section 8.7.

If a patient presents with an IRR at any dose level, the duration of the infusion may be extended per the investigator's discretion. Total time from modakafusp alfa dosing solution preparation until end of the infusion must not exceed 7 hours. Infusion and pharmacy staff are advised to be prepared accordingly for either a planned, extended infusion time or for potential infusion interruptions. See Pharmacy Manual for additional guidance.

More information about the management of IRRs is located in Section 8.6.2 and Section 8.7.1.1.

Parts 1 and 2: The initial dose should be based on a patient's weight at screening and only adjusted for a ≥10% change in body weight.

Modakafusp alfa doses <6 mg/kg will be administered over 1 hour (±10 minutes). Modakafusp alfa doses ≥6 mg/kg will be administered over >2 hours (±10 minutes). Any decrease in infusion duration must be discussed with and agreed upon by the sponsor.

Part 3: The 2 doses of 1.5 mg/kg and 3 mg/kg Q4W will be translated into 2 fixed doses of 120 and 240 mg based on the median bodyweight of approximately 80 kg (from Parts 1 and 2 of Study TAK-573-1501) for the Part 3 evaluation.

Modakafusp alfa doses of 120 and 240 mg will be administered over 1 hour (±10 minutes).

8.1.1 Administration of Dexamethasone in Modakafusp Alfa Plus Dexamethasone Cohort(s)

Dexamethasone will be added to the selected MTD/OBD of one or more schedule(s) as additional cohort(s). Dexamethasone will be given as a once weekly oral dose of 40 mg. Patients over 75 years of age will receive a reduced dose of dexamethasone (20 mg, same schedule).

Each dose of dexamethasone should be taken at approximately the same time relative to the modakafusp alfa infusion when applicable and should be taken with food or liquid (ie, milk) to avoid stomach irritation, according to the local label/practice. If a dose of dexamethasone is missed, the dose should be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose. Patient recollection of the dexamethasone doses taken at home should be recorded in the electronic case report form (eCRF).

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, Version 5.0.

Nonhematologic TEAEs of NCI CTCAE Grade ≥3 clearly unrelated to the underlying disease and occurring during the first cycle will be considered DLTs (see Section 10.2 for relatedness guidance), with the following exceptions:

- Asymptomatic laboratory changes (other than renal and hepatic laboratory values, and Grade 4 lipase/amylase) that can be successfully supplemented (reversion of Grade 4 events to Grade ≤2, reversion of Grade 3 events to Grade ≤1 or baseline) within 72 hours.
- Grade 3 nausea/vomiting that can be managed subsequently with antiemetics (Grade 3 nausea or vomiting that persists beyond 48 hours with or without appropriate medical intervention will be considered a DLT).
- Grade 3 fatigue lasting less than 72 hours.
- Grade 3 elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) that resolves to Grade ≤1 or baseline within 7 days.
- Grade 3 IRR that responds to symptomatic treatment, without recurrence of Grade 3 symptoms.

The following hematologic TEAEs Grade ≥3 clearly unrelated to the underlying disease and occurring during the first cycle will be considered DLTs:

- Grade ≥3 hemolysis.
- Grade 4 neutropenia lasting more than 7 consecutive days.
- Grade 4 thrombocytopenia lasting more than 14 consecutive days.
- Grade 3 thrombocytopenia with clinically significant bleeding.
- Any other Grade ≥4 hematologic toxicity with the exception of Grade 4 lymphopenia.

An incomplete recovery from treatment-related toxicity causing a >2-week delay in the next scheduled infusion before the initiation of Cycle 2 will be considered a DLT.

In Part 1, DLTs are events meeting the criteria above that occur before Cycle 2 Day 1 administration. Related TEAEs meeting DLT definitions occurring in later cycles or in Phase 2 (DLT-like events) will determine the suitability of the MTD/OBD dose for future studies.

Dose and schedule modifications for toxicity are described in Section 8.4.

Intrapatient dose escalation will be permitted only when patients in the next dose level cohort have completed assessments for Cycle 1 and a decision has been made that this dose level does not exceed the MTD. Patients eligible for intrapatient escalation can also be changed to a different schedule once the conditions described above are met (for example, a Schedule A patient receiving Q4W treatment from Cycle 7 onwards could be moved to the last cleared dose level with a different schedule).

8.3 Part 1 Dose Escalation Rules

Part 1 of the study followed a 3 + 3 dose escalation design to evaluate once-weekly (Schedule A) administration of modakafusp alfa for DLTs and to determine the MTD/OBD for further assessment in phase 2. A starting dose of 0.001 mg/kg was selected for Schedule A on the basis of a MABEL calculation (Section 4.6.1).

Patients were enrolled in cohorts of 3 and assessed for DLTs over a 28-day period (21 days for Schedule C) as detailed in Figure 8.a.

During Part 1, patients who missed one or more scheduled Cycle 1 doses of modakafusp alfa for reasons other than a DLT were to be replaced.

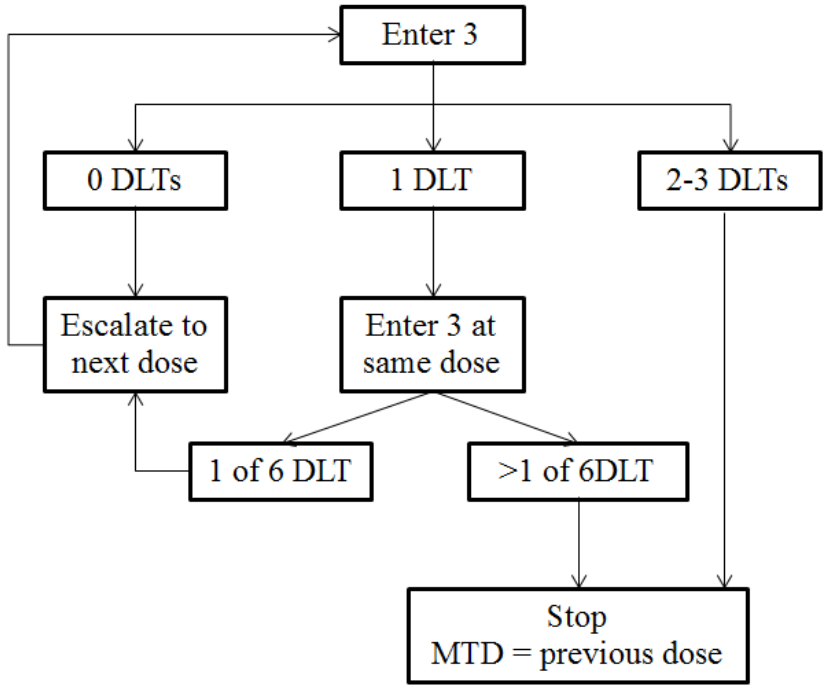
Details regarding the management of dose escalation decisions can be found in the Cohort Management Plan.

For the FIH evaluation of modakafusp alfa, a threshold of fatal AEs related to modakafusp alfa of 6% is proposed. Any rate of fatal events related to modakafusp alfa clearly in excess of this will result in the stopping of the trial. For the 30 patients expected to be treated at MTD/OBD between phase 1 and phase 2 with one specific dose and schedule, this means that the cohort will be stopped if 3 fatal AEs related to modakafusp alfa occur, or if 2 fatal AEs related to modakafusp alfa occur during the recruitment of the first 12 patients in each cohort.

The trial will also be stopped if the rate of modakafusp alfa–related Grade 4 events in any nonhematologic System Organ Class (SOC) exceeds 10% (with the exception of Grade 4 asymptomatic laboratory abnormalities). The trial will also be stopped if events meeting the criteria of a DLT occur with an incidence of greater than 40% at any point. The stop will result in an immediate halt in enrollment and may also necessitate the halting of treatment of ongoing patients, depending on the nature and severity of the safety risk. A final decision to terminate the study will be made only after a full review of the safety data by the sponsor's safety management team.

Figure 8.a is a diagrammatical representation of the dose escalation scheme.

Figure 8.a Dose Escalation Scheme



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

8.4 Dose Modification Guidelines

Dose modification guidelines for toxicities are described below for modakafusp alfa on the basis of the type and severity of AEs and causality determination by investigators. Further clarification can be obtained in consultation with the sponsor clinician (or designee).

8.4.1 Part 1 Dose Escalation

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 influenced decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Dose modifications were not permitted during Cycle 1 of therapy

unless the patient experiences a DLT. DLTs are defined in Section 8.2. Patients were to be evaluated at least weekly for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI CTCAE, Version 5.

If multiple toxicities were noted, the dose adjustments and/or delays were to be made according to the AE with the highest toxicity grade, and the same dose modification guidelines were to apply to subsequent cycles unless otherwise noted.

8.4.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with modakafusp alfa will use a cycle length of 28 days (21 days for Schedule C). For a new cycle of treatment to begin, the patient must meet the following criteria:

- Absolute neutrophil count must be ≥1000/mm^3. Granulocyte-colony stimulating factor (G-CSF) can be used to reach this level.
- Platelet count must be ≥50,000/mm^3.

For therapy to resume, toxicity considered to be related to treatment with modakafusp alfa must have resolved to Grade ≤1 or baseline (Grade 2 for platelets), or to a level considered acceptable by the physician. If the patient fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that week, the patient should be re-evaluated to determine whether the criteria for retreatment criteria have been met. If modakafusp alfa cannot be administered as scheduled, the patient can continue taking the weekly dexamethasone doses unless the investigator considers that it is in the patient's best interest to also hold dexamethasone.

If there is a delay of a subsequent cycle longer than 2 weeks because of a related AE, the patient may be withdrawn from treatment unless there is clinical benefit as assessed by the investigator, with agreement by the sponsor. Modakafusp alfa dosing may be continued at the previously established safe dose level or below.

For modakafusp alfa infusions within the same cycle (Schedules A and B [once every 2 weeks (Q2W)]), the decision to hold treatment is left to investigator discretion based on clinical and analytical data and based on the toxicity that the patient presented with previous infusions in the same cycle. The investigator should differentiate from acute toxicity (eg, an IRR) from which the patient has recovered at the time of the next infusion or subacute toxicity (eg, neutropenia) that might worsen with another infusion if it is not in a clear recovery path. If the dose cannot be administered on the scheduled day, the patient can be reviewed at the investigator's discretion in the following 48 hours. If modakafusp alfa cannot be administered within a cycle in this 48-hour window, the dose will be missed and the patient scheduled for the next administration per the schedule of events (SOE).

8.4.3 Criteria for Treatment Interruption and Dose Reductions

All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to modakafusp alfa may continue study treatment with the same dose, may have modakafusp alfa treatment held,

dose reduced, discontinued, or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE at the same dose level or at a reduced dose, depending on the nature and severity of the AE and whether it is the first occurrence or is recurrent unless otherwise specified in the protocol.

Table 8.a provides general dose modification recommendations for Parts 1 and 2, Table 8.b and Table 8.c provide dose modification guidelines for Part 3, and Table 8.e provides dose modification recommendations for bleeding TEAEs to mitigate the risk of fatal hemorrhagic events. When the dose of modakafusp alfa is withheld on the basis of these criteria, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed, until the toxicity resolves to Grade ≤1 or baseline. If there are transient laboratory abnormalities that, based on investigator assessment, are not clinically significant or drug related, continuation of therapy without dose modification is permissible upon discussion with the sponsor. See details for managing specific AEs in Section 8.7.1.

When a dose reduction occurs, the modakafusp alfa dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation. For Parts 1 and 2, if the initial dose adjustment does not provide sufficient relief, the dose of modakafusp alfa can be further reduced if the treating physician considers that the patient is receiving benefit. In general, after a dose is reduced, it should not be re-escalated even if there is minimal or no toxicity with the reduced dose. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug related, the dose may be re-escalated to the original dose level. For Parts 1 and 2, up to 2 dose level reductions of modakafusp alfa because of AE are generally recommended.

The dose of modakafusp alfa will not be reduced for an individual patient during Cycle 1 unless a DLT has been declared and it is still possible for the patient to receive treatment within the remaining dosing period scheduled. In this case, the patient can complete Cycle 1 at a reduced dose level.

8.4.3.1 Parts 1 and 2

Table 8.a Parts 1 and 2 Dose Modification Recommendations for Modakafusp Alfa Toxicities

This table does not include guidance for management of bleeding TEAEs and IRRs. Refer to Table 8.e for the management of bleeding TEAEs and Table 8.g and Table 8.h for the management of IRRs.

Criteria	Action
Grade 1 AEs	No dose reductions or interruptions.
Grade 2 AEs	Treat according to local practice. Whether to hold treatment or to continue it at the same or a reduced dose (Table 8.d) is at the discretion of the investigator. Patients experiencing Grade 2 AEs considered related to study treatment that are not easily managed or corrected and are not tolerable to the patient, or AEs that are not acceptable in the investigator's judgment, should have study treatment interrupted until the AE resolves to Grade ≤1 or baseline and then restarted at the same dose or, depending on the toxicity, at the previous safe dose level or below.
Grade 3, Grade 4 (not life-threatening), and Grade 4 asymptomatic laboratory AEs	Hold modakafusp alfa until resolution to Grade ≤1 or baseline, and then resume treatment at either the same dose or a reduced dose level at the discretion of the investigator.
Grade 4 (life-threatening) AEs	Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is receiving clinical benefit and has discussed this with the sponsor. Treatment may be restarted at a reduced dose level or below when toxicity recovers to Grade ≤1 or baseline.
AEs of all grades	If treatment has been held for >14 consecutive days without resolution of the toxicity (to baseline or Grade ≤1), consider permanently discontinuing study treatment unless there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval. Treatment can be resumed at a reduced dose level after resolution of AEs to Grade ≤1 or baseline.

AE: adverse event; IRR: infusion-related reaction; TEAE: treatment-emergent adverse event.
This table does not include guidance for the management of bleeding TEAEs, which is found in Table 8.e or for the management of IRRs, which is found in Table 8.g, Table 8.h, Section 8.7.1.1.1, and Section 8.7.1.1.2.

8.4.3.2 Part 3

Part 3 dose modification recommendations for hematologic and nonhematologic toxicities are detailed in Table 8.b and Table 8.c, respectively, and Part 3 dose reduction levels are found in Table 8.d.

Table 8.b Part 3 Dose Modification Recommendations for Modakafusp Alfa Hematological Toxicities

This table does not include guidance for management of bleeding TEAEs and IRRs. Refer to Table 8.e for the management of bleeding TEAEs and Table 8.g and Table 8.h for the management of IRRs.

Criteria	Action
Grade 1 and 2 AEs	No dose reductions or interruptions.
Grade 3 and 4 AEs	Hold modakafusp alfa next infusion until resolution to Grade ≤2 then resume treatment. Consider growth factors and/or transfusion according to local practice. If the next cycle of modakafusp alfa is delayed for >28 days, study treatment should be discontinued unless the investigator considers that the patient will receive benefit continuing in the study. Dose reduction can be considered.

AE: adverse event; IRR: infusion-related reaction; TEAE: treatment-emergent adverse event.
This table does not include guidance for the management of bleeding TEAEs, which is found in Table 8.e or for the management of IRRs, which is found in Table 8.g, Table 8.h, Section 8.7.1.1.1, and Section 8.7.1.1.2.

Table 8.c Part 3 Dose Modification Recommendations for Modakafusp Alfa Non Hematological Toxicities

This table does not include guidance for management of bleeding TEAEs and IRRs. Refer to Table 8.e for the management of bleeding TEAEs and Table 8.g and Table 8.h for the management of IRRs.

Criteria	Action
Grade 1 and 2 AEs	No dose reductions or interruptions. Treat according to local practice.
Grade 3 AEs and Asymptomatic Grade 4 laboratory AEs	Hold modakafusp alfa next infusion until resolution to Grade ≤1 or baseline, and then resume treatment. 1st occurrence: Resume treatment at either the same dose or reduced dose at the discretion of the investigator. Subsequent occurrence: Reduce modakafusp alfa by 1 dose level. If treatment has been held for >28 consecutive days without resolution of the toxicity (to baseline or Grade ≤1), consider permanently discontinuing study treatment unless there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval.
Grade 4 AEs (except asymptomatic Grade 4 laboratory AEs)	Permanently withdraw the patient from the study, except when the investigator determines that the patient is receiving clinical benefit and has discussed this with the sponsor.

AE: adverse event; IRR: infusion-related reaction; TEAE: treatment-emergent adverse event.
This table does not include guidance for the management of bleeding TEAEs, which is found in Table 8.e or for the management of IRRs, which is found in Table 8.g, Table 8.h, Section 8.7.1.1.1, and Section 8.7.1.1.2.

Potential dose modifications in Part 3 are to be discussed with the sponsor before implementation.

Table 8.d Part 3 Dose Reduction Levels

	120 mg	240 mg
1st dose level reduction	80 mg	160 mg
2nd dose level reduction	Discontinue treatment	120 mg
3rd dose level reduction	NA	Discontinue treatment

NA: not applicable.

8.4.3.3 Parts 1, 2, and 3

Table 8.e provides dose modification recommendations for bleeding TEAEs in Parts 1, 2, and 3 to mitigate the risk of fatal hemorrhagic events.

Table 8.e Parts 1, 2, and 3 Dose Modification Recommendations for Modakafusp Alfa Bleeding TEAEs

This table does not include guidance for management of IRRs. Refer to Table 8.g and Table 8.h for the management of IRRs.

Criteria	Action
Grade 1 and 2	No dose reductions or interruptions. Treat according to local practice.
Grade 3 without associated Grade 4 thrombocytopenia	Hold next infusion of modakafusp alfa until resolution to Grade ≤1 or baseline, and then resume treatment. Subsequent occurrence: Discontinue modakafusp alfa.
Grade 3 with associated Grade 4 thrombocytopenia	Discontinue modakafusp alfa.
Grade 4	Discontinue modakafusp alfa.

IRR: infusion-related reaction; TEAE: treatment-emergent adverse event.
This table does not include guidance for the management of IRRs, which is found in Table 8.g, Table 8.h, Section 8.7.1.1.1, and Section 8.7.1.1.2.

8.4.4 Criteria for Discontinuing Modakafusp Alfa

Potential discontinuations of modakafusp alfa should be discussed with the sponsor or contract research organization (CRO) before implementation.

Modakafusp alfa should be discontinued in patients experiencing an AE in Cycle 1 meeting criteria for a DLT for which the investigator considers that retreatment of the patient could be dangerous.

If the next cycle of modakafusp alfa is delayed for >14 days (>28 days for Part 3) because of modakafusp alfa–related toxicities, study treatment should be discontinued unless the investigator considers that the patient will receive benefit continuing in the study. Patients will

be evaluated 30 days (EOT visit) after the last dose of modakafusp alfa or right before the start of subsequent systemic anticancer therapy to permit the detection of any delayed TEAEs.

8.4.5 Dexamethasone Dose Modification

The decision and management of dexamethasone modifications will be according to investigator's discretion. Dose modifications should be recorded in the eCRF.

8.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Radiation therapy for disease under study. Local radiotherapy for bone pain is permitted after agreement with the sponsor and once PD is ruled out.
- Any investigational agent other than modakafusp alfa, including agents that are commercially available for indications other than MM that are under investigation for the treatment of MM.
- Concomitant chronic corticosteroid administration of >10 mg of prednisone or equivalent unless given as treatment or prophylaxis for IRRs, as premedication for administration of certain blood products or for exacerbations of respiratory tract disorders, acute pain management, suspected or confirmed immune-mediated thrombocytopenia, or if tumor flare is suspected.

8.6 Permitted Concomitant Medications and Procedures

8.6.1 Premedication

As of Amendment 06, based on the experience with infusion reactions in patients not receiving premedications, **it is strongly recommended that all patients receive premedication, including corticosteroids, before modakafusp alfa dosing**. Any decision to stop premedications must be discussed with and agreed upon by the sponsor.

Before each injection of modakafusp alfa at doses up to and including 3 mg/kg and for patients receiving a fixed dose in Part 3, patients should receive the following premedications (all or in part) per investigator discretion:

- Corticosteroid IV or orally (PO) (methylprednisolone 100 mg, dexamethasone 20 mg, or equivalent) 60 minutes to 2 hours before treatment; if a patient experiences no significant IRR, the dose of methylprednisolone may be decreased to 50 mg (or dexamethasone to 10 mg) after visit 4. Intermediate- or long-lasting steroids of equivalent dose can be substituted.
- 650 to 1000 mg acetaminophen PO 60 minutes to 2 hours before treatment.
- 25 to 50 mg diphenhydramine or equivalent PO approximately 12 hours before and again approximately 1 hour before Cycle 1 treatment; for all subsequent infusions, approximately 1 hour before.

Montelukast (10 mg PO) may be given to patients who are intolerant to diphenhydramine or for whom diphenhydramine is ineffective.

Patients who are receiving a modakafusp alfa dose of 6 mg/kg or higher must be premedicated with dexamethasone, acetaminophen, diphenhydramine, and montelukast, and it is recommended that the dose will be administered over >2 hours (±10 minutes). Any decrease in infusion duration must be discussed with and agreed upon by the sponsor.

8.6.2 Postinfusion Medication

Patients may receive 20 to 25 mg prednisone or 4 mg of dexamethasone PO or equivalent on the first and second days after all full-dose infusions. Other concomitant medications can be administered per institutional protocols.

During the infusion and for 2 hours postdose, the patient should be continually monitored by medically qualified staff with access to emergency medical equipment and medications to manage infusion reactions.

8.6.3 Other Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care will be available to patients as necessary. All blood products and concomitant medications will be recorded in the eCRFs as specified in the SOEs (Appendix A).

The following medications and procedures are permitted while the patient is receiving the study drug:

- Myeloid growth factors (eg, granulocyte colony stimulating factor, granulocyte macrophage-colony stimulating factor) and erythropoietin are permitted. Their use should follow the product label, published guidelines, and institutional practice. During Cycle 1, G-CSF is allowed for Grade 4 neutropenia. In addition, G-CSF is allowed to accelerate the recovery of neutropenia to enable the start of new cycle (Section 8.4.2).
- Patients should be transfused with red blood cells and platelets as clinically indicated. Transfusions must be recorded in the concomitant procedure pages of the eCRF. Platelet transfusion should not be applied only for the purpose of meeting the treatment criterion of platelet count to start a new cycle.
- Concomitant treatment with bisphosphonates will be encouraged for all patients with evidence of lytic destruction of bone or with osteopenia, according to the American Society of Clinical Oncology Clinical Practice Guidelines or institutional practice in accordance with the product label, unless specifically contraindicated. If bisphosphonate therapy was not started before the study start, it should be initiated as soon as clinically indicated.
- Topical or inhaled steroids (eg, for the treatment of asthma) are permitted.
- Systemic steroids for acute management of pain, suspected or confirmed immune-mediated thrombocytopenia or other disease or treatment-related complications are permitted.

- Plasmapheresis.
- IV immunoglobulins (IVIG) usage is acceptable for prolonged Grade 4 transfusion-dependent thrombocytopenia or other investigator criteria if it is considered that there is an underlying autoimmune mechanism.
- Thrombopoietin agonists are also allowed for thrombocytopenia management at the investigator's discretion.

8.7 Precautions and Restrictions

Modakafusp alfa has been shown to interfere with serological testing due to binding to CD38 on RBCs, which results in positive direct and indirect antiglobulin tests. Modakafusp alfa–mediated interference in both the direct and indirect antiglobulin tests was observed at clinically relevant concentrations of modakafusp alfa. The duration of modakafusp alfa–mediated positive direct and indirect antiglobulin tests have not yet been evaluated. The determination of a patient's ABO and Rh blood type are not affected by the presence of modakafusp alfa. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received modakafusp alfa. Type and screen patients before starting modakafusp alfa if this was not performed previously.

Fluid deficit should be corrected before initiation of treatment and during treatment.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given the reported NSAID-induced renal failure in patients with decreased renal function.

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

It is not known what effects modakafusp alfa has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet one of the following:

- Postmenopausal for at least 2 years before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential:
  - Agree to practice 1 highly effective method (Table 8.f) and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form (ICF) through 7 days after the last dose of study drug (whichever is longer), OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate an egg or eggs (ova) during the study and for 7 days after the last dose of study drug.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to one of the following:

- Agree to practice effective barrier contraception (Table 8.f) during the entire study treatment period and through 7 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate sperm during the study and for 7 days after the last dose of study drug.

Table 8.f Highly Effective Methods of Contraception

Highly effective methods	Additional effective (barrier) methods
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal	Male or female condom with or without spermicide (female and male condoms should not be used together)
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable • Implantable	
Intrauterine device (IUD)	Cap, diaphragm, or sponge with spermicide
Intrauterine hormone-releasing system (IUS)	
Bilateral tubal occlusion	
Vasectomized partner Sexual abstinence	

8.7.1 Management of Specific Adverse Reactions

8.7.1.1 Handling of IRRs

An IRR is a reaction that develops during or shortly after administration of a drug. Signs and symptoms may include pruritus, urticaria, fever, rigors/chills, diaphoresis, bronchospasms, and cardiovascular collapse. In this study, IRRs are designated as AESIs.

It is strongly recommended that all patients receive premedication, including corticosteroids, before modakafusp alfa dosing.

Patients who are receiving a modakafusp alfa dose of 6 mg/kg or higher must be premedicated with dexamethasone, acetaminophen, diphenhydramine, and montelukast.

Modakafusp alfa doses <6 mg/kg will be administered over 1 hour (±10 minutes). Modakafusp alfa doses ≥6 mg kg will be administered over 2 hours (±10 minutes). Any decrease in infusion duration must be discussed with and agreed upon by the sponsor.

If a patient presents with an IRR at any dose level, the duration of the infusion may be extended per investigator's discretion. Total time from modakafusp alfa dosing solution preparation until end of infusion must not exceed 7 hours. Infusion and pharmacy staff are advised to be prepared accordingly for either a planned, extended infusion time or for potential infusion interruptions. See the IB and Pharmacy Manual for additional guidance.

Patients should be carefully observed during modakafusp alfa infusions. Trained trial staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilators and medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside.

In case of an IRR, serum samples should be taken for central evaluation of immunogenicity and circulating biomarkers (as detailed in the SOEs).

Patients will be advised to promptly report signs and symptoms that may indicate IRRs, including fever, chills, dizziness, nausea, vomiting, flushing, cough, headache, and rash during or soon after end of infusion.

If the patient continues on treatment, premedication and postinfusion medication should be considered for future modakafusp alfa administrations per Sections 8.6.1 and 8.6.2.

All IRRs, including the signs and symptoms, will be reported in the eCRF per completion guidelines.

Serious AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner.

8.7.1.1.1 Grade 1 and 2 IRRs

The recommendations for managing Grade 1 and Grade 2 IRRs are presented in Table 8.g.

Table 8.g Recommendations for Managing Grade 1 and Grade 2 IRRs

IRR	Action
Grade 1 or 2	The infusion should be paused. When the patient's condition is stable, infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion. Consider premedication and postmedication before restarting the infusion and for future modakafusp alfa administrations.
Grade 2 event of laryngeal edema, or Grade 2 event of bronchospasm that does not respond to systemic therapy.	Patient must be withdrawn from treatment if the event does not resolve within 6 hours from onset.

IRR: infusion-related reaction.

8.7.1.1.2 Grade 3 or Higher IRRs

The recommendations for managing Grade ≥3 IRRs are presented in Table 8.h.

Table 8.h Recommendations for Managing Grade ≥3 IRRs

IRR	Action
Any Grade 4 event	Patient must be withdrawn from treatment.
Grade 3 bronchospasm or laryngeal edema	Patient must be withdrawn from treatment.
Grade 3 event other than bronchospasm or laryngeal edema	Infusion must be stopped, and the patient must be observed carefully until resolution of the IRR.
If the intensity of the IRR remains at Grade 3 after 2 hours:	Patient must be withdrawn from treatment.
If the intensity of the IRR decreases to Grades 1 or 2:	Infusion may be restarted at the investigator's discretion. Administer corticosteroids, acetaminophen, and antihistamines per Sections 8.6.1 and 8.6.2 before restarting infusion. Within 2 hours upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.
If the intensity of the IRR returns to Grade 3:	The procedure described above may be repeated after restart of the infusion at the investigator's discretion.
If the intensity of the IRR increases to Grade 3 for a third time:	Patient must be withdrawn from treatment.

IRR: infusion-related reaction.

8.7.1.2 Handling of Low Platelet Counts

Treatment decisions will be based on patient platelet counts assessed before any transfusion. Low platelet counts (Grade 4) should cause scheduled infusions to be postponed or to be

permanently discontinued. Please see Table 8.e for dose modifications for bleeding TEAEs for Parts 1, 2, and 3. If at any time the platelet count is less than 10×10^9/L the patient should be withdrawn from modakafusp alfa treatment unless clinical benefit is observed and the investigator considers that thrombocytopenia can be managed, including with dose modifications. The investigator can consider the usage of corticosteroids, IVIG, or thrombopoietin agonists in selected cases depending on severity, duration, transfusion requirements, and additional risk factors for bleeding and based on the suspected underlying mechanism. Platelet transfusion and daily monitoring of platelet counts are recommended.

8.8 Prophylaxis Against Risk of Infection

Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Prophylactic antiviral therapy such as acyclovir or valacyclovir should be initiated as clinically indicated.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

Modakafusp alfa is a humanized anti-CD38, IgG4, mAb fused to attenuated IFN-α 2b. Additional details can be found in the modakafusp alfa IB.

8.11 Preparation, Reconstitution, and Dispensation

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever the solution and container permit.

Modakafusp alfa is an anticancer drug; as with other potentially toxic compounds, caution should be exercised when handling modakafusp alfa.

Dexamethasone will be procured by the site from commercial sources. Additional details are provided in the package insert.

8.12 Packaging and Labeling

Supplies of modakafusp alfa will be labeled according to the current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements.

Dexamethasone will be site-sourced from commercial supply with commercial packaging and labeling.

Modakafusp alfa is supplied as a single-use stoppered glass vial with an aluminum flip-off seal, providing 10 mg/mL of modakafusp alfa.

8.13 Storage, Handling, and Accountability

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all modakafusp alfa received and that any discrepancies are reported and resolved as outlined in the Pharmacy Manual.

Modakafusp alfa should be stored in the original container as specified on the label (frozen at -20°C for frozen liquid or 2°C to 8°C for lyophilized formulation) and protected from light until it is used. Modakafusp alfa remains suitable for use until the expiration date printed on the primary container or carton if stored as directed. Modakafusp alfa should be thawed and equilibrated to room temperature or reconstituted as directed prior to administration.

Thawing, reconstitution, and dilution procedures for modakafusp alfa vials are provided in the IB and Pharmacy Manual.

Each modakafusp alfa shipment will include a packing slip listing the contents of the shipment, and any applicable forms.

Only patients enrolled in the study may receive modakafusp alfa, and only authorized staff at the investigational center may supply or administer modakafusp alfa. All modakafusp alfa must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator is responsible for ensuring that deliveries of modakafusp alfa and other study materials from the sponsor are correctly received, recorded, and handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

The investigator, institution, or head of the medical institution (where applicable) is responsible for modakafusp alfa accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of modakafusp alfa accountability (ie, modakafusp alfa and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused modakafusp alfa will be disposed of, retained, or returned to the sponsor or designee.

Further guidance and information are provided in the Pharmacy Manual.

9.0 STUDY CONDUCT

This study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, and

the CRO team may be found in the Study Operations Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/independent ethics committee (IEC).

9.3 Study Procedures

Refer to Appendix A, Appendix B, and Appendix C for timing of assessments. Additional details are provided as necessary in the sections that follow.

Sites will make every effort to see patients in the clinic to complete all study-specified assessments as outlined in the SOE (Appendix A).

In unavoidable circumstances, such as the coronavirus disease 2019 (COVID-19) public health emergency, exceptions can be made for alternative methods for conducting patient visits and performing laboratory and imaging assessments as detailed below. Remote visits and telemedicine must comply with national and local laws and regulations. Such instances will be documented in the study records and eCRF, if applicable, and the sponsor will be informed.

Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 4-day window for holidays, vacations, and other administrative reasons or a longer window after discussion with the Takeda study clinician or designee.

9.3.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Informed Consent Procedure: If necessary, informed consent from a potential or current trial participant may be obtained via electronic informed consent (eIC) capabilities or an electronic face-to-face consent interview if these individuals are unable to travel to the site.

9.3.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

9.3.3 Medical History

During the screening period, a complete medical history will be compiled for each patient. This includes initial diagnosis date and MM staging at initial diagnosis using International Staging System and Salmon-Durie stage. Known cytogenetic alterations should be collected, as well as prior treatment regimens, with each treatment duration (start and stop dates), and the best response obtained with each of them. Refractoriness to previous treatments should be collected

following IMWG criteria**.** In addition, concomitant medications will be recorded as specified in Section 9.3.8.

9.3.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A).

If an investigator considers it safe and appropriate for a subject to miss a protocol-specified physical examination for COVID-19-related reasons, the study site physician or other qualified site staff will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) to assess subject safety and overall clinical status with a plan for in-person evaluation if signs and symptoms warrant. Such instances will be documented in the study records and eCRF if applicable, and the sponsor will be informed.

9.3.5 Patient Height

Height will be measured during the screening visit only.

9.3.6 Patient Weight

Weight will be measured at the times specified in Appendix A. Initial dose should only be adjusted for a ≥10% change in body weight in Parts 1 and 2 (Section 8.1).

9.3.7 ECOG Performance Status

ECOG performance status as defined in Appendix G will be evaluated at the times specified in Appendix A.

9.3.8 Concomitant Medications and Procedures

Any prior or concomitant medication a patient has had from signing of the ICF through 30 (+10) days after the last dose of modakafusp alfa or the start of subsequent systemic anticancer therapy, whichever occurs first, will be recorded on the eCRF. Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication will be recorded. Medications used by the patient and therapeutic procedures (including any transfusion) completed by the patient will be recorded in the eCRF. See Section 8.5 and Section 8.6 for medications and therapies that are prohibited or allowed during the study.

9.3.9 Safety Evaluations

9.3.9.1 Vital Signs

Vital signs include temperature, pulse, respiratory rate, and oxygen saturation. They include also supine or seated measurements of diastolic and systolic blood pressure (after 3 to 5 minutes in this position; all measurements should be performed in the same initial position), heart rate, and body temperature. They will be measured at the times specified in Appendix A. Blood pressure

will be measured every 30 minutes (±5 minutes) during the first 4 infusions, after the end of the infusion, and at any moment if the patient complains of symptoms consistent with IRR. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient cannot be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour. Patients must be observed for at least 2 hours after the end of every modakafusp alfa infusion.

Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the eCRF as an AE and monitored as described in Section 10.2.

9.3.9.2 Pregnancy Testing

A participant of childbearing potential is defined as a participant with a uterus and ovary(ies) who: (1) has not undergone a hysterectomy or bilateral oophorectomy or, (2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

1) Screening/baseline: Participants of childbearing potential must have 2 negative pregnancy tests before starting study drug.

- A urine or serum pregnancy test will be required during screening (within 10 to 14 days before start of study drug); this test must be negative.
- A urine or serum pregnancy test must be performed at baseline (within 24 hours before the start of study drug). The results from these tests must be available and negative before the first dose of study drug is administered.

2) On-treatment: During the study, participants of childbearing potential must have a negative urine or serum pregnancy test result within 72 hours before dosing on Day 1 of each cycle during treatment prior to dosing. If a menstrual period is delayed, absence of pregnancy in participants of childbearing potential must be confirmed by a negative urine or serum pregnancy test.

- Pregnancy tests may also be repeated during the study as per request of IRB or if required by local regulations.

3) EOT: A urine or serum pregnancy test is required at EOT in participants of childbearing potential.

9.3.9.3 TEAEs

Monitoring of TEAEs, serious and nonserious, will be conducted throughout the study as specified in the SOEs (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of TEAEs and SAEs.

9.3.9.4 ECGs

A 12-lead ECG will be administered at the time points specified in the SOEs (Appendix A). A qualified person will interpret the ECG. In Parts 1 and 2, triplicate ECGs will be read centrally, and single ECGs will be read locally. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation.

Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered a TEAE, recorded on the source documentation and in the eCRF, and monitored as described in Section 10.2.

In Parts 1 and 2, triplicate ECGs for initial heart rate-corrected QT interval evaluation will be recorded and electronically stored at prespecified time points. These time points correspond with PK draws. Please refer to the PK Sampling Schedules (Appendix C).

The ECG measurements should be completed before the PK/ pharmacodynamic blood draw. It is recommended that patients refrain from eating or limit themselves to bland food for 1 hour before dosing and until completion of the scheduled ECG measurements (4 hours after dosing).

In Part 3, all patients will have single ECGs collected and read locally at screening, at the end of the infusion (+30 minutes), or in accordance with the SOEs in Appendix A.

9.3.9.5 Clinical Laboratory Evaluations

Parts 1 and 2: Clinical laboratory evaluations will be performed either locally or centrally as indicated in each section.

Part 3: Clinical laboratory evaluations will be performed by a central laboratory. For dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must also be sent to central laboratories.

In extenuating circumstances, such as during the COVID-19 public health emergency, laboratories closer to a patient's home may be utilized for local clinical laboratory assessments provided that pertinent laboratory information, including normal reference ranges, are provided to the sponsor or designee.

Central laboratory assessments must still be obtained at the site as needed and sent to sponsor-designated laboratories. Handling of central clinical laboratory blood samples is outlined in the Laboratory Manual.

Not all collections are applicable to all cohorts or patients within a cohort. Additionally, collection of samples for exploratory biomarkers are dependent upon local guidelines and regulations (including feasibility of sample export), as well as IRB/IEC approval.

9.3.9.6 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the SOEs (Appendix A). They will be performed locally only for Parts 1 and 2.

Central laboratory analysis is required for Part 3. Local hematology and chemistry laboratory results may be used for dosing decisions; however, samples must still be sent to the central laboratory as well. Hematology and chemistry panels may be collected up to 3 days before the day of dosing. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs) and if they are the basis for dose modification or other clinical intervention, the results must be recorded in the CRF.

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	**Chemistry**	
Hematocrit	Albumin	Standard C-reactive protein
Hemoglobin	Alkaline phosphatase	Chloride
Leukocytes with differential [c]	Alanine aminotransferase	Glucose (nonfasting)
Neutrophils (ANC)	Aspartate aminotransferase	Lactate dehydrogenase
Platelet (count)	Bilirubin (total)	Magnesium
Other	Blood urea nitrogen	Phosphate
Antiplatelet antibody testing [a, b]	Calcium	Potassium
Thyroid function tests (TSH, free or total T3, and free or total T4) [a]	Bicarbonate (HCO_3^-) or carbon dioxide (CO_2)	Sodium
PT/INR, aPTT, fibrinogen, D-Dimer [a, d]	Creatinine	Urate

ANC: absolute neutrophil count; aPTT: activated partial thromboplastin time; INR: international normalized ratio; PT: prothrombin time; TSH: thyroid stimulating hormone.
[a] Analyzed locally.
[b] Only applicable for Parts 1 and 2.
[c] Differential to include basophils, eosinophils, lymphocytes, monocytes, and neutrophils.
[d] To be collected if clinically significant bleeding is observed.

Table 9.b Clinical Urinalysis Tests

Urinalysis		
Bilirubin	Nitrite	Specific gravity
Glucose	Occult blood	Turbidity and color
Ketones	pH	Urobilinogen
Leukocytes	Protein	Microscopic analysis (only if macroscopic parameters abnormal; Part 3 only)

If creatinine clearance is to be estimated, the Cockcroft-Gault formula will be employed as follows:

$$\text{Estimated creatinine clearance} = [(140 - \text{Age}) \bullet \text{Mass (kg)}\ ] / [72 \bullet \text{serum creatinine (mg/dL)}]$$

For female patients, the result of the formula above should be multiplied by 0.85.

9.3.9.7 β_2-Microglobulin

A blood sample will be collected at screening for serum β_2-microglobulin testing. For Parts 1 and 2 results will be analyzed locally. **Central laboratory analysis is required for Part 3.**

9.3.10 Disease Assessment

Patients will be assessed for disease response according to the European Group for Blood and Marrow Transplant criteria, modified and updated by the IMWG criteria (Appendix F).

For Parts 1 and 2, response assessments will be made on the basis of local laboratory data. **For Part 3, response assessments will be made on the basis of central laboratory data.**

Assessments should occur every cycle during treatment and every 4 weeks during the PFS/survival follow up period until disease progression (see SOEs). If the start of a cycle is delayed, serum M-protein and serum FLCs are to be collected for central laboratory analysis if not previously sent within the preceding 10 days. If a patient has collected a 24-hour urine sample and brought it to a visit, the sample should be sent for central laboratory analysis of urine M-protein even if not on Day 1 of a cycle.

Serum and urine response assessments will be performed as indicated in the SOEs (Appendix A). Imaging tests for qualifying patients (see Sections 9.3.10.1 and 9.3.10.2) are to be performed every other cycle beginning with Cycle 3 only for patients with extramedullary disease at screening or when there is a clinical suspicion of extramedullary progression. In extenuating circumstances, such as during the COVID-19 public health emergency, patients may use an alternative site for imaging with prior notification to the sponsor or designee.

CR should be confirmed follow up assessments (by local laboratories for Parts 1 and 2 and by central laboratories for Part 3) of serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), immunofixation of blood and urine, and serum FLCs as outlined in the SOEs (Appendix A). One bone marrow assessment (locally evaluated for Parts 1, 2 and 3) is required to document CR; no second bone marrow confirmation is needed.

Please note that to determine a response of sCR, bone marrow immunohistochemistry or immunofluorescence for the $\kappa:\lambda$ ratio, as well as serum FLC assay, should be performed for all patients suspected to be in CR to meet this response category's requirements.

For Parts 1 and 2, PD may be confirmed per standard clinical practice at the site. Local laboratories may be used to confirm PD. For Part 3, PD must be confirmed based on central laboratories.

The following disease assessments will be performed as indicated in the SOEs (Appendix A).

For Part 3, imaging assessments to summarize status of known lesions will be collected and should be based on available imaging at each respective time point.

9.3.10.1 Extramedullary Disease Imaging

Imaging will be evaluated locally for all patients. For patients with previously documented extramedullary disease or with suspicion of extramedullary progression, a positron emission tomography-computed tomography (PET-CT) scan, computed tomography (CT) scan, or magnetic resonance imaging (MRI) scan will be performed at screening (if the patient has adequate image test performed within 5 weeks of the planned first dose of study drug, they can be used as baseline and do not need to be repeated as part of screening) as needed for evaluation of disease. If extramedullary disease is documented at screening, a repeat PET-CT scan, CT scan, or MRI scan should be performed every other cycle beginning with Cycle 3.

All follow-up scans should use the same imaging modality as used at screening.

For Part 3, imaging to assess extramedullary disease is required for all patients at screening by PET-CT, MRI, or CT. Imaging performed within 5 weeks of the planned first dose of study drug can be used as baseline evaluations and does not need to be repeated as part of screening. If extramedullary disease is documented at screening, repeat imaging using the same modality every 3 cycles until a plateau or complete response is reached, or as clinically indicated, and then at suspected progression (Hillengass et al. 2019). Imaging tests for patients with extramedullary disease should be performed if new symptoms suggest PD.

For Part 3, imaging assessments to summarize status of known lesions will be collected and should be based on available imaging at each respective time point.

9.3.10.2 Bone Imaging

Imaging will be evaluated locally for all patients. A complete skeletal survey, using plain x-ray or low-dose total body CT scan, will be performed at screening (if the patient has adequate image test performed within 5 weeks of the planned first dose of study drug, they can be used as baseline and do not need to be repeated as part of screening). If there are symptoms or signs that suggest increased or new bone lesions, the skeletal survey or plain film of symptomatic sites may be repeated any time during the study and at the EOT visit. A PET-CT may be done at screening in place of a skeletal survey provided that the same modality for assessment is used throughout the study.

Patients with a normal skeletal survey at baseline do not need to repeat the test periodically unless bone progressive disease is clinically suspected.

Radiographs will be analyzed locally and reports maintained with the patient record for retrieval during monitoring visits.

For Part 3, imaging to assess bone disease is required for all patients at screening. Imaging performed within 5 weeks of the planned first dose of study drug can be used as baseline evaluations and does not need to be repeated as part of screening. Low-dose whole-body CT is recommended over conventional skeletal survey for the evaluation of multiple myeloma bone disease. Conventional skeletal survey can be used for the diagnosis of multiple myeloma when whole-body CT or other novel imaging methods are not available. Additional assessments for

bone disease can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions PD). The same modality for assessment should be used throughout the study.

For Part 3, imaging assessments to summarize status of known lesions will be collected and should be based on available imaging at each respective time point.

9.3.10.3 Quantification of Immunoglobulins

A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained as specified in Appendix A. For the rare patient with known IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points throughout the treatment period and PFS follow-up period as quantitative Igs (in addition to quantitative IgM, IgG, and IgA). Analysis of Ig will be performed locally for Parts 1 and 2. **Central laboratory collection is required for Part 3.**

9.3.10.4 Quantification of M-Protein in Serum and Urine

A blood and 24-hour urine sample will be obtained as specified in the SOE (Appendix A). Urine collection and testing will be repeated at the times specified only for patients with a baseline urine M-protein of ≥200 mg/24 hours in Parts 1 and 2. Urine collection and testing (centrally) will be repeated at each cycle in Part 3.

M-protein in serum and urine will be quantified by SPEP and UPEP. These samples will be tested locally for Parts 1 and 2. **Central laboratory collection is required for Part 3**.

9.3.10.5 Serum FLC Assay

Blood samples will be obtained as specified in Appendix A for the serum FLC assay (including quantification of κ and λ chains and the κ:λ ratio). Samples must be obtained at the time of suspected CR. Blood samples will be analyzed locally for Parts 1 and 2. **Central laboratory collection is required for Part 3.**

9.3.10.6 Immunofixation of Serum and Urine

Serum and urine samples will be obtained as specified in the SOE (Appendix A) at screening and to confirm CR. Only for Parts 1 and 2, immunofixation of serum and/or urine may be omitted at screening if a previous local laboratory report for the serum and/or urine protein electrophoresis states that the observed monoclonal spike is consistent with one previously characterized by immunofixation and specifies the heavy chain and light chain previously identified. Immunofixation testing will be performed in the local laboratory for Parts 1 and 2. **Central laboratory collection is required for Part 3.**

9.3.10.7 Interference Assay

For Part 3 only:

IgG mAbs given recently as prior therapy can interfere with assays used to monitor endogenous M-protein. The SPEP and serum immunofixation can be positive due to mAb. This interference

can impact the determination of CR and of disease progression in some patients with IgG myeloma protein.

Therefore, in patients with persistent VGPR by IMWG criteria where mAb interference is suspected or whenever the SPEP values reach ≤0.2 g/dL for 2 consecutive disease evaluations during a period of time when the mAb could be circulating at detectable levels, a CR should be suspected triggering the need for interference testing on the M-protein sample at the central laboratory. Currently, if the interference test results are positive, the assay is considered positive for endogenous protein, and thus there is still disease present. If the interference test result is negative, the assay is considered negative for endogenous protein, and thus the remaining protein is likely the mAb. This is communicated back to the sites, and the sites can proceed to perform a confirmatory BMA evaluation for possible CR if not already performed earlier.

9.3.10.8 Bone Marrow Aspiration

Bone marrow samples will be analyzed locally as detailed in Appendix B (Parts 1 and 2) and in Appendix A for Part 3.

Bone marrow morphology is not required for Part 3.

9.3.10.8.1 Bone Marrow Central Laboratory Evaluations

A standard BMA and biopsy drawn prior to consent is acceptable for local analyses provided it is collected within 5 weeks of the first dose. However, this sample is not acceptable for central laboratory biomarker and MRD assessments; therefore, a fresh BMA is required at screening for central analyses.

If CR is suspected based on laboratory values, a BMA and biopsy are required to locally confirm CR (Appendix F) as per routine clinical practice. At the time of this procedure, one sample must be collected for MRD assessment and frozen in accordance with the procedures outlined in the Laboratory Manual. Central MRD assessments should be done every 6 months for patients continuing in CR.

Part 3: BMA collections for central MRD and cytogenetic evaluations are required at screening. In addition to the BMA for MRD collected at suspected CR, BMAs will be collected every 6 months following the collection of the suspected CR MRD sample for further evaluation of MRD. An optional BMA collection at the time of progression is requested for those patients who had previously responded to treatment in order to gain insight into resistance mechanisms.

Screening MRD samples will be obtained in China based on acceptability of method chosen.

9.3.10.8.2 Bone Marrow Local Laboratory Evaluations

9.3.10.8.2.1 Disease Assessment

A BMA will be obtained at screening for disease assessment and at any time during treatment to assess CR or to investigate suspected PD if it is in accordance with standard local practice. This evaluation will be performed locally. Clonality for sCR should be established by showing κλ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence in bone marrow (Appendix A and Appendix B).

9.3.10.8.2.2 Cytogenetics

For Parts 1 and 2 cytogenetic evaluation will be analyzed locally, according to local standards, if the site has the capability to perform analysis. These analyses should be performed at screening using fluorescence *in situ* hybridization and/or conventional cytogenetics (karyotype).

In Part 3, cytogenetic results from samples taken within 5 weeks before the first dose are acceptable for stratification. All patients should also have a sample from screening sent for central analysis. If a previous result is not available and the patient is known to have high-risk disease [ie, del17, t(4;14) and/or t(14;16) from prior cytogenetic testing, regardless of timing], they should be stratified as high risk for the purpose of enrollment.

9.3.10.8.2.3 Bone Marrow Morphology

A BMA or biopsy will be obtained for local pathology review from a subset of patients at screening, and at the time of on-treatment BMA collections to assess plasma cell count and morphology of bone marrow precursor cells with special attention to megakaryocytes. The sponsor will communicate to the sites when a sufficient number of evaluable samples have been obtained to stop the collection.

Bone morphology will not be assessed in Part 3.

9.3.11 PK, Immunogenicity, Biomarker, and Pharmacodynamic Samples

9.3.11.1 Primary Specimen Collection for PK, Immunology, and Biomarker Assessments

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in the SOE (Appendix C) for serum concentration measurements of modakafusp alfa and biomarker assessments. Bone marrow biopsy and aspirate collections are detailed in Appendix B for Parts 1 and 2 and found within the SOE (Appendix A) for Part 3. The primary specimen collection schema is presented in Table 9.c.

If necessary, serum samples collected for PK assessments may also be used for exploration of pharmacodynamic biomarkers. These serum PK samples may only be used for this purpose after final PK analysis has been completed.

Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

Table 9.c Primary Specimen Collection

Specimen Name in Schedule of Events	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Parts 1 and 2 Sample Collection	Part 3 Sample Collection [a]
Fresh bone marrow aspirate sample for pharmacodynamics	Bone marrow aspirate	BMMC Cell Pellet	N/A	CD38 immunoprofiling	Mandatory at screening and 2 postdose time points. Optional at PD after response.[a]	N/A
		BMA Cell Pellet	DNA	T-cell and B-cell receptor sequencing		
Fresh bone marrow aspirate sample for RNA	Bone marrow aspirate	RNA	N/A	Pharmacodynamic measurements (RNA-seq)	Mandatory at Screening and 2 postdose time points. Optional at PD after response.[b]	N/A
Fresh bone marrow aspirate sample for MRD	Bone marrow aspirate	DNA	N/A	Biomarker measurements	Mandatory at screening and suspected CR.[c]	Mandatory at screening, suspected CR, and every 6 months after suspected CR. [c]
Fresh Bone Marrow Aspirate for cytogenetics	Bone marrow aspirate	Plasma	N/A	Biomarker measurements	N/A	Mandatory at screening
		CD138+ cryopreserved cells	DNA and RNA	Cytogenetics and biomarker measurements		
		CD138- Cryopreserved cells	DNA and RNA	Biomarker measurements		
Fresh Bone Marrow Aspirate	Bone marrow aspirate	Plasma	N/A	Biomarker measurements	N/A	Optional at progression after response
		CD138+ cryopreserved cells	DNA and RNA	Biomarker measurements		
		CD138- Cryopreserved cells	DNA and RNA	Biomarker measurements		
Blood sample for flow cytometry (immunoprofiling) [d]	Blood	PBMC	N/A	Pharmacodynamic measurements (immunoprofiling)	Mandatory	N/A
Blood sample for flow cytometry (CD38 occupancy) [d]	Blood	PBMC	N/A	Pharmacodynamic measurements (CD38 occupancy)	Mandatory	N/A

Table 9.c Primary Specimen Collection

Specimen Name in Schedule of Events	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Parts 1 and 2 Sample Collection	Part 3 Sample Collection [a]
Blood sample for TBNK assay (*local analysis if available*)	Blood	PBMC	N/A	Pharmacodynamic measurements	Mandatory	N/A
Serum sample for circulating biomarkers	Serum	N/A	N/A	Biomarker measurements	Mandatory	Mandatory
Serum sample for immunogenicity (ADA and NAb)	Serum	N/A	N/A	Immunogenicity measurements (ADA and NAb)	Mandatory	Mandatory
Blood sample for DNA	Blood	DNA	N/A	Pharmacogenetic measurements	Mandatory	N/A
Buccal epithelial cell sample for DNA	Buccal epithelial cells	DNA	N/A	Pharmacogenetic measurements	N/A	Mandatory
Plasma sample for ctDNA	Plasma	DNA	N/A	Biomarker measurements	N/A	Mandatory
Blood sample for receptor sequencing	Blood	DNA	N/A	Pharmacodynamic measurements	Mandatory	Mandatory
Blood sample for RNA	Blood	RNA	N/A	Pharmacodynamic measurements	Mandatory	Mandatory
Serum sample for modakafusp alfa PK analysis	Serum	N/A	N/A	PK measurements (drug concentrations)	Mandatory	Mandatory

ADA: antidrug antibody; BMA: bone marrow aspirate; BMMC: bone marrow mononuclear cells; CR: complete response; ctDNA: circulating tumor DNA; CxDx: Cycle x Day x; MM: multiple myeloma; MRD: minimal residual disease; N/A: not applicable; NAb: neutralizing antibodies; PBMC: peripheral blood mononuclear cells; PD: progressive disease; PK: pharmacokinetics; PR: partial response; TBNK: T-lymphocyte, B-lymphocyte, and natural killer cells.
[a] Not all collections are applicable to all cohorts or patients within a cohort.
[b] See Appendix B for details.
[c] Screening MRD samples will be obtained in China based on acceptability of method chosen.
[d] Not all collections are applicable to all cohorts or patients within a cohort.

9.3.11.2 PK Measurements

Details regarding the preparation, handling, and shipping of the PK samples are provided in the Laboratory Manual. Serum samples for PK will be collected at the time points specified in Appendix C.

The timing but not the total number of samples may be modified during the study on the basis of emerging PK data if a change in sampling scheme is considered necessary to better characterize the PK of modakafusp alfa.

9.3.11.3 Biomarkers and Pharmacodynamic Measurements

In this study, several biomarkers will be assessed to test for correlation with safety and, if possible, with efficacy. These biomarkers will be used to identify potential pharmacodynamic activity and patients who have a higher probability of response or of adverse reactions to modakafusp alfa. The biomarker sample analyses will be performed if or when required.

Collection of samples for exploratory biomarkers are dependent upon local guidelines and regulations (including feasibility of sample or data export), as well as IRB/IEC approval. Because new techniques continue to be developed, the method and laboratory that will be recommended for the biomarker analysis cannot always be anticipated, but will be, if required by local guidelines and regulations.

For this purpose, blood samples and BMA samples will be collected as detailed in Appendix A and Appendix B.

9.3.11.3.1 Biomarker Measurements

Serum samples will be collected to evaluate circulating biomarkers at baseline and changes in them upon treatment. These biomarkers will be used to identify potential pharmacodynamic activity and patients who have a higher probability of response or of adverse reactions to modakafusp alfa. The biomarker sample analyses will be performed if or when required.

In case of an infusion reaction, blood collection should be performed for central evaluation of circulating biomarkers (see Section 8.7.1.1).

9.3.11.3.2 Pharmacodynamic Measurements

9.3.11.3.2.1 Fresh BMA Samples for Pharmacodynamics (Parts 1 and 2 Only)

BMA samples will be collected for analyzing CD38 expression on the surface of MM cells, immunoprofiling and molecular analysis. These BMA samples should be collected at the time points specified in Appendix B (screening and 2 postdose time points based on the schedule for which the subject is enrolled). These evaluations will be performed at a central laboratory.

An optional aspirate and biopsy for pharmacodynamic analysis may also be collected at the time of disease progression only if the patient had previously responded to study drug and consents to this procedure. This sample may be collected at the time of PD confirmation, at the EOT visit or prior to starting a new therapy and will be sent directly to the central laboratory for analysis.

9.3.11.3.2.2 Fresh BMA for Cytogenetics/Fresh BMA (Part 3 Only)

During the screening period for Part 3, an additional sample of bone marrow (fresh BMA for cytogenetics) will be collected to centrally analyze cytogenetic abnormalities, CD38 expression on the surface of MM and immune cells, immunoprofiling, molecular analysis, and plasma biomarkers. For patients who have had a response to modakafusp alfa treatment, an optional BMA sample (fresh BMA) may be collected at the time of progression to gain insight into potential resistance mechanisms. These evaluations will be performed at a central laboratory.

9.3.11.3.2.3 Fresh BMA Samples for MRD

BMA samples will be collected for MRD analysis. These BMA samples should be collected at the time points specified in Appendix B for Parts 1 and 2 and Appendix A for Part 3 (for Parts 1 and 2: screening and suspected CR; Part 3: screening, suspected CR, and every 6 months after the suspected CR MRD sample was drawn). Screening MRD samples will be obtained in China based on acceptability of method chosen. These evaluations will be performed at a central laboratory.

9.3.11.3.2.4 Fresh BMA Samples for RNA (Parts 1 and 2 Only)

BMA samples for RNA should be collected at the time points specified in Appendix B (screening, 2 postdose time points based on the patient's treatment schedule, and an optional sample at PD following response to treatment). The RNA will be sequenced for assessment of gene expression changes linked to pharmacodynamic activity. These evaluations will be performed at a central laboratory.

9.3.11.3.2.5 Blood Sample for Flow Cytometry

Blood samples for receptor occupancy and density (Parts 1 and 2 only) and for immunoprofiling will be collected for profiling of immune cells before, during, and at the end of treatment. These blood samples will be analyzed for the presence and changes of immune cells by flow cytometry or mass cytometry, including but not limited to B and T lymphocytes, monocytes, NK cells, etc; and CD38 occupancy in PBMC at baseline and at multiple time points after modakafusp alfa infusion (Parts 1 and 2 only). Within Parts 1 and 2, lymphocyte subpopulations will be quantified in peripheral blood using the locally available T-lymphocyte, B-lymphocyte, natural killer cells (TBNK) panel at the time points indicated in the SOE (Appendix A).

9.3.11.3.2.6 Blood Sample for RNA

Blood samples for RNA will be collected at the time points specified in the SOE (Appendix A), unless local regulations prohibit testing, for sequencing to monitor gene expression changes as a pharmacodynamic effect of modakafusp alfa administration and for associations with response and/or resistance. Sample analysis will be performed at a central laboratory.

9.3.11.3.2.7 Blood Sample for Receptor Sequencing

To monitor for induction of an adaptive immune response, blood samples will be collected to sequence T-cell and B-cell receptors before, during, and at the end of treatment. Sample analysis will be performed at a central laboratory.

9.3.11.4 DNA Measurements

In this study, a blood sample (Parts 1 and 2) or buccal epithelial cells (Part 3) will be collected from each patient (unless local regulations prohibit testing) for a potential pharmacogenetic assessment. The pharmacogenetic assessment would evaluate polymorphisms in mechanism and pathway-related genes including type I IFN inborne errors, STAT2, and IFN lambda 4 and the

relationship to response. Data from these samples will be used as a positive control for tumor DNA sequencing for identification of somatic alterations.

Additionally, in Part 3, a plasma sample for circulating tumor DNA will also be collected unless prohibited by country regulations. These samples will be analyzed in a central laboratory.

9.3.11.5 Immunogenicity Measurements

Serum samples for the assessment of ADA will be collected at the time points specified in the SOEs (Appendix A) as outlined in the Laboratory Manual. Samples must be collected before study drug is administered on a dosing day, and it is strongly suggested that samples be obtained at unscheduled visits for a patient who experiences Grade ≥2 hypersensitivity/IRR (Section 8.7.1). All ADA samples will be first analyzed in a screening assay. Positively screened samples will be further analyzed in a confirmatory assay. Confirmed positive ADA samples will be further characterized for their titer, binding domain specificity characterization, and neutralizing capacity (NAb).

In case of an IRR, blood should be collected for central evaluation of immunogenicity (see Section 8.7.1.1).

9.3.12 PRO Assessments

For patients with advanced and life-threatening diseases such as cancer, reducing symptom burden and preserving their HRQOL are among the most important therapeutic goals. To inform the PRO instrument selection and endpoint design, patient-focused qualitative research was conducted to help identify the most relevant PRO concepts (particularly the core symptoms of MM) in MM. A targeted literature review on both the PRO concepts and instruments was performed to better understand core concepts most relevant to this patient population and treatment modality and to ensure the alignment with the guidance from key stakeholders. Healthcare providers and patient organizations were consulted/interviewed to explore the clinical perspective on treatment and observed patient experience, respectively. Engagement with MM patients, including RRMM patients, was conducted to gather patient symptoms, patient-reported symptomatic AEs, functioning, and HRQOL impact experience. Results from these research activities were then triangulated to select the most appropriate patient-relevant instruments and patient-derived endpoints for this study.

In Part 3 of this study, patient-reported symptoms and HRQOL/health status will be evaluated using the EORTC QLQ-MY20 and the EQ-5D-5L, respectively. These measures were superior to others identified in terms of overall use in MM clinical studies, regulatory precedence, and content coverage that was confirmed by clinical experts and patient interviews. All questionnaires have evidence of reliability and validity within the specific context of use and are instruments regularly employed in clinical research.

During the Part 3 Extension, the EORTC QLQ-MY20 and the EQ-5D-5L will be administered electronically per the SOEs (Appendix A) to all randomized patients. Paper versions of the questionnaire are not permitted. The PRO assessments will be collected regularly during treatment, and at the EOT visit. All PROs should be administered on Day 8 of each cycle, except

for Cycle 1 when the EORTC QLQ-MY20 should be administered on Day 1 and 8 (ie, C1D1 and C1D8) and the EQ-5D-5L on Day 1 (ie, C1D1). On C1D1, PROs may be completed within a +1-day window; on all other days, PROs may be completed within a ±2-day window.

On days when PROs are administered during clinic visits (Appendix A), the EORTC QLQ-MY20 and EQ-5D-5L should be completed by patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures are performed. The patient should be given sufficient space and time to complete the questionnaires. The patient should complete the questionnaires on their own without any assistance or interpretation from site staff. The questionnaires will be administered to patients in their local language, using the version provided by the sponsor.

During the Part 3 Extension, the PRO assessments will be collected regularly during treatment and at the EOT visit. On days when PRO assessments are not completed at the clinic (ie, Day 8 of each cycle starting with Cycle 3), site staff should remind each patient at every cycle to complete their PRO questionnaires. Site staff should regularly remind patients to contact their health care provider for any concerning signs or symptoms and inform patients that their responses to the PRO measures will not be shared with site staff or members of their health care team.

Although PRO measures may assist in the overall understanding of a therapy's safety and tolerability, PRO data without clinical interpretation are not considered safety data, and there is no expectation that PRO data will be reported to the Food and Drug Administration (FDA) directly as safety data in cancer trials (Kim et al. 2018).

9.3.12.1 EORTC QLQ-MY20

The EORTC QLQ-MY20 has 20 items across 4 subscales: 2 functional subscales (body image and future perspective) and 2 symptoms scales (disease symptoms and side effects of treatment) (Appendix A). On each of the 20 items, respondents will indicate the extent to which (not at all, a little, quite a bit, very much) they have experienced symptoms or problems "during the past week."

The QLQ-MY20 raw scores are converted into scale scores ranging from 0 to 100. For functional subscales, higher scores represent better health. For symptom subscales, higher scores represent worse symptoms/problems. All items in this questionnaire have a recall period of 1 week. For items with missing responses, the response will be managed as per the scoring manual.

9.3.12.2 EQ-5D-5L

The EQ-5D-5L is a self-administered preference-based measure of HRQOL/health status suitable for calculating quality-adjusted life years to inform economic evaluations. EQ-5D-5L includes 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with 5 response levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). Patients are asked to indicate their health state "today" by selecting the most appropriate level of severity on each of the 5 dimensions. Patient responses to the 5 dimensions of the EQ-5D-5L represent the patient's health state. As part of this instrument, there is also a

visual analogue scale used by respondents to rate their health "today" on a scale from best (100) to worst health imaginable (0).

9.3.13 Healthcare Resource Utilization

Healthcare resource utilization, including hospitalizations and outpatient visits, will be evaluated as a secondary endpoint. Healthcare resource utilization, including information related to hospitalization or outpatient clinics, will be collected from all patients, regardless of the reason for the medical care encounter on Day 1 of each cycle and at EOT per the SOE (Appendix A).

Examples of data to be collected include the length of hospital stay, types of hospital stay (eg, intensive care unit), types of outpatient visits (eg, emergency room visit), and reasons for hospitalization and outpatient visits.

9.4 Completion of Study Treatment (for Individual Patients)

Patients in Parts 1 and 2 may receive modakafusp alfa for up to 1 year; however, patients with clinical benefit can continue treatment beyond 1 year with explicit sponsor approval. Patients in Part 3 may continue treatment until disease progression.

Patients will be considered to have completed study treatment if they discontinue study drug for any reason outlined in this section.

Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for subjects to continue. In evaluating such requests, the sponsor will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.

9.4.1 Discontinuation of Treatment with Study Drug and Patient Replacement

Study drug must be permanently discontinued for patients meeting any of the following criteria:

- Patient experiences an AE or other medical condition that indicates to the investigator that continued participation is not in the best interest of the patient.

Treatment with study drug may also be discontinued for any of the following reasons:

- AE.
- Complete 1 year of treatment (unless exception is granted by the sponsor) in Parts 1 and 2 only.
- Protocol deviation (after discussion with sponsor).
- Progressive disease (if the investigator considers that treatment after PD is in the patient’s best interest, it can be approved after consultation with the sponsor).
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.

- Study terminated by sponsor.
- Withdrawal by subject.
- Female patient has confirmed pregnancy.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

In Part 1, patients who miss 1 or more modakafusp alfa infusions during Cycle 1 for reasons other than a DLT will be replaced. In Part 2 and Part 3, patients who receive 1 or more infusions of study drug will not be replaced.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the SOE (Appendix A) until PD or withdrawal of consent.

9.4.2 Withdrawal of Patients From Study

A patient must be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by subject.
- Completed study.
- Transfer of patient to a long-term safety study, single-patient investigational new drug application, or similar program.
- Death.
- Other.

9.5 Posttreatment Follow-up Assessments

Patients in Parts 1 and 2 may receive modakafusp alfa for up to 1 year; however, patients with clinical benefit can continue treatment beyond 1 year with explicit sponsor approval. Patients in Part 3 may continue treatment until PD.

The PFS visits should occur every 4 weeks from the EOT visit until the occurrence of progression, death, the start of subsequent systemic antineoplastic therapy, study termination (Section 9.4), or until 6 months after the discontinuation of study treatment, whichever occurs first. OS follow-up continues every 12 weeks from the EOT visit until death, study termination, or patient withdrawal. For all patients who received study therapy and then receive subsequent anticancer therapy, next lines of therapy will be recorded, including dates of initiation and termination, regardless of whether it is initiated before or after PD. Information about disease

response/status should also be recorded. Imaging tests for patients with extramedullary disease should be performed every 12 weeks or if new symptoms suggest PD.

See the SOE (Appendix A) for appropriate assessments during follow-up.

NOTE: Treatment-related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

9.6 Study Compliance

Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 Adverse Events of Special Interest

An adverse events of special interest (AESI), serious or nonserious, is an AE of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to Takeda sponsor is appropriate. Such events may require further investigation in order to characterize and understand them. In modakafusp alfa studies, IRRs are designated as AESIs. Instructions regarding how and when AESIs should be reported to Takeda are provided in Section 10.2.

10.1.4 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.)
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE v 5.0 . Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are not synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is not the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is

considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). For Parts 1 and 2, this should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Operations Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF. For Part 3, SAEs should be reported by completing the corresponding SAE eCRF in the electronic data capture (EDC) system which will automatically notify the Takeda Global Pharmacovigilance department or designee (contact information provided below).

SAE Reporting Contact Information

Cognizant Worldwide

1-202-315-3560

Planned hospital admissions or surgical procedures for an illness or disease that existed *before study drug was given* are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0. The criteria are provided in the Study Operations Manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: “Is there a reasonable possibility that the AE is associated with the study drug?”

10.2.1 Monitoring and Reporting IRRs

An IRR is a type of reaction that develops during or shortly after administration of a drug. Signs and symptoms and management guidelines are detailed in Section 8.7.1. In modakafusp alfa studies, IRRs are designated as AESIs. When reporting IRRs in the eCRF, the signs and symptoms should be recorded and should be marked as an IRR.

Serious AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner irrespective of the event’s causal relationship.

Further, patients will be advised to promptly report signs and symptoms that may indicate IRRs, including fever, chills, dizziness, nausea, vomiting, flushing, cough, headache, and rash during or soon after end of infusion.

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from *the signing of informed consent* through *30 days* after administration of the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs.
- SAEs:
  - Serious pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug and will also be recorded in the eCRF.
  - Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 30 days after administration of the last dose of study drug, even if the patient starts nonprotocol therapy, and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be caused by a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via email address provided below.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. If a potential medication error situation (including overdose) is deemed related to a product quality complaint, then this too should be immediately reported via the email address provided below.

Product	E-mail
modakafusp alfa	ctmcomplaint@takeda.com

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Cognizant (refer to Section 10.2).

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs or IECs as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

Study specific committees are detailed in Section 3.3.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, pretreatment events, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and arrange to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs. ePROs and therefore PRO data are not included in the eCRF and should not be reviewed by the principal investigator.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

For the phase 2 Part 3 extension cohorts, the primary analysis of the primary endpoint will be performed when enrolled patients have had the opportunity to be assessed for response for at least 6 months after modakafusp alfa administration. Additional details of analyses will be provided in the SAP.

13.1.1 Analysis Sets

Full analysis set: The full analysis set will include all patients who receive at least 1 dose, even an incomplete dose, of modakafusp alfa, in the Part 3 extension cohorts. The full analysis set will be used for efficacy analysis.

Safety analysis set: The safety analysis set will include all enrolled patients who receive at least 1 dose, even an incomplete dose, of modakafusp alfa. The safety analysis set will be used for safety analysis.

Response-evaluable analysis set: The subset of the safety analysis set of patients treated at the MTD/OBD from the Part 2 dose expansion cohorts with measurable disease at baseline and at least 1 posttreatment efficacy evaluation. The response-evaluable analysis set will be used in the futility analysis of the Part 2 expansion.

PK analysis set: The PK analysis set will include those patients from the safety analysis set who have sufficient data to calculate at least 1 PK parameter for modakafusp alfa.

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.

PRO analysis set: The PRO analysis set includes all patients with a baseline and at least one postbaseline measurement of any PRO. The analyses of PROs will be based on the PRO analysis set.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications, and therapies, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

13.1.3 Efficacy Analysis

Part 2

For the Part 2 expansion cohorts, the efficacy of modakafusp alfa will be evaluated by measuring the confirmed ORR defined as the proportion of patients who achieved a confirmed PR or better during study, duration of response, best overall response, CBR, DCR, TTP and PFS as defined by the IMWG Uniform Response Criteria (Appendix F). When appropriate, data from patients in the expansion cohorts will be summarized together with data from patients in the dose escalation phase.

For each cohort, the investigator-assessed best overall response and confirmed response (sCR, CR, VGPR, PR, MR, SD, or PD according to IMWG) for each patient who received at least 1 dose of study medication will be listed, and the exact 2-sided 95% CIs for the investigator-assessed confirmed ORR will be calculated based on the binomial distribution. Duration of response (in responders), PFS, and OS will be analyzed by using the Kaplan-Meier method. Descriptive statistics will be used to summarize the time to response in responders. All patients receiving at least 1 dose of modakafusp alfa will be considered evaluable for efficacy.

Part 3

The primary analysis for all efficacy endpoints in Part 3 extension cohorts will be based on the full analysis set. No formal statistical analysis will be performed to compare the 2 treatment arms.

The primary analysis of the primary endpoint ORR will be based on the responses assessed by the IRC. The number and percentage of patients with different response status will be presented. The ORR by IRC and the corresponding 95% exact CI will also be provided. Patients with unknown or missing response status will be treated as nonresponders, ie, these participants will be included in the denominator when calculating percentages of response.

Analysis of secondary endpoints will include the investigator-assessed ORR, DOR, CBR, duration of clinical benefit, DCR, duration of disease control, PFS, TTP, and OS as defined in Section 5.4.3. The investigator-assessed ORR, the IRC-assessed and investigator-assessed CBR and DCR will also be reported in the same approach as the primary endpoint. For all the time-to-event endpoints, the median time to event with 95% CI will be estimated by the Kaplan-Meier method. A Kaplan-Meier survival curve will be generated. The number and percentage of patients who had the event or were censored will also be reported.

Descriptive subgroup analyses of the primary endpoint by key baseline prognostic factors may be performed if data permit.

13.1.4 PK Analysis

PK parameters will be estimated using noncompartmental methods with Phoenix WinNonlin. The PK parameters will be estimated from the concentration-time profiles for the PK population. The following PK parameters will be determined in Parts 1 and 2, and in Chinese patients with the intensive PK schedule in Part 3, as permitted by data:

- C_{max}.
- t_{max}.
- AUC_{∞}.
- AUC_{last}.
- λ_z.
- $t_{1/2z}$.
- CL.
- V_{ss}.
- Accumulation ratio based on AUC_{τ} (area under the concentration-time curve during a dosing interval).

PK parameters will be summarized using descriptive statistics. Individual modakafusp alfa concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort.

The PK data collected in this study 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 be reported separately.

13.1.5 Biomarker and Pharmacodynamic Analysis

During the clinical development of modakafusp alfa, several biomarkers will be assessed to test for their correlation with safety and, if possible, with efficacy. Markers that will be studied are markers linked either to the drug itself or to the treated disease. Markers of immune system activation (neopterin and others) will be summarized using descriptive statistics. Individual data will be listed. Summaries will be provided separately for each study phase and by dose, as applicable.

13.1.6 PRO Analyses

The PRO analysis will be based on the EORTC QLQ-MY20 subscale scores. The actual value and change from baseline of the EORTC QLQ-MY20 subscale scores will be summarized using descriptive statistics overall and by dose over time. The difference between baseline scores and scores over may be also explored using linear mixed models. EQ-5D-5L will be assessed using descriptive statistics over time.

The percentage of missing items for all questionnaires at each cycle will be described, as well as the number and percentages of patients with evaluable questionnaire (ie, questionnaire with at least 1 nonmissing item). PRO compliance and PRO completion over time will be calculated at the questionnaire level for the QLQ-MY20 at each cycle from baseline to provide context for the interpretation of PRO results. Rate of PRO score completion will be calculated as follows: (number of participants with the PRO score available at the visit) / (number of participants for

whom a PRO score is expected at the visit). Rate of available PRO scores over time will be calculated as follows: (number of participants with the PRO score available at the visit) / (total number of participants in the PRO analysis population). The PRO analysis population includes all patients with a baseline and at least 1 postbaseline measurement of any PRO.

13.1.7 Immunogenicity Analyses

The proportion of subjects with positive ADA (incidence, titer, and domain specificity) and NAb during the study will be summarized. The effect of immunogenicity on PK, pharmacodynamics, safety, and efficacy will be examined, if possible.

Analysis will be based on available data from patients with a baseline assessment and at least 1 post-baseline immunogenicity assessment (immunogenicity-evaluable analysis set). Summaries will be provided separately for each study phase and by dose, as applicable. All analyses will be descriptive and exploratory in nature.

13.1.8 Safety Analysis

The safety and tolerability of modakafusp alfa will be assessed by the recording of TEAEs (using NCI CTCAE, Version 5.0), vital signs, physical examination, chemistry, hematology, urinalysis, ECG, and concomitant medications.

TEAEs will be summarized using the safety analysis set and will be coded using the MedDRA. Data will be summarized using preferred terms and the primary SOC.

All patients receiving at least 1 dose of modakafusp alfa will be considered evaluable for the safety analysis. The AE incidence rates and the frequency of occurrence of overall toxicity, categorized by toxicity grades (severity), will be presented. Listings of laboratory test results and vital signs will be generated. Descriptive statistics summarizing the changes in laboratory tests over time will be reported.

13.2 Interim Analyses and Criteria for Early Termination

13.2.1 Part 2 Dose Expansion

A futility analysis will be conducted when 10 response-evaluable patients in a Part 2 arm have been followed for at least 3 cycles or have already responded or withdrawn. An arm with a posterior probability of success (PPOS) (ie, having 11 or more responders out of 25 patients) of <15% (ie, 3 or fewer responders in 10 patients) will stop enrollment for futility. Unless all 25 patients have already been enrolled, another futility analysis with the same decision rule based on PPOS will be conducted when 15 response-evaluable patients in a Part 2 arm have been followed for at least 3 cycles or have already responded or withdrawn. If there are 5 or fewer responders in 15 patients, enrollment will stop for futility.

13.2.2 Part 3 Extension

13.2.2.1 Part 3 Futility Stopping Rules

Two interim analyses for futility are planned for the Part 3 extension cohorts when approximately 15 and 48 patients of the planned 118 patients per arm are enrolled and treated for at least 3 cycles or have discontinued treatment prematurely. The futility stopping boundary will be determined based on the predictive probability of success at the primary analysis, using a Bayesian efficacy monitoring approach (Lee and Liu 2008). The treatment arm will be dropped for futility if the predictive probability of success at the primary analysis is found to be <10% based on the data from the interim analysis. Various prior distributions for the ORR are used for each treatment arm due to different prior efficacy information at different dose levels collected in Parts 1 and 2 of the study. To reflect the prior efficacy information for the 120 mg arm (40% ORR) collected in Parts 1 and 2, a weakly informative prior of Beta (1.2, 1.8) is used. However, because of comparatively limited efficacy data available at the 3 mg/kg (240 mg) dose, a noninformative prior of Beta (0.5, 0.5) is used. Based on these prior distributions, Table 13.a shows the stopping rules used for the treatment arms of 240 mg and 120 mg at each interim futility analysis. The details of the operating characteristics of the futility stopping rules are described in Appendix H.

There is no plan to stop for efficacy based on the interim analysis data.

Table 13.a Stopping Boundaries for 240 and 120 mg Arms at Each Interim Futility Analyses

	Number of patients enrolled and followed up for 3 months	**Recommend terminating the corresponding treatment arm due to lack of efficacy when number of responders is:**	
		240 mg Arm	120 mg Arm
1st Interim Futility Analysis	15	≤2	≤1
2nd Interim Futility Analysis	48	≤10	≤10

13.2.2.2 Part 3 Continuous Safety Monitoring Plan and Stopping Rules

In the Part 3 extension cohorts, an IDMC will review accumulating safety, tolerability, and efficacy data. Grade ≥4 nonhematologic treatment-related TEAEs, as well as treatment-related deaths, will be continuously monitored at the following time points using a Bayesian toxicity monitoring approach based on posterior probability (Table 13.b).

Table 13.b Safety Monitoring Time Points Based on Bayesian Stopping Rules

	Time Point
1st DMC Safety review	20 patients have been treated (10 patients in each arm).
2nd DMC Safety review (first futility analysis)	15 patients in each arm treated for at least 3 cycles or discontinued treatment prematurely.
3rd DMC Safety review (second futility analysis)	48 patients in each arm treated for at least 3 cycles or discontinued treatment prematurely.

DMC: Data Monitoring Committee.

The stopping rules will be determined based on the posterior probability of the unacceptable toxicity event rate >25%, and the unacceptable treatment-related death rate >5%. If there is at least an 80% probability that the true toxicity event (Grade ≥4 nonhematologic treatment-related TEAEs) rate is greater than 25% given the observed toxicity data, the enrollment will be paused until the IDMC reviews the data to avoid putting more patients at risk.

Similarly, if there is at least an 80% probability that the true treatment-related death rate is greater than 5% given the observed death data, the enrollment will be paused until the IDMC reviews the data. Details of the Bayesian toxicity monitoring plan and the operating characteristics can be found in Appendix I.

If the trial is stopped or paused for unacceptable toxicity or death, the regulatory agencies and investigators will be informed.

13.3 Determination of Sample Size

Part 1 of the study will follow a standard 3 + 3 dose escalation design. Under this design, the probability of dose escalation according to the true DLT rate is as follows:

True DLT rate	5%	10%	20%	30%	40%	50%	60%	70%
Probability of escalating	97%	91%	71%	49%	31%	17%	8%	3%

DLT: dose-limiting toxicity.

The probability of not observing a DLT in a sample size of 6 patients according to the true DLT rate is as follows:

True DLT rate	5%	10%	20%	30%	40%	50%	60%	70%
Probability of no toxicity	74%	53%	26%	12%	4.7%	1.6%	0.4%	<0.1%

DLT: dose-limiting toxicity.

Patients will be considered evaluable in Part 1 for MTD/OBD assessment provided they have not missed any of their infusions of modakafusp alfa in Cycle 1 and have not had a DLT. Patients who are not considered evaluable as defined above will be replaced.

Part 2 Expansion

The study will enroll up to 25 patients in each arm to further characterize safety of the OBD/MTD and obtain preliminary clinical efficacy data. An OBD/MTD dose will be considered clinically relevant if at least 11 out of 25 response evaluable patients have a confirmed PR or better. With a vague beta prior with shape parameters 0.428 and 1 for ORR (ie, mean of 30%), 11 responders out of 25 gives a greater than 90% posterior probability of true ORR being greater than 30%. The design has reasonable operating characteristics. With a true ORR of 30%, the probability of declaring success is 7%. In contrast, with a true ORR of 50%, the probability of declaring success is 70%.

Part 3 Extension

The primary objective of Part 3 of the study is to determine the confirmed ORR, including PR, VGPR, CR, and sCR assessed according to the IMWG criteria (Appendix F) to modakafusp alfa in patients with MM previously treated with ≥3 lines and with evidence of disease progression who are refractory to, or intolerant of, a PI, an IMiD, and an anti-CD38 mAb (triple refractory).The sample size was determined to claim that the true ORR is greater than the threshold response rate of 20% within each treatment arm. A total sample size of approximately 236 enrolled patients (118 patients per arm) will allow the study to have over 90% power to rule out an uninteresting response rate of 20% if the true rate is 35% with a 1-sided alpha of 0.025.

The purpose of the China continuation cohort is to allow continued evaluation of efficacy and any emerging safety signals in Chinese patients enrolled in China. After global patient enrollment is completed in Part 3, enrollment will continue for the China continuation cohort until about 15% of the total sample size is reached at the selected dose(s) (eg, 18 patients based on 118 patients treated at the selected dose[s]).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. If monitors are not allowed to perform on-site visits for data verification due to exceptional circumstances (eg, COVID-19), remote electronic medical records access visits may be conducted (where allowed by local laws and regulations). Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix D. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has

direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent are given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if

applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to subject entering the study; however, the Sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, the US FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and

the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov, clinicaltrialsregister.eu, or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants to find a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established

subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, clinicaltrialsregister.eu, or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Appendix A Table 1 Part 1 Schedule A Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1								Treatment Phase – Cycle 2					
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Cycle Day		C1D1	C1D2	C1D4	C1D8	C1D15	C1D16	C1D18	C1D22	C2D1	C2D2	C2D4	C2D8	C2D15	C2D22
Window Allowed	≤21	0	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Informed consent [a]	X														
Eligibility criteria	X														
Demographics	X														
Medical history	X														
Prior medication and treatment history	X														
Height and weight [b]	X									X					
ECOG performance status	X									X					
12-lead ECG [c]	X	X			X	X				X					
12-lead ECG (triplicate) [c]		X	X			X									
Physical examination	X	X			X					X					
Vital signs [d]	X	X			X	X			X	X			X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or start of subsequent anticancer therapy, whichever occurs first.														
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or start of subsequent anticancer therapy, whichever occurs first.														
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.														
Dosing															
Modakafusp alfa infusion [e]		X			X	X			X	X			X	X	X

Appendix A Table 1 Part 1 Schedule A Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1								Treatment Phase – Cycle 2					
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Cycle Day		C1D1	C1D2	C1D4	C1D8	C1D15	C1D16	C1D18	C1D22	C2D1	C2D2	C2D4	C2D8	C2D15	C2D22
Window Allowed	≤21	0	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Imaging Assessments															
Skeletal survey [f]	X														
CT or MRI scan [f]	(X)														
Laboratory Assessments															
Chemistry [g]	X	(X)			X	X			X	X			X	X	X
Hematology [h]	X	(X)			X	X			X	X			X	X	X
Urinalysis [i]	X									X					
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.														
Pregnancy test [j]	X														
Serum M-protein [k, o]	X	X				X				X				X	
24-Hour urine M-protein [l, o]	X									(X)					
Serum FLC assay [o]	X									X					
Immunofixation - serum and urine [m]	X														
Quantification of Ig [n]	X									X					
Bone marrow aspiration/biopsy [p]	X						X								
Serum sample for modakafusp alfa PK [q]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for flow cytometry (immunoprofiling) [r]		X [s]	X			X [s]	X								

Appendix A Table 1 Part 1 Schedule A Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1								Treatment Phase – Cycle 2					
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Cycle Day		C1D1	C1D2	C1D4	C1D8	C1D15	C1D16	C1D18	C1D22	C2D1	C2D2	C2D4	C2D8	C2D15	C2D22
Window Allowed	≤21	0	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Blood sample for flow cytometry (CD38 occupancy in PBMCs)		X [t]	X			X [t]	X								
Serum sample for circulating biomarkers [e]		X [t]	X	X		X [t]	X	X							
Serum sample for immunogenicity (ADA and NAb) [e, u]		X				X				X				X	
Blood sample for DNA [v]	X														
Blood sample for RNA		X [s]	X			X [s]	X								
Blood sample for receptor sequencing [s]	X					X									

Footnotes are on last page of SOE tables (Schedule A, B, C, and D End of Treatment and Follow-Up).

Appendix A Table 2 Part 1 Schedule A Schedule of Events, continued: Cycle 3 to Cycle 13 and Beyond

Study Period	**Treatment Phase**															
Visit Number	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27-29**	**V30**	**V31**	**V32**	**V33+**
Cycle Day	**C3D1**	**C3D2**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**	**C7D1**	**C7D2**	**C8D1 to C10D1**	**C11D1**	**C11D2**	**C12D1**	**C13D1+**
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**
Height and weight [b]	X			X		X		X		X		X	X		X	X
ECOG performance status	X			X		X		X		X		X	X		X	X
12-lead ECG [c]																
Physical examination	X			X		X		X		X		X	X		X	X
Vital signs [d]	X		X	X	X	X	X	X	X	X		X	X		X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.															
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.															
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.															
Dosing																
Modakafusp alfa infusion [e]	X		X	X	X	X	X	X	X	X		X	X		X	X
Imaging Assessments																
Skeletal survey [f]																
CT or MRI scan [f]	(X)					(X)				(X)		(X)	(X)			(X)
Laboratory Assessments																
Chemistry [g]	X		X	X	X	X	X	X	X	X		X	X		X	X
Hematology [h]	X		X	X	X	X	X	X	X	X		X	X		X	X

Appendix A Table 2 Part 1 Schedule A Schedule of Events, continued: Cycle 3 to Cycle 13 and Beyond

Study Period	Treatment Phase															
Visit Number	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27-29**	**V30**	**V31**	**V32**	**V33+**
Cycle Day	**C3D1**	**C3D2**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**	**C7D1**	**C7D2**	**C8D1 to C10D1**	**C11D1**	**C11D2**	**C12D1**	**C13D1+**
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**
Urinalysis [i]	X			X		X		X		X		X	X		X	X
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.															
Pregnancy test [j]																
Serum M-protein [o]	X			X		X		X		X		X	X		X	X
24-Hour urine M-protein [l, o]	(X)			(X)		(X)		(X)		(X)		(X)	(X)		(X)	(X)
Serum FLC assay [o]	X			X		X		X		X		X	X		X	X
Immunofixation - serum and urine [m]																
Quantification of Ig [n]	X			X		X		X		X		X	X		X	X
Bone marrow aspiration/biopsy [p]		X														
Serum sample for modakafusp alfa PK [q]	X	X	X	X	X	X	X	X	X	X		X	X		X	X
Blood sample for flow cytometry (immunoprofiling) [r]	X [s]	X								X [s]	X		X [s]	X		
Serum sample for circulating biomarkers [e]	X [t]	X								X [t]	X		X [t]	X		
Serum sample for immunogenicity (ADA and NAb) [e, u]	X			X		X		X		X		X	X		X	X

Appendix A Table 2 Part 1 Schedule A Schedule of Events, continued: Cycle 3 to Cycle 13 and Beyond

Study Period	Treatment Phase															
Visit Number	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27-29	V30	V31	V32	V33+
Cycle Day	C3D1	C3D2	C3D15	C4D1	C4D15	C5D1	C5D15	C6D1	C6D15	C7D1	C7D2	C8D1 to C10D1	C11D1	C11D2	C12D1	C13D1+
Window Allowed	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d
Blood sample for RNA	X[s]	X								X[s]	X		X[s]	X		
Blood sample for receptor sequencing [s]	X									X			X			

Footnotes are on last page of SOE tables (Schedule A, B, C, and D End of Treatment and Follow-Up).

Appendix A Table 3 Part 1 Schedule B (Q2W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening				Treatment Phase – Cycle 1				Treatment Phase – Cycle 2			
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Cycle Day		**C1D1**	**C1D2**	**C1D8**	**C1D15**	**C1D16**	**C1D22**	**C2D1**	**C2D2**	**C2D8**	**C2D15**	**C2D22**
Window Allowed	**≤21 d**	**0**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Informed consent [a]	X											
Eligibility criteria	X											
Demographics	X											
Medical history	X											
Prior medication and treatment history	X											
Height and weight [b]	X							X				
ECOG performance status	X							X				
12-lead ECG [c]	X	X			X			X				
12-lead ECGs (triplicate) [c]		X	X					X	X			
Physical examination	X	X						X				
Vital signs [d]	X	X			X			X			X	
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.											
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.											
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.											
Dosing												
Modakafusp alfa infusion [e, bb]		X			X			X			X	
Imaging Assessments												
Skeletal survey [f]	(X)											
CT, PET-CT, or MRI scan [f]	(X)											

Appendix A Table 3 Part 1 Schedule B (Q2W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening				Treatment Phase – Cycle 1				Treatment Phase – Cycle 2			
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Cycle Day		C1D1	C1D2	C1D8	C1D15	C1D16	C1D22	C2D1	C2D2	C2D8	C2D15	C2D22
Window Allowed	≤21 d	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Laboratory Assessments												
Chemistry [g]	X	(X)		X	X		X	X		X	X	X
Hematology [h]	X	(X)		X	X		X	X		X	X	X
Antiplatelet antibody [cc]	X	X						X				
Urinalysis [i]	X							X				
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.											
Pregnancy test [j]	X											
Serum M-protein [k, o]	X	(X)			X			X			X	
24-Hour urine M-protein [l, o]	X	(X)			(X)			(X)			(X)	
Serum FLC assay [o]	X	(X)			X			X			X	
Immunofixation - serum and urine [m, o]	X	(X)			X			X			X	
Investigator assessment of disease response/status [o]								X				
Quantification of Ig [k, n]	X	(X)						X				
Bone marrow aspiration/biopsy [p]	X					X						
Serum sample for modakafusp alfa PK [q]		X	X		X	X		X	X			
Blood sample for flow cytometry (immunoprofiling) [r]		X [s]	X		X [s]	X						
Blood sample for TBNK assay (*local analysis if available*)		X [s]			X [s]			X [s]		X [s]		
Blood sample for flow cytometry (CD38 occupancy in PBMCs)		X [ee]	X		X [ee]	X						
Serum sample for circulating biomarkers [e]		X [ee]	X	X	X [ee]	X	X					

Appendix A Table 3 Part 1 Schedule B (Q2W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening				Treatment Phase – Cycle 1				Treatment Phase – Cycle 2			
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Cycle Day		C1D1	C1D2	C1D8	C1D15	C1D16	C1D22	C2D1	C2D2	C2D8	C2D15	C2D22
Window Allowed	≤21 d	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Serum sample for immunogenicity (ADA and NAb) [e, u]		X			X			X			X	
Blood sample for DNA [v]	X											
Blood sample for RNA		X [s]	X		X [s]	X						
Blood sample for receptor sequencing [s]	X				X							

Footnotes are on last page of SOE tables (Schedule A, B, C, and D End of Treatment and Follow-Up).

Appendix A Table 4 Part 1 Schedule B (Q2W) Schedule of Events, continued: Cycle 3 to Cycle 7

Study Period	Treatment Phase											
Visit Number	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24
Cycle Day (Window Allowed ±2 d)	C3D1	C3D2	C3D15	C4D1	C4D15	C5D1	C5D15	C6D1	C6D15	C7D1	C7D2	C7D15
Height and weight [b]	X			X		X		X		X		
ECOG performance status	X			X		X		X		X		
12-lead ECG [c]												
Physical examination	X			X		X		X		X		
Vital signs [d]	X		X	X	X	X	X	X	X	X		X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.											
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.											
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.											
Dosing												
Modakafusp alfa infusion [e, bb]	X		X	X	X	X	X	X	X	X		X
Imaging Assessments												
Skeletal survey [f]	(X)					(X)				(X)		
CT, PET-CT, or MRI scan [f]	(X)					(X)				(X)		
Laboratory Assessments												
Chemistry [g]	X		X	X	X	X	X	X	X	X		X
Hematology [h]	X		X	X	X	X	X	X	X	X		X
Antiplatelet antibody [cc]	X			X		X		X		X		
Urinalysis [i]	X			X		X		X		X		
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.											

Appendix A Table 4 Part 1 Schedule B (Q2W) Schedule of Events, continued: Cycle 3 to Cycle 7

Study Period	Treatment Phase											
Visit Number	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24
Cycle Day (Window Allowed ±2 d)	C3D1	C3D2	C3D15	C4D1	C4D15	C5D1	C5D15	C6D1	C6D15	C7D1	C7D2	C7D15
Pregnancy test [j]												
Serum M-protein [o]	X			X		X		X		X		
24-Hour urine M-protein [l, o]	(X)			(X)		(X)		(X)		(X)		
Serum FLC assay [o]	X			X		X		X		X		
Immunofixation - serum and urine [m, o]	X			X		X		X		X		
Investigator assessment of disease response/status [o]	X			X		X		X		X		
Quantification of Ig [n]	X			X		X		X		X		
Bone marrow aspiration/biopsy [p]		X										
Serum sample for modakafusp alfa PK [q]	X	X	X	X	X	X	X	X	X	X		X
Blood sample for flow cytometry (immunoprofiling) [r]	X [s]	X								X [s]	X	
Blood sample for TBNK assay (*local analysis*)	X[s]											
Serum sample for circulating biomarkers [e]	X [ee]	X								X [ee]	X	
Serum sample for immunogenicity (ADA and NAb) [e, u]	X			X		X		X		X		
Blood sample for RNA	X [s]	X								X [s]	X	
Blood sample for receptor sequencing [s]	X									X		

Footnotes are on last page of SOE tables (Schedule A, B, C, and D End of Treatment and Follow-Up).

Appendix A Table 5 Part 1 Schedule B (Q2W) Schedule of Events, continued: Cycle 8 to Cycle 13 and Beyond

Study Period	Treatment Phase												
Visit Number	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**
Cycle Day (Window Allowed ±2 d)	**C8D1**	**C8D15**	**C9D1**	**C9D15**	**C10D1**	**C10D15**	**C11D1**	**C11D2**	**C11D15**	**C12D1**	**C12D15**	**C13D1**	**C13D15+**
Height and weight [b]	X		X		X		X			X		X	
ECOG performance status	X		X		X		X			X		X	
12-lead ECG [c]													
Physical examination	X		X		X		X			X		X	
Vital signs [d]	X	X	X	X	X	X	X		X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.												
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.												
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.												
Dosing													
Modakafusp alfa infusion [e, bb]	X	X	X	X	X	X	X		X	X	X	X	X
Imaging Assessments													
Skeletal survey [f]			(X)				(X)					(X)	
CT, PET-CT, or MRI scan [f]			(X)				(X)					(X)	
Laboratory Assessments													
Chemistry [g]	X	X	X	X	X	X	X		X	X	X	X	X
Hematology [h]	X	X	X	X	X	X	X		X	X	X	X	X
Antiplatelet antibody [cc]	X		X		X		X			X		X	
Urinalysis [i]	X		X		X		X			X		X	
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.												
Pregnancy test [j]													

Appendix A Table 5 Part 1 Schedule B (Q2W) Schedule of Events, continued: Cycle 8 to Cycle 13 and Beyond

Study Period	Treatment Phase												
Visit Number	V25	V26	V27	V28	V29	V30	V31	V32	V33	V34	V35	V36	V37
Cycle Day (Window Allowed ±2 d)	C8D1	C8D15	C9D1	C9D15	C10D1	C10D15	C11D1	C11D2	C11D15	C12D1	C12D15	C13D1	C13D15+
Serum M-protein [o]	X		X		X		X			X		X	
24-Hour urine M-protein [l, o]	(X)		(X)		(X)		(X)			(X)		(X)	
Serum FLC assay [o]	X		X		X		X			X		X	
Immunofixation - serum and urine [m, o]	X		X		X		X			X		X	
Investigator assessment of disease response/status [o]	X		X		X		X			X		X	
Quantification of Ig [n]	X		X		X		X			X		X	
Bone marrow aspiration/biopsy [p]													
Serum sample for modakafusp alfa PK [q]	X	X	X	X	X	X	X		X	X	X	X	X
Blood sample for flow cytometry (immunoprofiling) [r]							X [s]	X					
Serum sample for circulating biomarkers [e]							X [ee]	X					
Serum sample for immunogenicity (ADA and NAb) [e, u]	X		X		X		X			X		X	
Blood sample for RNA							X [s]	X					
Blood sample for receptor sequencing [s]							X						

Footnotes are on last page of SOE tables (Schedule A, B, C, and D End of Treatment and Follow-Up).

Appendix A Table 6 Part 1 and Part 2 Schedule C (Q3W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1					Treatment Phase – Cycle 2				
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Cycle Day		C1D1	C1D2	C1D3	C1D8	C1D15	C2D1	C2D2	C2D3	C2D8	C2D15
Window Allowed	≤21 d	0	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Informed consent [a]	X										
Eligibility criteria	X										
Demographics	X										
Medical history	X										
Prior medication and treatment history	X										
Height and weight [b]	X						X				
ECOG performance status	X						X				
12-lead ECG [c]	X	X					X				
12-lead ECG (triplicate ECGs) [c]		X	X	X	X	X	X	X	X	X	X
Physical examination	X	X					X				
Vital signs [d]	X	X					X				
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.										
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.										
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol therapy.										
Dosing											
Modakafusp alfa infusion [e, bb]		X					X				
Imaging Assessments											
Skeletal survey [f]	(X)										
CT, PET-CT, or MRI scan [f]	(X)										

Appendix A Table 6 Part 1 and Part 2 Schedule C (Q3W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1					Treatment Phase – Cycle 2				
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Cycle Day		C1D1	C1D2	C1D3	C1D8	C1D15	C2D1	C2D2	C2D3	C2D8	C2D15
Window Allowed	≤21 d	0	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Laboratory Assessments											
Chemistry [g]	X	(X)			X	X	X			X	X
Hematology [h]	X	(X)			X	X	X			X	X
Antiplatelet antibody [cc]	X	X					X				
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.										
Urinalysis [i]	X						X				
Pregnancy test [j]	X	X									
Serum M-protein [k, o]	X	(X)					X				
24-Hour urine M-protein [l, o]	X	(X)					(X)				
Serum FLC assay [o]	X	(X)					X				
Immunofixation - serum and urine [m, o]	(X)	(X)					X				
Investigator assessment of disease response/status [o]							X				
Quantification of Ig [k, m]	X	(X)					X				
Bone marrow aspiration/biopsy [p]	X							X			
Serum sample for modakafusp alfa PK [q]		X	X	X	X	X	X	X	X	X	X
Blood sample for flow cytometry (immunoprofiling) [r]		X [s]	X	X		X	X [s]	X	X		
Blood sample for flow cytometry (CD38 occupancy in PBMCs)		X [ee]	X	X		X	X [ee]	X	X		
Blood sample for TBNK assay (*local analysis*)		X [s]			X [s]		X [s]			X [s]	
Serum sample for circulating biomarkers [e]		X [dd]	X	X	X	X	X [dd]	X	X	X	

Appendix A Table 6 Part 1 and Part 2 Schedule C (Q3W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1					Treatment Phase – Cycle 2				
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Cycle Day		C1D1	C1D2	C1D3	C1D8	C1D15	C2D1	C2D2	C2D3	C2D8	C2D15
Window Allowed	≤21 d	0	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Serum sample for immunogenicity (ADA and NAb) [e, u]		X					X				
Blood sample for DNA [v]	X										
Blood sample for RNA		X [s]	X	X			X [s]	X	X		
Blood sample for receptor sequencing [s]	X					X					

Footnotes are on last page of SOE tables (Schedule A, B, C, and D End of Treatment and Follow-Up).

Appendix A Table 7 Part 1 and Part 2 Schedule C (Q3W) Schedule of Events, continued: Cycle 3 to Cycle 9

Study Period	Treatment Phase								
Visit Number	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**
Cycle Day	**C3D1**	**C4D1**	**C4D2**	**C5D1**	**C6D1**	**C7D1**	**C8D1**	**C9D1**	**C9D2**
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**
Height and weight [b]	X	X		X	X	X	X	X	
ECOG performance status	X	X		X	X	X	X	X	
12-lead ECG [c]									
Physical examination	X	X		X	X	X	X	X	
Vital signs [d]	X	X		X	X	X	X	X	
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol therapy.								
Dosing									
Modakafusp alfa infusion [e, bb]	X	X		X	X	X	X	X	
Imaging Assessments									
Skeletal survey [f]	(X)			(X)		(X)		(X)	
CT, PET-CT, or MRI scan [f]	(X)			(X)		(X)		(X)	
Laboratory Assessments									
Chemistry [g]	X	X		X	X	X	X	X	
Hematology [h]	X	X		X	X	X	X	X	
Antiplatelet antibody [cc]	X	X		X	X	X	X	X	
Urinalysis [i]	X	X		X	X	X	X	X	
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.								

Appendix A Table 7 Part 1 and Part 2 Schedule C (Q3W) Schedule of Events, continued: Cycle 3 to Cycle 9

Study Period	Treatment Phase								
Visit Number	V12	V13	V14	V15	V16	V17	V18	V19	V20
Cycle Day	C3D1	C4D1	C4D2	C5D1	C6D1	C7D1	C8D1	C9D1	C9D2
Window Allowed	±2 d	±2 d	±2 d	±2 d	±2 d	±4 d	±4 d	±4 d	±4 d
Pregnancy test [j]									
Serum M-protein [o]	X	X		X	X	X	X	X	
24-Hour urine M-protein [l, o]	(X)	(X)		(X)	(X)	(X)	(X)	(X)	
Serum FLC assay [o]	X	X		X	X	X	X	X	
Immunofixation - serum and urine [m, o]	X	X		X	X	X	X	X	
Investigator assessment of disease response/status [o]	X	X		X	X	X	X	X	
Quantification of Ig [n]	X	X		X	X	X	X	X	
Bone marrow aspiration/biopsy [p]			X						
Serum sample for modakafusp alfa PK [q]	X	X		X	X	X	X	X	
Blood sample for flow cytometry (immunoprofiling) [r]		X [s]	X					X [s]	X
Blood sample for TBNK assay (*local analysis*)	X [s]								
Serum sample for circulating biomarkers [e]		X [dd]	X					X [dd]	X
Serum sample for immunogenicity (ADA and NAb) [e, u]	X	X		X	X	X	X	X	
Blood sample for RNA		X [s]	X					X [s]	X
Blood sample for receptor sequencing [s]		X						X	

Footnotes are on last page of SOE tables (Schedule A, B, C, and D End of Treatment and Follow-Up).

Appendix A Table 8 Part 1 and Part 2 Schedule C (Q3W) Schedule of Events, continued: Cycle 10 to Cycle 17 and Beyond

Study Period	Treatment Phase								
Visit Number	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29+**
Cycle Day	**C10D1**	**C11D1**	**C12D1**	**C13D1**	**C14D1**	**C15D1**	**C15D2**	**C16D1**	**C17D1+**
Window Allowed	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**	**±4 d**
Height and weight [b]	X	X	X	X	X	X		X	X
ECOG performance status	X	X	X	X	X	X		X	X
12-lead ECG [c]									
Physical examination	X	X	X	X	X	X		X	X
Vital signs [d]	X	X	X	X	X	X		X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol therapy.								
Dosing									
Modakafusp alfa infusion [e, bb]	X	X	X	X	X	X		X	X
Imaging Assessments									
Skeletal survey [f]		(X)		(X)		(X)			(X)
CT, PET-CT, or MRI scan [f]		(X)		(X)		(X)			(X)
Laboratory Assessments									
Chemistry [g]	X	X	X	X	X	X		X	X
Hematology [h]	X	X	X	X	X	X		X	X
Antiplatelet antibody [cc]	X	X	X	X	X	X		X	X
Urinalysis [i]	X	X	X	X	X	X		X	X
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.								

Appendix A Table 8 Part 1 and Part 2 Schedule C (Q3W) Schedule of Events, continued: Cycle 10 to Cycle 17 and Beyond

Study Period	Treatment Phase								
Visit Number	V21	V22	V23	V24	V25	V26	V27	V28	V29+
Cycle Day	C10D1	C11D1	C12D1	C13D1	C14D1	C15D1	C15D2	C16D1	C17D1+
Window Allowed	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d
Serum M-protein [o]	X	X	X	X	X	X		X	X
24-Hour urine M-protein [l, o]	(X)	(X)	(X)	(X)	(X)	(X)		(X)	(X)
Serum FLC assay [o]	X	X	X	X	X	X		X	X
Immunofixation - serum and urine [m, o]	X	X	X	X	X	X		X	X
Investigator assessment of disease response/status [o]	X	X	X	X	X	X		X	X
Quantification of Ig [n]	X	X	X	X	X	X		X	X
Bone marrow aspiration/biopsy [p]									
Serum sample for modakafusp alfa PK [q]	X	X	X	X	X	X		X	X
Blood sample for flow cytometry (immunoprofiling) [r]						X [s]	X		
Serum sample for circulating biomarkers [e]						X [dd]	X		
Serum sample for immunogenicity (ADA and NAb) [e, u]	X	X	X	X	X	X		X	X
Blood sample for RNA						X [s]	X		
Blood sample for receptor sequencing [s]						X			

Footnotes are on last page of SOE tables (Schedule A, B, C, and D End of Treatment and Follow-Up).

Appendix A Table 9 Part 1 and Part 2 Schedule D (Q4W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1						Treatment Phase – Cycle 2					
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Cycle Day		C1D1	C1D2	C1D3 [z]	C1D8	C1D15	C1D22	C2D1	C2D2	C2D3 [z]	C2D8	C2D15	C2D22
Window Allowed	≤21 d	0	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Informed consent [a]	X												
Eligibility criteria	X												
Demographics	X												
Medical history	X												
Prior medication and treatment history	X												
Height and weight [b]	X							X					
ECOG performance status	X							X					
12-lead ECG [c]	X	X						X					
12-lead ECG (triplicate) [c]		X	X	X	X	X		X	X	X	X	X	
Physical examination	X	X						X					
Vital signs [d]	X	X						X					
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.												
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.												
	Recorded from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.												
Dosing													
Modakafusp alfa infusion [e, bb]		X						X					
Imaging Assessments													
Skeletal survey [f]	(X)												
CT, PET-CT, or MRI scan [f]	(X)												

Appendix A Table 9 Part 1 and Part 2 Schedule D (Q4W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1						Treatment Phase – Cycle 2					
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Cycle Day		C1D1	C1D2	C1D3 [z]	C1D8	C1D15	C1D22	C2D1	C2D2	C2D3 [z]	C2D8	C2D15	C2D22
Window Allowed	≤21 d	0	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Laboratory Assessments													
Chemistry [g]	X	(X)			X	X	X	X			X	X	X
Hematology [h]	X	(X)			X	X	X	X			X	X	X
Antiplatelet antibody [cc]	X	X						X					
Urinalysis [i]	X							X					
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.												
Serum M-protein [k, o]	X	(X)				X		X				X	
24-Hour urine M-protein [l, o]	X	(X)				(X)		(X)				(X)	
Serum FLC assay [o]	X	(X)				X		X				X	
Immunofixation - serum and urine [m, o]	(X)	(X)				X		X				X	
Investigator assessment of disease response/status [o]								X					
Quantification of Ig [k, o]	X	(X)						X					
Bone marrow aspiration/biopsy [p]	X					X							
Serum sample for modakafusp alfa PK [q]		X	X	X	X	X	X [ee]	X	X	X	X	X	X [ee]
Blood sample for flow cytometry (immunoprofiling) [r]		X [s]	X	X	X	X		X [s]	X	X	X		
Blood sample for TBNK assay (*local analysis*)		X [s]			X [s]			X [s]			X [s]		

Appendix A Table 9 Part 1 and Part 2 Schedule D (Q4W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1						Treatment Phase – Cycle 2					
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Cycle Day		C1D1	C1D2	C1D3 [z]	C1D8	C1D15	C1D22	C2D1	C2D2	C2D3 [z]	C2D8	C2D15	C2D22
Window Allowed	≤21 d	0	0	0	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d
Blood sample for flow cytometry (CD38 occupancy in PBMCs)		X [dd]	X	X	X	X		X [dd]	X	X	X		
Serum sample for circulating biomarkers [e]		X [dd]	X	X	X	X		X [dd]	X	X	X		
Serum sample for immunogenicity (ADA and NAb) [e, u]		X				X		X				X	
Blood sample for DNA [v]	X												
Blood sample for RNA		X [s]	X	X	X	X		X [s]	X	X	X		
Blood sample for receptor sequencing [s]	X					X							

Footnotes are on last page of SOE tables (Schedule A, B, C, and D End of Treatment and Follow-Up).

Appendix A Table 10 Part 1 and Part 2 Schedule D (Q4W) Schedule of Events, continued: Cycle 3 to Cycle 13 and Beyond

Study Period	Treatment Phase											
Visit Number	V14	V15	V16	V17	V18	V19	V20	V21-23	V24	V25	V26	V27+
Cycle Day	C3D1	C3D2	C4D1	C5D1	C6D1	C7D1	C7D2	C8D1 to C10D1	C11D1	C11D2	C12D1	C13D1+
Window Allowed	±2 d	±2 d	±2 d	±2 d	±2 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d
Height and weight [b]	X		X	X	X	X		X	X		X	X
ECOG performance status	X		X	X	X	X		X	X		X	X
12-lead ECG [c]												
12-lead ECG (triplicate) [c]												
Physical examination	X		X	X	X	X		X	X		X	X
Vital signs [d]	X		X	X	X	X		X	X		X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first											
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first											
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy											
Dosing												
Modakafusp alfa infusion [e, bb]	X		X	X	X	X		X	X		X	X
Imaging Assessments												
Skeletal survey [f]	(X)			(X)		(X)		(X) [w]	(X)			(X)
CT, PET-CT, or MRI scan [f]	(X)			(X)		(X)		(X) [w]	(X)			(X)
Laboratory Assessments												
Chemistry [g]	X		X	X	X	X		X	X		X	X
Hematology [h]	X		X	X	X	X		X	X		X	X
Antiplatelet antibody [cc]	X		X	X	X	X		X	X		X	X
Coagulation panel [ff] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.											

Appendix A Table 10 Part 1 and Part 2 Schedule D (Q4W) Schedule of Events, continued: Cycle 3 to Cycle 13 and Beyond

Study Period	Treatment Phase											
Visit Number	V14	V15	V16	V17	V18	V19	V20	V21-23	V24	V25	V26	V27+
Cycle Day	C3D1	C3D2	C4D1	C5D1	C6D1	C7D1	C7D2	C8D1 to C10D1	C11D1	C11D2	C12D1	C13D1+
Window Allowed	±2 d	±2 d	±2 d	±2 d	±2 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d
Urinalysis [i]	X		X	X	X	X		X	X		X	X
Pregnancy test [j]												
Serum M-protein [o]	X		X	X	X	X		X	X		X	X
24-Hour urine M-protein [l, o]	(X)		(X)	(X)	(X)	(X)		(X)	(X)		(X)	(X)
Serum FLC assay [o]	X		X	X	X	X		X	X		X	X
Immunofixation - serum and urine [m, o]	X		X	X	X	X		X	X		X	X
Investigator assessment of disease response/status [o]	X		X	X	X	X		X	X		X	X
Quantification of Ig [n]	X		X	X	X	X		X	X		X	X
Bone marrow aspiration/biopsy [p]		X										
Serum sample for modakafusp alfa PK [q]	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for flow cytometry (immunoprofiling) [r]	X [s]	X				X [s]	X		X [s]	X		
Blood sample for TBNK assay (*local analysis*)	X [s]											
Serum sample for circulating biomarkers [e]	X [dd]	X				X [dd]	X		X [dd]	X		
Serum sample for immunogenicity (ADA and NAb) [e, u]	X		X	X	X	X		X	X		X	X
Blood sample for RNA	X[s]	X				X [s]	X		X [s]	X		
Blood sample for receptor sequencing [s]	X					X			X			

ADA: antidrug antibody; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; C: cycle; CO_2: carbon dioxide; CR: complete response; CT: computed tomography; D, d: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLC: free light chain; HCO_3^-: bicarbonate; ICF: informed consent form; IRR: infusion-related reaction; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; NAb:

neutralizing antibodies; OBD: optimal biological dose; PBMC: peripheral blood mononuclear cells; PD: progressive disease; PET-CT: positron emission tomography-computed tomography; PFS: progression-free survival; PK: pharmacokinetic(s); Q12wk: every 12 weeks; SAE: serious adverse event; TBNK: T-lymphocyte, B-lymphocyte, and natural killer cells; V: visit; WB: wide beam; WBC: white blood cell.

Note: Crosses in parentheses "(X)" indicate tests are to be performed only under certain circumstances as indicated in associated footnote(s).

a. Written informed consent must be obtained before performing any protocol-specific procedure. Test results from routine clinical management are acceptable for screening if obtained within the specified time window.

b. Height will be measured only at the screening visit.

c. For all patients in the trial, 1 standard local ECG will be collected and read at screening and at the end of the infusion (+30 minutes) on the days indicated in these Schedule of Events. Triplicate ECGs will be obtained as described in these Schedule of Events and in Appendix C starting in Cohort 3 (0.1 mg/kg) or earlier if there is evidence of biological effect, read centrally. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation. When a standard single ECG is to be collected during a cycle/day that is other than on C1D1, C1D8 and C1D15, 1 standard ECG will be collected at the end of the infusion (+30 minutes) on the days indicated in this Schedule of Events, read locally.

d. Vital signs measured before starting the infusion and after the completion of the infusion. Vital signs include temperature, pulse, respiratory rate, oxygen saturation, and blood pressure. Blood pressure will be measured every 30 minutes (±5 minutes) during the first 4 infusions, after the end of the infusion, and at any moment if the patient complains of symptoms consistent with IRR.

e. In case of an IRR, blood draws should be performed for central evaluation of immune markers, cytokines, and complement (see Section 8.7.1.1). The following samples should be collected: serum sample for circulating biomarkers (cytokines, complement, neopterin), and serum sample for immunogenicity. Modakafusp alfa doses <6 mg/kg will be administered over 1 hour (±10 minutes). Modakafusp alfa doses ≥6 mg/kg will be administered over 2 hours (±10 minutes). Any decrease in infusion duration must be discussed with and agreed upon by the sponsor. If a patient presents with an IRR at any dose level, the duration of the infusion may be extended per investigator's discretion. Total time from modakafusp alfa dosing solution preparation until end of infusion must not exceed 7 hours. Infusion and pharmacy staff are advised to be prepared accordingly for either a planned, extended infusion time or for potential infusion interruptions. See Pharmacy Manual for additional guidance.

f. For patients with no previously documented extramedullary disease at screening, a complete skeletal survey, using plain x-ray or low-dose total body CT scan, will be performed at screening (if the patient has adequate imaging test(s) performed within 5 weeks of the planned first dose of study drug, they can be used as baseline evaluations and do not need to be repeated as part of screening). If there are symptoms or signs that suggest increased or new bone lesions, the skeletal survey or plain film of symptomatic sites may be repeated any time during the study and at the EOT visit. A PET-CT may be done at screening in place of a skeletal survey provided that the same modality for assessment is used throughout the study. Patients with normal skeletal survey at baseline do not need to repeat the test periodically unless bone progressive disease is clinically suspected.
For patients with previously documented extramedullary disease or with suspicion of extramedullary progression, a PET-CT scan, CT scan, or MRI scan will be performed at screening (if the patient has adequate imaging test(s) performed within 5 weeks of the planned first dose of study drug, they can be used as baseline evaluations and do not need to be repeated as part of screening) and as needed for evaluation of disease. If extramedullary disease is documented at screening, then a repeat PET-CT scan, CT scan, or MRI scan should be performed every other cycle starting on Cycle 3. For posttreatment follow-up of patients with extramedullary disease who stop treatment for reason other than PD, PET-CT scan, CT scan, or MRI scan should be performed every 12 weeks or if new symptoms suggest PD.

g. Chemistry will consist of albumin, ALT, alkaline phosphatase, AST, HCO_3^- or CO_2, blood urea nitrogen, calcium, chloride, potassium, sodium, phosphate, creatinine, total bilirubin, LDH, urate, blood glucose (nonfasting), and standard C-reactive protein. Thyroid function tests (thyroid stimulating hormone, free

or total T3, and free or total T4) will also be performed. Serum β2 microglobulin levels will be measured at baseline only. It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 4 days old. Hepatitis B serology (hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody) and hepatitis C serology will be performed at screening. Patients with known chronic hepatitis C and/or positive serology (unless due to vaccination or passive immunization due to Ig therapy) for chronic hepatitis B are excluded.

h. Hematology will consist of hemoglobin, hematocrit, platelet count, WBC count, and WBC differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils). It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 4 days old.

i. Urinalysis (dipstick) will include bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, pH, protein, specific gravity, turbidity and color, and urobilinogen. Microscopic if clinically indicated only: bacteria, RBCs, WBCs, casts, and crystals.

j. Pregnancy test (refer to Section 9.3.9.2).
   - Screening/Baseline: Participants of childbearing potential must have 2 negative pregnancy tests before starting study drug.
     - A urine or serum pregnancy test will be required during screening (within 10 to 14 days before start of study drug); this test must be negative.
     - A urine or serum pregnancy test must be performed at baseline (within 24 hours before the start of study drug). The results from these tests must be available and negative before the first dose of study drug is administered.
   - On-treatment: During the study, participants of childbearing potential must have a negative urine or serum pregnancy test result within 72 hours before dosing on Day 1 of each cycle during treatment prior to dosing. If a menstrual period is delayed, absence of pregnancy in participants of childbearing potential must be confirmed by a negative urine or serum pregnancy test.
     - Pregnancy tests may also be repeated during the study as per request of IRB or if required by local regulations.
   - EOT: A urine or serum pregnancy test is required at EOT in participants of childbearing potential.

k. To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

l. Urine M-protein 24-hour urine sample required while on treatment and during follow-up only if urine M-protein is measurable at baseline (urine M-protein ≥200 mg/24 hours).

m. Immunofixation of serum and/or urine may be omitted at screening if a previous local laboratory report for the serum and/or urine protein electrophoresis states that the observed monoclonal spike is consistent with one previously characterized by immunofixation and specifies the heavy chain and light chain previously identified. Immunofixation in serum and urine is required for patients evaluated for CR.

n. A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained. For the rare patient with known IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points throughout the treatment period and PFS follow-up period as quantitative Igs (in addition to quantitative IgM, IgG, and IgA).

o. All responses, including PD, must be confirmed by central laboratory evaluation. If the start of a cycle is delayed, serum M-protein and serum FLCs are to be collected for central laboratory analysis if not previously sent within the preceding 10 days. If a patient has collected a 24-hour urine sample and brought it to a visit, the sample should be sent for central laboratory analysis of urine M-protein even if not on Day 1 of a cycle.

p. See Appendix B for details.

q. Blood samples for PK will be collected at time points specified in Appendix C.

r. Immunoprofiling consists of flow cytometric analysis of T, B, and NK lymphocyte subsets, and will be analyzed centrally.

s. Predose.

t. Predose and at 8 hours after the start of infusion.

u. Blood samples for immunogenicity (ADA and NAb) testing will be collected before the dose on indicated visits while the patient remains in treatment and, if

possible, at the EOT follow-up visit. In case of an infusion reaction, blood draws should be performed for central evaluation of immunogenicity (see Section 8.7.1.1).

v. One blood sample for DNA will be taken at either screening or C1D1 predose (when it is not possible to collect at screening, samples can be collected at the next visit).

w. Cycle 9 Day 1 only.

x. Only repeat tests in parentheses for patients terminating treatment due to PD, if they were not performed before for PD determination at the last visit, and for patients discontinuing due to treatment completion or CR if not performed before for CR confirmation.

y. Patients who discontinue for reasons other than 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.

z. End-of-treatment laboratory assessments are to be performed prior to the patient starting a new treatment or a maximum of 30 days following the last dose.

aa. Schedule D Visits for C1D3 and C2D3 may be removed at a future time if no longer needed depending on MTD/OBD.

bb. Dexamethasone will be added to the MTD/OBD of one or more schedule(s) as additional cohort(s). Dexamethasone will be given as a once weekly oral dose of 40 mg. Patients over 75 years of age will receive a reduced dose of dexamethasone (20 mg, same schedule) (refer to Section 8.1).

cc. Antiplatelet antibodies will be collected as indicated in the Schedule of Events until the sponsor communicates to the sites that a sufficient number of samples have been obtained to stop the collection.

dd. Predose and at 4 hours (± 30 minutes) after the end of infusion.

ee. Strongly recommended for >6 mg/kg dose group only.

ff. Coagulation panel (prothrombin time/international normalized ratio, activated partial thromboplastin time, fibrinogen, D-Dimer) to be performed if clinically significant bleeding occurs.

Appendix A Table 11 Part 1 and Part 2 EOT and Follow-up

Study Period	**End of Treatment** [p, r]	**Disease Assessment**	
Visit Name	**30 (+10) days after last dose or the start of subsequent systemic anticancer therapy, whichever occurs first**	**(PFS Follow-Up)** [q]	**OS Follow-Up** [q]
Window Allowed		**Every 4±1 week**	**Every 12 weeks ±1 week**
ECOG performance status	X		
12-lead ECG [c]	X		
Physical examination [b]	X		
Vital signs [d]	X		
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 (+10) days after last dose of study drug or start of subsequent systemic anticancer therapy, whichever occurs first.		
AE reporting	Recorded from signing of the ICF through 30 (+10) days after last dose of study drug or start of subsequent systemic anticancer therapy, whichever occurs first.		
	SAEs will be reported from signing of ICF through 30 (+10) days after last dose of study drug, even if the patient starts nonprotocol therapy.	Only study drug-related SAEs will be reported	
Imaging Assessments			
Skeletal survey [e]	(X)	(X)	
CT, PET-CT, or MRI scan [e]	(X)	(X)	
Laboratory Assessments			
Serum chemistry [f]	X		
Hematology [g]	X		
Antiplatelet antibody [s]	X		
Coagulation panel [t] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.		
Urinalysis [h]	X		

Appendix A Table 11 Part 1 and Part 2 EOT and Follow-up

Study Period	**End of Treatment** [p, r]	**Disease Assessment**	
Visit Name	**30 (+10) days after last dose or the start of subsequent systemic anticancer therapy, whichever occurs first**	**(PFS Follow-Up)** [q]	**OS Follow-Up** [q]
Window Allowed		**Every 4±1 week**	**Every 12 weeks ±1 week**
Pregnancy test [i]	X		
Serum M-protein	(X)	X	
24-hour urine M-protein [j]	(X)	(X)	
Serum FLC assay	(X)	X	
Immunofixation - serum and urine [k]	(X)	X	
Quantification of Ig [l]	(X)	X	
Bone marrow aspiration/biopsy [m]	(X)	(X)	
Blood sample for flow cytometry (immunoprofiling) [n]	X		
Serum sample for circulating biomarkers	X		
Serum sample for immunogenicity (ADA) and NAb [o]	X		

ADA: antidrug antibody; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; C: cycle; CO_2: carbon dioxide; CR: complete response; CT: computed tomography; D, d: day; ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; EOT: end of treatment; FLC: free light chain; HCO_3^-: bicarbonate; ICF: informed consent form; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; OS: overall survival; PBMC: peripheral blood mononuclear cells; PD: progressive disease; PET-CT: positron emission tomography-computed tomography; PFS: progression-free survival; PK: pharmacokinetic(s); q12wk: every 12 weeks; RBC: red blood cell; SAE: serious adverse event; TBNK: T-lymphocyte, B-lymphocyte, and natural killer cells; V: visit; WB: wide beam; WBC: white blood cell.

Note: Crosses in parentheses "(X)" indicate tests are to be performed only under certain circumstances as indicated in associated footnote(s).

a. Written informed consent must be obtained before performing any protocol-specific procedure. Test results from routine clinical management are acceptable for screening if obtained within the specified time window.

b. Height will be measured only at the screening visit.

c. For all patients in the trial, 1 standard local ECG will be collected and read at screening and at the end of the infusion (+30 minutes) on the days indicated in these Schedule of Events. Triplicate ECGs will be obtained as described in these Schedule of Events and in Appendix C starting in Cohort 3 (0.1 mg/kg) or earlier if there is evidence of biological effect, read centrally. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation. When a standard single ECG is to be collected during a cycle/day that is other than on C1D1, C1D8 and C1D15, 1 standard ECG will be collected at the end of the infusion (+30 minutes) on the days indicated in this Schedule of Events, read locally.

d. Vital signs include temperature, pulse, respiratory rate, oxygen saturation, and blood pressure.

e. For patients with no previously documented extramedullary disease at screening, a complete skeletal survey, using plain x-ray or low-dose total body CT scan, will be performed at screening (if the patient has adequate imaging test(s) performed within 5 weeks of the planned first dose of study drug, they can be used as baseline evaluations and do not need to be repeated as part of screening). If there are symptoms or signs that suggest increased or new bone lesions, the skeletal survey or plain film of symptomatic sites may be repeated any time during the study and at the EOT visit. A PET-CT may be done at screening in place of a skeletal survey provided that the same modality for assessment is used throughout the study. Patients with normal skeletal survey at baseline do not need to repeat the test periodically unless bone progressive disease is clinically suspected. For patients with previously documented extramedullary disease or with suspicion of extramedullary progression, a PET-CT scan, CT scan, or MRI scan will be performed at screening (if the patient has adequate imaging test(s) performed within 5 weeks of the planned first dose of study drug, they can be used as baseline evaluations and do not need to be repeated as part of screening) and as needed for evaluation of disease. If extramedullary disease is documented at screening, then a repeat PET-CT scan, CT scan, or MRI scan should be performed every other cycle starting on Cycle 3. For posttreatment follow-up of patients with extramedullary disease who stop treatment for reason other than PD, PET-CT scan, CT scan, or MRI scan should be performed every 12 weeks or if new symptoms suggest PD.

f. Chemistry will consist of albumin, ALT, alkaline phosphatase, AST, HCO_3^- or CO_2, blood urea nitrogen, calcium, chloride, potassium, sodium, phosphate, creatinine, total bilirubin, LDH, urate, blood glucose (nonfasting), and standard C-reactive protein. Serum β2 microglobulin levels will be measured at baseline only.

g. Hematology will consist of hemoglobin, hematocrit, platelet count, WBC count, and WBC differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils). It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 4 days old.

h. Urinalysis (dipstick) will include bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, pH, protein, specific gravity, turbidity and color, and urobilinogen. Microscopic if clinically indicated only: bacteria, RBCs, WBCs, casts, and crystals.

i. Pregnancy test (refer to Section 9.3.9.2). A urine or serum pregnancy test is required at EOT in women of childbearing potential. If menstrual period is delayed, absence of pregnancy in women of childbearing potential must be confirmed by serum pregnancy test.

j. Urine M-protein 24-hour urine sample required while on treatment and during follow-up only if urine M-protein is measurable at baseline (urine M-protein ≥200 mg/24 hours).

k. Immunofixation of serum and/or urine may be omitted at screening if a previous local laboratory report for the serum and/or urine protein electrophoresis states that the observed monoclonal spike is consistent with one previously characterized by immunofixation and specifies the heavy chain and light chain previously identified. Immunofixation in serum and urine is required for patients evaluated for CR.

l. A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained. For the rare patient with known IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points throughout the treatment period and PFS follow-up period as quantitative Igs (in addition to quantitative IgM, IgG, and IgA).

m. See Appendix B for details.

n. Immunoprofiling consists of flow cytometric analysis of T, B, and NK lymphocyte subsets and will be analyzed centrally.

o. Blood samples for immunogenicity (ADA and NAb) testing will be collected, if possible, at the EOT follow-up visit.

p. Only repeat tests in parentheses for patients terminating treatment due to PD, if they were not performed before for PD determination at the last visit, and for patients discontinuing due to treatment completion or CR if not performed before for CR confirmation.

q. Patients who discontinue for reasons other than 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.

r. End-of-treatment laboratory assessments are to be performed prior to the patient starting a new treatment or a maximum of 30 days following the last dose.
s. Antiplatelet antibodies will be collected and analyzed locally until the sponsor communicates to the sites that a sufficient number of samples have been obtained to stop the collection.
t. Coagulation panel (prothrombin time/international normalized ratio, activated partial thromboplastin time, fibrinogen, D-Dimer) to be performed if clinically significant bleeding occurs.

Appendix A Table 12 Part 3 Extension Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**					**Treatment Phase – Cycle 2**				
Cycle Day		**C1D1**	**C1D2**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D2**	**C2D8**	**C2D15**	**C2D22**
Window Allowed	**≤21**	**0**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±0 d**	**±2 d**	**±2 d**	**±2 d**
Informed consent [a]	X										
Eligibility criteria	X										
Demographics	X										
Medical history	X										
Prior medication and treatment history	X										
Height and weight [b]	X						X				
ECOG performance status	X						X				
12-lead ECG [c]	X	X		X	X		X				
Physical examination (may be symptom-directed following screening visit)	X	X		X			X				
Vital signs [d]	X	X		X	X	X	X		X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or start of subsequent anticancer therapy, whichever occurs first.										
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or start of subsequent anticancer therapy, whichever occurs first.										
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.										
Dosing											
Modakafusp alfa infusion [f]		X					X				
Safety Laboratory Assessments											
Chemistry [i] *(central analysis)*	X	(X)		X	X	X	X		X	X	X
Hematology [g] *(central analysis)*	X	(X)		X	X	X	X		X	X	X
Thyroid function tests [i] *(local analysis)*	X										
Urinalysis [k] *(local analysis)*	X						X				
Pregnancy test [l] *(local analysis)*	X	X					X				

Appendix A Table 12 Part 3 Extension Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**					**Treatment Phase – Cycle 2**				
Cycle Day		**C1D1**	**C1D2**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D2**	**C2D8**	**C2D15**	**C2D22**
Window Allowed	**≤21**	**0**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±0 d**	**±2 d**	**±2 d**	**±2 d**
Serology [j] *(local analysis)*	(X)										
Coagulation panel [x] *(local analysis)*	To be undertaken if clinically significant bleeding is observed.										
Disease Assessments											
Serum M-protein [m, n] (central analysis)	X	(X) [n]					X				
24-hour urine M-protein [o, p] *(central analysis)*	X	(X) [o, p]					X [o, p]				
Serum FLC assay *(central analysis)* [m, q]	X	(X) [q]					X				
Immunofixation - serum and urine [r] *(central analysis)*	X	(X) [r]					X				
Serum sample for interference testing [kk] *(central analysis)*							(X)				
Quantification of Ig *(central analysis)* [s]	X	(X) [s]					X				
BMA for disease assessment *(local analysis)* [t, ii]	X	Sample to be collected at suspected CR to confirm response (CR/sCR); optional at the time of progression.									
BMA for cytogenetics *(central analysis)* [v, gg, ii, jj]	X										
BMA for MRD *(central analysis)* [ff]	X	Sample to be collected at suspected CR and every 6 months thereafter for patients in CR.									
Investigator assessment of disease response/status							X				
Imaging Assessments											
Bone imaging [g]	X	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD).									
Extramedullary disease imaging [h]	X	Additional assessments for extramedullary disease per the imaging schedule (Section 9.3.10.1).									
Clinical assessment of imaging response/status [e, g, h]		X									
Biologic Assessments *(central analysis)*											
Fresh bone marrow aspirate sample [ll]		Optional sample to be collected at progression after response. [hh]									
Serum sample for modakafusp alfa PK [u]		X	X [o]	X	X		X	X [o]	X	X	
Serum sample for circulating biomarkers [f]		X [dd]	X [o]	X	X		X [dd]	X [o]	X		

Appendix A Table 12 Part 3 Extension Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2

Study Period	Screening	Treatment Phase – Cycle 1					Treatment Phase – Cycle 2				
Cycle Day		C1D1	C1D2	C1D8	C1D15	C1D22	C2D1	C2D2	C2D8	C2D15	C2D22
Window Allowed	≤21	0	0	±2 d	±2 d	±2 d	±2 d	±0 d	±2 d	±2 d	±2 d
Serum sample for immunogenicity (ADA/NAb) [y]		X			X		X			X	
Blood sample for RNA [hh]		X [dd]	X [o]				X [dd]	X [o]			
Blood sample for receptor sequencing [hh]		X [w]			X		X [w]				
Plasma for ctDNA [hh]	X										
Buccal epithelial cells sample for DNA [hh]	X										
PRO and Healthcare Resource Utilization Assessments											
EORTC QLQ-MY20 [ee]		X		X					X		
EQ-5D-5L [ee]		X							X		
Healthcare resource utilization data [ee]		X									

Appendix A Table 13 Part 3 Extension Schedule of Events, Continued: Cycle 3 through EOT and FU

Study Period	**Treatment Phase**												**FU**	
Cycle Day	**C3 D1**	**C4 D1**	**C5 D1**	**C5 D2**	**C6 D1**	**C7 D1**	**C8D1 to C10D1**	**C11 D1**	**C11 D2**	**C12 D1**	**C13 D1+**	**EOT** 30 (+10) days after last dose or the start of subsequent systemic anticancer therapy, whichever occurs first [aa]	**PFS** every 4±1 weeks [bb]	**OS** Every 12 weeks ±1week [cc]
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±0 d**	**±2 d**	**±4 d**	**±4 d**	**±4 d**	**±0 d**	**±4 d**	**±4 d**			
Weight	X	X	X		X	X	X	X		X	X			
ECOG performance status	X	X	X		X	X	X	X		X	X	X		
12-lead ECG [c]												X		
Physical examination (may be symptom-directed)	X	X	X		X	X	X	X		X	X	X		
Vital signs [d]	X	X	X		X	X	X	X		X	X	X		
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first													
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first													
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy													
Dosing														
Modakafusp alfa infusion [f]	X	X	X		X	X	X	X		X	X			
Imaging Assessments														
Bone imaging [g]	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD).													
Extramedullary disease imaging [h]	Additional assessments for extramedullary disease per the imaging schedule (Section 9.3.10.1).													

Appendix A Table 13 Part 3 Extension Schedule of Events, Continued: Cycle 3 through EOT and FU

Study Period	**Treatment Phase**												**FU**	
Cycle Day	**C3 D1**	**C4 D1**	**C5 D1**	**C5 D2**	**C6 D1**	**C7 D1**	**C8D1 to C10D1**	**C11 D1**	**C11 D2**	**C12 D1**	**C13 D1+**	**EOT** 30 (+10) days after last dose or the start of subsequent systemic anticancer therapy, whichever occurs first [aa]	**PFS** every 4±1 weeks [bb]	**OS** Every 12 weeks ±1week [cc]
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±0 d**	**±2 d**	**±4 d**	**±4 d**	**±4 d**	**±0 d**	**±4 d**	**±4 d**			
Clinical assessment of imaging response/status [e, g, h]	Additional assessments to be done per the imaging schedule Section 9.3.10.													
Safety Laboratory Assessments														
Chemistry [i] *(central analysis)*	X	X	X		X	X	X	X		X	X	X		
Hematology *(central analysis)*	X	X	X		X	X	X	X		X	X	X		
Serology [j] *(local analysis)*														
Urinalysis [k] *(local analysis)*	X	X	X		X	X	X	X		X	X	X		
Pregnancy test [l] *(local analysis)*	X	X	X		X	X	X	X		X	X	X		
Thyroid function tests [i] (local analysis)	X				X		(X)			X	(X)			
Coagulation panel *(local analysis)* [x]	To be undertaken if clinically significant bleeding is observed.													
Disease Assessments														
Serum M-protein [m] *(central analysis)*	X	X	X		X	X	X	X		X	X	(X) [z]	X	
24-hour urine M-protein [o, p] *(central analysis)*	X	X	X		X	X	X	X		X	X	(X) [z]	X	

Appendix A Table 13 Part 3 Extension Schedule of Events, Continued: Cycle 3 through EOT and FU

Study Period	**Treatment Phase**												**FU**	
Cycle Day	**C3 D1**	**C4 D1**	**C5 D1**	**C5 D2**	**C6 D1**	**C7 D1**	**C8D1 to C10D1**	**C11 D1**	**C11 D2**	**C12 D1**	**C13 D1+**	**EOT** 30 (+10) days after last dose or the start of subsequent systemic anticancer therapy, whichever occurs first [aa]	**PFS** every 4±1 weeks [bb]	**OS** Every 12 weeks ±1week [cc]
Window Allowed	±2 d	±2 d	±2 d	±0 d	±2 d	±4 d	±4 d	±4 d	±0 d	±4 d	±4 d			
Serum FLC assay *(central analysis)* [m, q]	X	X	X		X	X	X	X		X	X	(X) [z]	X	
Immunofixation - serum & urine [r] *(central analysis)*	X	X	X		X	X	X	X		X	X	(X) [z]	X	
Serum sample for interference testing [kk] *(central analysis)*	(X)	(X)	(X)		(X)	(X)						(X) [z]	(X)	
Quantification of Ig [s] *(central analysis)*	X	X	X		X	X	X	X		X	X	(X) [z]	X	
BMA for disease assessment [t, ii] *(local analysis)*	Sample to be collected at suspected CR to confirm response (CR/sCR); optional at the time of progression.													
BMA for MRD *(central analysis)* [ff]	Sample to be collected at suspected CR and every 6 months thereafter for patients in CR.													
Investigator assessment of disease/response status	X	X	X		X	X	X	X	X	X	X	X	X	
Subsequent therapies/disease status														X
Biologic Assessments *(central analysis)*														
Serum sample for modakafusp alfa PK [u]	X	X	X	X °	X	X	X	X	X °	X	X	X		
Fresh BMA [ii]	Optional sample to be collected at progression after response. [hh]													

Appendix A Table 13 Part 3 Extension Schedule of Events, Continued: Cycle 3 through EOT and FU

Study Period	**Treatment Phase**												**FU**	
Cycle Day	**C3 D1**	**C4 D1**	**C5 D1**	**C5 D2**	**C6 D1**	**C7 D1**	**C8D1 to C10D1**	**C11 D1**	**C11 D2**	**C12 D1**	**C13 D1+**	**EOT** 30 (+10) days after last dose or the start of subsequent systemic anticancer therapy, whichever occurs first [aa]	**PFS** every 4±1 weeks [bb]	**OS** Every 12 weeks ±1week [cc]
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±0 d**	**±2 d**	**±4 d**	**±4 d**	**±4 d**	**±0 d**	**±4 d**	**±4 d**			
Serum sample for circulating biomarkers [f]			X [dd]	X [o]				X [dd]	X [o]			X		
Serum sample for immunogenicity (ADA/NAb) [f, y]	X	X	X		X	X	X	X		X	X	X	X	
Blood sample for RNA [hh]			X [dd]	X [o]				X [dd]	X [o]					
Blood sample for receptor sequencing [w, hh]	X		X			X		X						
Plasma sample for ctDNA [w, hh]			X					X						
PRO and Healthcare Resource Utilization Assessments														
EORTC QLQ-MY20 [ee]	At Cycle 2 and beyond, PROs data are collected on Day 8											X		
EQ-5D-5L [ee]	At Cycle 2 and beyond, PROs data are collected on Day 8.											X		
Healthcare resource utilization data [ee]	Day 1 of every cycle.											X		

ADA: antidrug antibody; AE: adverse event; ALT: alanine aminotransferase; anti-HBs: antibodies to hepatitis B surface antigen; AST: aspartate aminotransferase; BMA: bone marrow aspiration; C: cycle; CO2: carbon dioxide; CR: complete response; CT: computed tomography; D, d: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer QLQ Questionnaire Multiple Myeloma Module; EOT: end of treatment; EQ-5D-5L: EuroQoL-5 Dimensions-5 Levels; FLC: free light chain; FU: follow-up; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCO3-: bicarbonate; ICF: informed consent form; LDH: lactate dehydrogenase; MRD: minimal residual disease; MRI: magnetic resonance imaging; PBMC: peripheral blood mononuclear cells; PCR: polymerase chain reaction; PD: progressive disease; PET-CT:

positron emission tomography-computed tomography; PFS: progression-free survival; PK: pharmacokinetic(s); PRO: patient-reported outcome; q12wk: every 12 weeks; SAE: serious adverse event; TBNK: T-lymphocyte, B-lymphocyte, and natural killer cells; V: visit; WBC: white blood cell.

Note: Crosses in parentheses "(X)" indicate tests are to be performed only under certain circumstances as indicated in associated footnote(s).

a. Written informed consent must be obtained before performing any protocol-specific procedure. Test results from routine clinical management are acceptable for screening if obtained within the specified time window.
b. Height will be measured only at the screening visit.
c. All patients will have 1 standard local ECG collected and read locally at screening and at the end of the infusion (+30 minutes) on the days indicated.
d. Vital signs measured before starting the infusion and after the completion of the infusion. Vital signs include temperature, pulse, respiratory rate, oxygen saturation, and blood pressure. Blood pressure will be measured every 30 minutes (±5 minutes) during the first 4 infusions, after the end of the infusion, and at any time a patient complains of symptoms consistent with IRR.
e. Clinical imaging assessments to summarize status of known lesions should be based on available imaging at each respective time point.
f. In case of an IRR, the following samples should be collected: serum sample for circulating biomarkers and serum sample for immunogenicity. Any decrease in infusion duration must be discussed with and agreed upon by the sponsor. If a patient presents with an IRR at any dose level, the duration of the infusion may be extended per investigator's discretion. Total time from modakafusp alfa dosing solution preparation until end of infusion must not exceed 7 hours. Infusion and pharmacy staff are advised to be prepared accordingly for either a planned, extended infusion time or for potential infusion interruptions. See Pharmacy Manual for additional guidance.
g. Imaging to assess bone disease is required for all patients at screening. Imaging performed within 5 weeks of the planned first dose of study drug can be used as baseline evaluations and does not need to be repeated as part of screening. Low-dose whole-body CT is recommended over conventional skeletal survey for the evaluation of multiple myeloma bone disease. Conventional skeletal survey can be used for the diagnosis of multiple myeloma when whole-body CT or other novel imaging methods are not available. Additional assessments for bone disease can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions PD). The same modality for assessment should be used throughout the study.
h. Imaging to assess extramedullary disease is required for all patients at screening by PET-CT, MRI, or CT. Imaging performed within 5 weeks of the planned first dose of study drug can be used as baseline evaluations and does not need to be repeated as part of screening. If extramedullary disease is documented at screening, repeat imaging using the same modality every 3 cycles until a plateau or complete response is reached, or as clinically indicated, and then at suspected progression. Imaging tests for patients with extramedullary disease should be performed if new symptoms suggest PD.
i. Local laboratory results may be used for dosing decisions; however, all samples (other than thyroid function tests) must still be sent to the central laboratory until the occurrence of progression, death, the start of subsequent systemic antineoplastic therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first. Chemistry will consist of albumin, ALT, alkaline phosphatase, AST, HCO_3^- or CO_2, blood urea nitrogen, calcium, chloride, magnesium, potassium, sodium, phosphate, creatinine, total bilirubin, LDH, urate, blood glucose (nonfasting), and standard C-reactive protein and may be collected up to 3 days prior to dosing. Thyroid function tests (thyroid stimulating hormone, free or total T3, and free or total T4) will be performed during screening, Cycle 3, and every 3 cycles thereafter and will be analyzed locally. Serum β2 microglobulin levels will be measured at screening only and must be done by central laboratory (see Section 9.3.9.6 for further details on chemistry evaluations) It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 3 days old.
j. As required by country regulations, hepatitis B serology (HBsAg, hepatitis B core antibody, hepatitis B surface antibody) and hepatitis C serology will be performed at screening. Patients with known chronic hepatitis C and/or positive serology (unless due to vaccination or passive immunization due to Ig therapy) for chronic hepatitis B are excluded. Patients who are seropositive for hepatitis B (defined as a positive test for HBsAg) are excluded. Patients with

resolved infection (that is, participants who are HBsAg negative but positive for antibodies to hepatitis B core antigen and/or anti-HBs) must be screened using real-time PCR measurement of HBV DNA levels. Those who are PCR positive will be excluded. *Exception*: Patients with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.

k. Urinalysis (dipstick) includes bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, pH, protein, specific gravity, turbidity and color, and urobilinogen. Microscopic analysis only if clinically indicated: bacteria, RBCs, WBCs, casts, and crystals.

l. Pregnancy test (refer to Section 9.3.9.2).
Screening/baseline: Participants of childbearing potential must have 2 negative pregnancy tests before starting study drug.
- A urine or serum pregnancy test will be required during screening (within 10 to 14 days before start of study drug); this test must be negative.
- A urine or serum pregnancy test must be performed at baseline (within 24 hours before the start of study drug). The results from these tests must be available and negative before the first dose of study drug is administered.

On-treatment: During the study, participants of childbearing potential must have a negative urine or serum pregnancy test result within 72 hours before dosing on Day 1 of each cycle during treatment prior to dosing.
- If a menstrual period is delayed, absence of pregnancy in participants of childbearing potential must be confirmed by a negative urine or serum pregnancy test.
- Pregnancy tests may also be repeated during the study as per request of IRB or if required by local regulations.

EOT: At EOT, a urine or serum pregnancy test is required in participants of childbearing potential.

m. All responses, including PD, must be confirmed by central laboratory evaluation. If the start of a cycle is delayed, serum M-protein and serum FLCs are to be collected for central laboratory analysis if not previously sent within the preceding 10 days. If a patient has collected a 24-hour urine sample and brought it to a visit, the sample should be sent for central laboratory analysis of urine M-protein even if not on Day 1 of a cycle.

n. Screening levels for Part 3 must be ≥500 mg/dL. To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

o. Sample to be collected at any time on Day 2 of the cycle.

p. Urine M-protein 24-hour urine sample required while on treatment and during follow-up. To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

q. Serum FLC to be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

r. Immunofixation in serum and urine is required for patients evaluated for CR; see Sections 9.3.10.6. To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

s. A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained. For the rare patient with known IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points throughout the treatment period and PFS follow-up period as quantitative Igs (in addition to quantitative IgM, IgG, and IgA) (see Section 9.3.10.3). To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

t. For local analysis of disease assessment and cytogenetics at screening, a standard BMA drawn before consent is acceptable provided this is collected within 5 weeks of the first dose. All patients should also have a sample from screening sent for central cytogenetic analysis ("BMA for cytogenetics").

u. Blood samples for PK will be collected at time points specified in Appendix C, Tables 9 and 10.

v. All patients should have a fresh BMA sample from screening sent for central cytogenetic analysis.

w. Predose.

x. Coagulation panel (prothrombin time/international normalized ratio, activated partial thromboplastin time, fibrinogen, D-Dimer) to be performed if clinically

significant bleeding occurs.

y. Blood samples for immunogenicity (ADA/NAb) testing will be collected before the dose on indicated visits during treatment and, if possible, at the EOT visit. In case of an infusion reaction, blood draws should be performed for central evaluation of immunogenicity (see Section 8.7.1.1). On days when dosing is not required, samples may be collected at any point during the clinic visit.

z. Only repeat tests in parentheses for patients terminating treatment due to PD if they were not performed before for PD determination at the last visit, and for patients in CR if not performed before for CR confirmation.

aa. End-of-treatment laboratory assessments are to be performed prior to the patient starting a new treatment or a maximum of 30 days following the last dose.

bb. Patients will have 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.

cc. OS follow-up continues every 12 weeks until death, study termination, or patient withdrawal.

dd. Predose and at 4 hours (± 60 minutes) after the end of infusion.

ee. All PROs should be administered D8 of each cycle, except for C1 when the EORTC QLQ-MY20 should be administered on D1 and D8 (ie, C1D1 and C1D8) and the EQ-5D-5L on D1 (ie, C1D1). On C1D1, PROs may be completed within a +1-day window, and on the rest of the days PROs may be completed within a 2-day window. On days when PROs are administered during clinic visits, the EORTC QLQ-MY20 and EQ-5D-5L should be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures being performed (see Section 9.3.12). On days when PROs are not completed at the clinic (ie, Day 8 of each cycle starting with Cycle 3), site staff should remind each patient at every cycle to complete their PROs. Healthcare utilization data is collected on D1 of every cycle, starting at C1, and at EOT.

ff. Immediately following the bone marrow aspiration/biopsy obtained for local disease assessment at screening and for confirmation of a suspected CR, BMA will be collected for evaluation of minimal residual disease and sent to a central laboratory for analysis. If a BMA/biopsy drawn before consent, within 5 weeks of first dose, is used for local disease assessment at screening, the first BMA pull will be drawn for the MRD sample. Additionally, BMAs will be requested for MRD assessment every 6 months after suspected CR to further characterize MRD status. Screening MRD samples will be obtained in China based on acceptability of method chosen.

gg. Following the collection of BMA for MRD sample at screening, an additional 3 mL pull of BMA will be collected for cytogenetic analysis and central evaluation of both tumor and immune fractions of bone marrow.

hh. Sample collection not applicable to patients enrolled in China. See Sections 9.3.11.3.2.6, 9.3.11.3.2.7 and 9.3.11.4.

ii. Cytogenetic results from samples taken within 5 weeks prior to first dose are acceptable for stratification. If a previous result is not available and the patient is known to have high-risk disease [ie, del17, t(4;14) and/or t(14;16)] from prior cytogenetic testing, regardless of timing, they should be stratified as high risk for the purpose of enrollment. Additionally, all patients should have a sample from screening sent for central cytogenetic analysis ("BMA for cytogenetics").

jj. A portion of this sample will be used for exploratory analyses.

kk. See Section 9.3.10.7 for details regarding interference testing for patients who received an IgG MAb as recent prior therapy.

ll. For patients who have had a response to modakafusp alfa treatment, a 3mL BMA collection at progression is optional. Sample to be used for central evaluation of both tumor and immune fractions of the bone marrow to inform potential resistance mechanisms.

Appendix B Bone Marrow Collection and Assessment Schedules (Part 1 and Part 2)

Appendix B Table 1 Part 1 Schedules A, B (Q2W), and D (Q4W) and Part 2 Bone Marrow Collection and Assessment Schedule

Study Period	**Screening**	**Treatment Phase**		**Follow-up**		
Cycle Day (Schedules A, B/Schedule D)		**C1D16 / C1D15**	**C3D2**	**EOT**	**PFS Follow-up**	
Window Allowed	**≤21 d**	**±2 d**	**±2 d**	**30 (+10) days after last dose of study drug or the start of subsequent systemic anticancer therapy, whichever occurs first**	**Every 4 weeks ±1 week**	**Suspected CR**
Bone marrow aspiration/biopsy for disease assessment and bone marrow morphology (*local analysis*) [a, e]	X [d]	X	X	(X)	(X)	X
Bone marrow aspiration/biopsy for cytogenetics (*local analysis*) [a]	X [d]					
Fresh bone marrow aspiration sample for pharmacodynamics (*central analysis*) [b]	X	X	X	X [c]		
Fresh BMA sample for RNA (*central analysis*) [b]	X	X	X	X [c]		
Fresh bone marrow aspiration to assess minimal residual disease (*central analysis*) [a]	X					X

BMA: bone marrow aspirate; CR: complete response; EOT: end of treatment; PFS: progression-free survival; Q2W: once every 2 weeks; Q4W: once every 4 weeks.
Footnotes are below Appendix C.

Appendix B Table 2 Part 1 Schedule C (Q3W): Bone Marrow Collection and Assessment Schedule

Study Period	Screening	Treatment Phase		Follow-up		
Visit Number/Name	V1	V8	V19	EOT	PFS Follow-up	Suspected CR
Cycle Day		C2D2	C4D2			
Window Allowed	≤21 d	±2 d	±2 d	30 (+10) days after last dose or the start of subsequent systemic anticancer therapy, whichever occurs first	Every 4 Weeks ±1 weeks	
Bone marrow aspiration/biopsy for disease assessment and bone marrow morphology (*local analysis*) [a, e]	X [d]	X	X	(X)	(X)	X
Bone marrow aspiration/biopsy for cytogenetics (*local analysis*) [a]	X [d]					
Fresh bone marrow aspiration sample for pharmacodynamics (*central analysis*) [b]	X	X	X	X [c]		
Fresh BMA sample for RNA (*central analysis*) [b]	X	X	X	X [c]		
Fresh bone marrow aspiration to assess minimal residual disease (*central analysis*) [a]	X					X

BMA: bone marrow aspirate; CR: complete response; CxDx: Cycle x Day x; EOT: end of treatment; MRD: minimal residual disease; PFS: progression-free survival; Q3W: once every 3 weeks; RNA: ribonucleic acid; V: visit.

a. In addition to the BMA/biopsy that will be obtained for local disease assessment at screening and confirmation of a suspected CR, BMA will be collected at screening and at suspected CR for evaluation of MRD (1st or 2nd pull preferred) and sent to a central laboratory for analysis.

b. A BMA (1st or 2nd pull preferred) will be obtained at screening to establish a baseline for the pharmacodynamic assessments of the tumor microenvironment. Additionally, BMAs (1st or 2nd pull preferred) will be collected at 2 postdose time points based on the schedule for which the subject is enrolled for longitudinal pharmacodynamic assessment of modulation in comparison to the baseline values. These samples will be divided into 2 samples at the site and sent for central analysis: 1) 1 for CD38 receptor occupancy and density, immunoprofiling, and diversity of T-cell receptor repertoire (fresh BMA for pharmacodynamics) and 2) 1 for preservation of RNA (fresh BMA for RNA).

c. It is highly encouraged (optional) to perform a bone aspiration procedure for pharmacodynamic and RNA assessment of patients who have PD following a response to treatment at time of PD confirmation, at the EOT visit, or before starting a new therapy.

d. For local analysis of disease assessment and cytogenetics at screening, a standard BMA and biopsy drawn before consent is acceptable provided this is collected within 5 weeks of the first dose.

e. A subset of patients will have BMA collected for local pathology review to assess plasma cell count and morphology of bone marrow precursor cells at screening and at the time of on-treatment BMA collections for the corresponding Schedule B, C or D (Bone Marrow Morphology).

Appendix C PK Sampling Schedules

Appendix C Table 1 Part 1 Schedule A PK Sampling: Cycle 1

	Cycle 1								
	Day 1 [a] Into Day 2		Day 4	Day 8	Day 15		Day 16	Day 18	Day 22 [a]
Time Points	Triplicate ECG [b]	PK	PK	PK	Triplicate ECG [b]	PK	PK	PK	PK
Predose (within 1 hour before infusion)	X [c]	X		X	X	X			X
1 hour after start of infusion (±10 min)	X	X			X	X			
2 hours after start of infusion (±20 min)	X	X			X	X			
4 hours after start of infusion (±30 min)	X [d]	X		X	X [d]	X			X
6 hours after start of infusion (±30 min)	X	X			X	X			
8 hours after start of infusion (±30 min)	X	X			X	X			
24 hours after start of infusion (±1 hour)	X	X			X		X		
72 hours after start of infusion (±1 hour)			X					X	

ECG: electrocardiogram; PK: pharmacokinetic.

Note: When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements will be collected using sponsor provided Holter equipment and should be completed immediately before the corresponding PK blood draw. Triplicate ECGs for initial heart rate-corrected QT interval evaluation will be recorded and electronically stored during Cycle 1 at prespecified time points starting in Cohort 3 (0.1 mg/kg) or earlier if there is evidence of biological effect.

a. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous days of the cycle.

b. Collection of triplicate ECG begins after patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs occurs within 3 minutes of each other and over a 10-minute window. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation. On Days 1 and 15, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours prior to collection of the pre-dose ECGs until after collection of the 4-hour after start of infusion ECGs. Immediately following the 4-hour ECG and PK collection, patients will be administered a light meal, following which they will again abstain from eating until collection of the 8-hour ECG sample. On Day 2, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours prior to collection of the 24-hour and 72-hour after start of infusion ECGs until after collection of the ECGs on those days. In patients unable to comply with these recommendations, any food intake should be limited to the smallest required portion of bland food.

c. Collection of triplicate ECG must occur prior to any drug infusion.

d. Collection of the triplicate ECG at 4 hours post start of infusion should be completed prior to turning off the infusion pump.

Appendix C Table 2 Part 1 Schedule A PK Sampling: Cycle 2

Time Points	Cycle 2					
	Day 1 [a]	**Day 2**	**Day 4**	**Day 8 [a]**	**Day 15 [a]**	**Day 22 [a]**
Predose (within 1 hour before infusion)	X			X	X	X
1 hour after start of infusion (±10 min)	X					
2 hours after start of infusion (±20 min)	X					
4 hours after start of infusion (±30 min)	X			X	X	X
6 hours after start of infusion (±30 min)	X					
8 hours after start of infusion (±30 min)	X					
24 hours after start of infusion (±1 hour)		X				
72 hours after start of infusion (±1 hour)			X			

ECG: electrocardiogram; PK: pharmacokinetic.

Note: When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

[a.] The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous days of the cycle.

Appendix C Table 3 Part 1 Schedule A PK Sampling: Cycle 3 to Cycle 13

Time Points	Cycle 3			Cycle 4 to Cycle 6		Cycles 7-13
	Day 1 [a]	Day 2	Day 15 [a]	Day 1 [a]	Day 15	Day 1 [a]
Predose (within 1 hour before infusion)	X		X	X	X	X
4 hours after start of infusion (±30 min)	X		X	X	X	X
24 hours after end of infusion (±1 hour)		X				

ECG: electrocardiogram; PK: pharmacokinetic.

Note: When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

[a.] Modakafusp alfa infusion. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous days of the cycle.

Appendix C Table 4 Part 1 Schedule B (Q2W) PK Sampling: Cycle 1 and Cycle 2

	Day 1 [a]		Day 2 [a]		Day 15 [a]	Day 16
Time Points	**Triplicate ECG [b]**	**PK**	**Triplicate ECG [b]**	**PK**	**PK**	**PK**
Predose (within 30 min prior to start of infusion)	X [c]	X			X	
End of infusion (±5 min)	X	X			X	
1 hour after end of infusion (±10 min)	X	X			X	
2 hours after end of infusion (±20 min)	X	X			X	
4 hours after end of infusion (±30 min)	X	X			X	
6 hours after end of infusion (±30 min)	X	X			X	
24 hours after end of infusion (±1 hour)			X	X		X

ECG: electrocardiogram; PK: pharmacokinetic; Q2W; every 2 weeks.

Note: When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

a. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous days of the cycle.

b. Collection of triplicate ECG begins after patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs occur within 3 minutes of each other and over a 10-minute window. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation. On Day 1, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours prior to collection of the predose ECGs until after collection of the 2-hour after end of infusion ECGs. Immediately following the 2-hour ECG and PK collection, patients will be administered a light meal, following which they will again abstain from eating until collection of the 6-hour ECG sample. On Day 2, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours prior to collection of the ECGs until after collection of the ECGs on those days. In patients unable to comply with these recommendations, any food intake should be limited to the smallest required portion of bland food.

c. Collection of triplicate ECG must occur prior to any drug infusion.

Appendix C Table 5 Part 1 Schedule B (Q2W) PK Sampling: Cycle 3 and Beyond

Time Points	Cycle 3			Cycle 4 and Beyond	
	Day 1 [a]	Day 2	Day 15 [a]	Day 1 [a]	Day 15 [a]
Predose (within 30 min prior to start of infusion)	X		X	X	X
End of infusion (+5 min)	X		X	X	X
2 to 4 hours after end of infusion (±30 min)	X		X	X	X
24 hours after end of infusion (±1 hour)		X			

PK: pharmacokinetic; Q2W: every 2 weeks.

[a.] Modakafusp alfa infusion. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous days of the cycle.

Appendix C Table 6 Part 1 Schedule C (Q3W) PK Sampling: Cycle 1 and Cycle 2

Time Points	Cycle 1 and Cycle 2							
	Day 1 into Day 2 [a]		Day 3		Day 8 [a]		Day 15 [a]	
	Triplicate ECG [b]	PK	Triplicate ECG [b]	PK	Triplicate ECG [b]	PK	Triplicate ECG [b]	PK
Predose (within 30 min prior to start of infusion)	X [c]	X						
End of infusion (±5 min)	X	X						
1 hour after end of infusion (±15 min)	X	X						
2 hours after end of infusion (±15 min)	X	X						
4 hours after end of infusion (±30 min)	X	X						
6 hours after end of infusion (±30 min)	X	X						
24 hours after end of infusion (±1 hour)	X	X						
48 hours after end of infusion (±1 hour)			X	X				
168 hours after end of infusion (±2 hour)					X	X		
336 hours after end of infusion (±4 hour)							X	X

ECG: electrocardiogram; PK: pharmacokinetic; Q3W: once every 3 weeks.

Note: When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

a. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous days of the cycle.

b. Collection of triplicate ECG begins after patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs occur within 3 minutes of each other and over a 10-minute window. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation. On Day 1, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours prior to collection of the pre-dose ECGs until after collection of the 2-hour after end of infusion ECGs. Immediately following the 2-hour ECG and PK collection, patients will be administered a light meal, following which they will again abstain from eating until collection of the 6-hour ECG sample. On Days 2, 4, 8 and 15, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours prior to collection of the planned ECGs until after collection of the triplicate ECGs on those days. In patients unable to comply with these recommendations, any food intake should be limited to the smallest required portion of bland food.

c. Collection of triplicate ECG must occur prior to any drug infusion.

Appendix C Table 7 Part 1 Schedule C (Q3W) PK Sampling: Cycle 3 and Beyond

Timepoints	Cycle 3 and beyond
	Day 1 [a]
Predose (within 30 min prior to start of infusion)	X
End of infusion (+5 min)	X
2 to 4 hours after end of infusion (±30 min)	X

PK: pharmacokinetic; Q3W: once every 3 weeks.

a. Modakafusp alfa infusion. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous infusion visits.

Appendix C Table 8 Parts 1 and 2 Schedule D (Q4W) PK Sampling: Cycles 1 and 2

	Day 1 into Day 2 [a]		Day 3 [a]		Day 8 [a]		Day 15 [a]		Day 22 [d]
Time Points	**Triplicate ECG [b]**	**PK**	**Triplicate ECG [b]**	**PK**	**Triplicate ECG [b]**	**PK**	**Triplicate ECG [b]**	**PK**	**PK**
Predose (within 30 min prior to start of infusion)	X [c]	X							
End of infusion (±5 min)	X	X							
2 hours after end of infusion (±30 min)	X	X							
4 hours after end of infusion (±30 min)	X	X							
6 hours after end of infusion (±30 min)	X	X							
24 hours after end of infusion (±1 hour)	X	X							
48 hours after end of infusion (±1 hour)			X	X					
168 hours after end of infusion (±2 hour)					X	X			
336 hours after end of infusion (±4 hour)							X	X	
504 hours after end of infusion (± 4 hour)									X

ECG: electrocardiogram; PK: pharmacokinetic; Q4W: once every 4 weeks.
Note: When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

a. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous days of the cycle.
b. Collection of triplicate ECG begins after patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs occur within 3 minutes of each other and over a 10-minute window. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation. On Day 1, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours prior to collection of the predose ECGs until after collection of the 2-hour after end of infusion ECGs. Immediately following the 2-hour ECG and PK collection, patients will be administered a light meal, following which they will again abstain from eating until collection of the 6-hour ECG sample. On Days 2, 4, 8, and 15, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours prior to collection of the planned ECGs until after collection of the triplicate ECGs on those days. In patients unable to comply with these recommendations, any food intake should be limited to the smallest required portion of bland food.
c. Collection of triplicate ECG must occur prior to any drug infusion.
d. Strongly recommended for > 6 mg/kg dose group only.

Appendix C Table 9 Parts 1 and 2 Schedule D (Q4W) PK Sampling: Cycle 3 and Beyond

Time Points	Day 1 [a]	Day 2 [b]
Predose (within 30 min prior to start of infusion)	X	
End of infusion (±10 min)	X	
2 to 4 hours after end of infusion (±30 min)	X	
24 hours after the end of the infusion (±1 hr)		X

PK: pharmacokinetic; Q4W: every 4 weeks.

a. Mofakafusp alfa infusion. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous infusion visits.

b. Day 2 of Cycles 3, 7, and 11 only.

Appendix C Table 10 Part 3 Extension PK Sampling: Cycles 1 and 2 [a]

Timepoints	Cycle 1				Cycle 2			
	Day 1	Day 2	Day 8	Day 15	Day 1	Day 2	Day 8	Day 15
Predose (within 30 min prior to start of infusion)	X				X			
End of infusion (±10 min)	X				X			
2 to 4 hours after end of infusion (±30 min)	X				X			
During the clinic visit		X	X	X		X	X	X

PK: pharmacokinetic.

[a] Not applicable to patients enrolled in China with intensive PK schedule (Table 11), but applicable to all other patients enrolled in China.

Appendix C Table 11 Part 3 Extension PK Sampling for Chinese Patients With Intensive PK Schedule: Cycles 1 and 2

Time Points	Day 1 into Day 2 [a]	Day 3	Day 8	Day 15	Day 22
Predose (within 30 min prior to start of infusion)	X				
End of infusion (±10 min)	X				
2 hours after end of infusion (±30 min)	X				
4 hours after end of infusion (±30 min)	X				
6 hours after end of infusion (±30 min)	X				
24 hours after end of infusion (±1 hour)	X				
48 hours after end of infusion (±1 hour)		X			
168 hours after end of infusion (±2 hour)			X		
336 hours after end of infusion (±4 hour)				X	
504 hours after end of infusion (± 4 hour)					X

PK: pharmacokinetics.

Note: Intensive PK samples will be collected only in up to 8 Chinese patients enrolled in China per dose upon laboratory kit availability.

The timing of the morning visits should occur at approximately the same time as the morning dosing on previous dosing visits.

[a] Blood sample for Day 1 predose will be collected within 30 minutes before start of any drug administration.

Appendix C Table 12 Part 3 Extension PK Sampling: Cycle 3 and Beyond

Time Points	Cycle 3 and beyond		
	Day 1	Day 2 [a]	EOT
Predose (within 30 min prior to start of infusion)	X		
End of infusion (±10 min)	X		
2 to 4 hours after end of infusion (±30 min)	X		
During the clinic visit		X	X

PK: pharmacokinetic.

[a.] Day 2 of Cycles 5 and 11 only.

Appendix D Responsibilities of the Investigator

Clinical research studies Sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix E Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix F IMWG Definition of MM (Kumar et al. 2016)

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of the normal range or >2.75 mmol/L (>11 mg/dL).
- Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL).
- Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L.
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡.

Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage* ≥60%.
- Involved: uninvolved serum FLC ratio§ ≥100.
- >1 focal lesions on MRI studies.

PET-CT, [^{18}F]fluorodeoxyglucose PET with CT.
* Clonality should be established by showing κλ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
† Measured or estimated by validated equations.
‡ If bone marrow has less than 10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
§ These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, United Kingdom). The involved FLC must be ≥100 mg/L. Each focal lesion must be 5 mm or more in size.

IMWG Uniform Criteria for Response

Response Category	Response Criteria
sCR	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; 2 consecutive assessments are needed [a].
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours; in patients for whom only measurable disease is by serum FLC level, >90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; 2 consecutive assessments are needed [c].
PR	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours. If the serum and urine M-protein are not measurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided the baseline percentage was ≥30%. In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required. Two consecutive assessments are needed [a] no known evidence of progressive or new bone lesions if radiographic studies were performed.
MR[b]	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. In addition to the above criteria, if present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
SD [c]	Does not meet the response criteria for CR (any variant), VGPR, PR, MR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed.
PD	See text below.

BM: bone marrow; CR: complete response; FLC: free light chain; MR: minimal response; ORR: objective response rate; PR: partial response; PD: progression of disease; RRMM: relapsed refractory multiple myeloma; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.

[a] Clonality should be established by showing κλ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. For this

Response Category	Response Criteria

trial 2 consecutive BM assessments are not required.

[b] For RRMM only.

[c] These categories do not contribute to the ORR.

Before the institution of any new therapy, sCR, CR, and VGPR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

PD is defined as an increase of ≥25% from lowest response value in any of the following:

a) Serum M-protein (absolute increase must be ≥0.5 g/dL); serum M component increases ≥1 g/dL are sufficient to define relapse if starting M component is ≥5 g/dL), and/or

b) Urine M-protein (absolute increase must be ≥200 mg/24 hour), and/or

c) Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL).

d) Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥10%).

OR

a) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

b) Development of hypercalcemia (corrected serum calcium >11.0 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

A diagnosis of PD must be confirmed by 2 consecutive assessments.

Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M-protein and by FLC levels; “25% increase” refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia, and the “lowest response value” does not need to be a confirmed value.

Appendix G ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM et al, 1982(Oken et al. 1982).

ECOG: Eastern Cooperative Oncology Group.

Appendix H Operating Characteristics of the Futility Stopping Rules

The stopping rules used for the treatment arms of 240 mg and 120 mg at each interim futility analysis were chosen to have reasonable operating characteristics as displayed in this section (Appendix H Table 1 and Appendix H Table 2).

Based on the proposed 2 interim futility analyses criteria (Section 13.2.2.1 Part 3 Futility Stopping Rules), the design operating characteristics were calculated for each of the treatment arms under different true ORR scenarios.

Appendix H Table 1 displays the corresponding operating characteristics for the treatment arm of 240 mg, including cumulative probability of terminating the arm early at each interim analysis, average number of patients enrolled and followed up for 3 months, average number of responders observed, and probability of success (PoS) at primary analysis. As there is no plan for efficacy claim based on any of the interim analyses, the only time to claim a positive efficacy conclusion (success for each arm) will be at the primary analysis. The success criterion will be a minimal of 33 responders among 118 treated patients, achieving the goal of lower limit of 95% CI above 20% uninteresting rate.

Appendix H Table 1 Operating Characteristics for the Treatment Arm of 240 mg

True ORR	Cumulative probability of terminating the arm early at		PoS at primary analysis	Average number of patients enrolled and followed up for 3 months	Average number of observed responders
	1st IA for Futility	2nd IA for futility			
10%	82%	99%	0%	21	2
20%	40%	70%	2%	56	11
30%	13%	19%	64%	101	30
35%	6%	8%	89%	111	39
40%	3%	3%	97%	115	46
50%	<1%	<1%	100%	118	59

IA: interim analysis; ORR: objective response rate; PoS: probability of success.

As shown in Appendix H Table 1, when the true ORR is 20%, there is about 40% chance to terminate the 240 mg arm at the first interim futility analysis; about 70% chance to terminate the arm at either the first or second interim futility analysis; probability of success at primary analysis is around only 2%. When the true response rate is 35%, the cumulative probabilities of terminating the arm are reduced to 6% and 8% at the first and second interim futility analyses, the probability of success at primary analysis is 89%.

A similar operating characteristics table was created for the treatment arm of 120 mg (Appendix H Table 2).

Appendix H Table 2 Operating Characteristics for the Treatment Arm of 120 mg

True ORR	Cumulative probability of terminating the arm early at		PoS at primary analysis	Average number of patients enrolled and followed up for 3 months	Average number of observed responders
	1st IA for Futility	2nd IA for futility			
10%	55%	99%	0%	30	3
20%	17%	66%	2%	67	13
30%	4%	13%	68%	108	32
35%	1%	4%	93%	115	40
40%	1%	1%	99%	117	47
50%	<1%	<1%	100%	118	59

IA: interim analysis; ORR: objective response rate; PoS: probability of success

Similarly, as shown in Appendix H Table 2, when the true ORR is 20%, there is about 17% chance to terminate the 120 mg arm at the first interim futility analysis; about 66% chance to terminate the arm at either the first or second interim futility analysis; PoS at primary analysis is around only 2%. When the true response rate is 35%, the cumulative probabilities of terminating the arm are reduced to 1% and 4% at the first and second interim futility analyses, the probability of success at primary analysis is about 93%.

Appendix I Statistical Guidance on Unacceptable Toxicity and Treatment Related Death

The Bayesian toxicity monitoring approach based on posterior probability will be implemented to each DMC data review up to the second interim futility analysis to continuously monitor the unacceptable toxicity (particularly for Grade ≥4 nonhematologic treatment-related TEAEs) and treatment-related death within each treatment arm separately at various time points.

These toxicity monitoring rules can be translated to toxicity boundaries in terms of the number of patients with Grade ≥4 nonhematologic treatment-related TEAEs and the number of treatment related death among all patients treated for each arm at each safety review. Appendix I Table 1 illustrates the toxicity boundaries with the expected numbers of treated patients for each IDMC safety review based on our most recent enrollment projection. The actual toxicity boundaries will be recalculated based on the observed number of treated patients at each safety review using the same posterior probability stopping rule.

Appendix I Table 1 Bayesian Toxicity Monitoring Boundaries for Grade ≥4 Nonhematologic Treatment-Related TEAEs and Treatment Related-Deaths for Each Treatment Arm

Number of treated patients per arm	Unacceptable toxicity if the number of patients with Grade ≥4 nonhematologic treatment-related TEAEs	Unacceptable toxicity if the number of patients with treatment-related death
10	≥4	≥1
35 [a]	≥11	≥3
65 [a]	≥20	≥5

[a] The expected numbers of patients treated at IA1 and IA2 based on most recent enrollment projection.

Based on the toxicity boundaries presented in Appendix I Table 1, the corresponding operating characteristics for Grade ≥4 nonhematologic treatment-related TEAE monitoring for each treatment arm and the cumulative probability of early detection of unacceptable toxicity under different true toxicity rates with the expected number of patient treated at each safety review are displayed in Appendix I Table 2.

Appendix I Table 2 Operating Characteristics for Monitoring Grade ≥4 Nonhematologic Treatment-Related TEAEs Within Each Treatment Arm

True Toxicity rate	**Cumulative probability of early detection with number of treated patients**		
	10 patients	35 patients	65 patients
15%	5%	6%	6%
20%	12%	16%	17%
25%	22%	35%	39%
30%	35%	58%	67%
35%	49%	78%	88%

TEAE: treatment-emergent adverse event.

As shown in Appendix I Table 2, when the true toxicity rate is as low as 15%, there are low cumulative probabilities of 5% to 6% for early calls of unacceptable toxicity at each safety review; when the true toxicity rate is as high as 35%, there are about 49% to 88% cumulative probabilities of early call for unacceptable toxicity at each safety review. When the true DLT rate is 25% (the maximum toxicity allowed), there is about 39% cumulative probability to have an early call for unacceptable toxicity.

Similar operating characteristics table was created for monitoring of treatment-related death for each treatment arm, shown in Appendix I Table 3.

Appendix I Table 3 Operating Characteristics for Monitoring Treatment-Related Death Within Each Treatment Arm

True Toxicity rate	Cumulative probability of early detection with number of treated patients		
	10 patients	35 patients	65 patients
1%	10%	10%	10%
3%	26%	29%	30%
5%	40%	48%	52%
7%	52%	64%	71%
9%	61%	76%	85%

As shown in Appendix I Table 3, when the true treatment-related death rate is as low as 1%, there is about 10% cumulative probability of early call of unacceptable toxicity at each safety review; when the true treatment related death rate is as high as 9%, there are about 61% to 85% cumulative probabilities of early toxicity call at each safety review. When the true treatment-related death rate is 5% (the maximum toxicity allowed), there is about 52% cumulative probability to alarm the unacceptable toxicity early.

Appendix J Protocol History Including EUCTR Consolidation Table

Protocol History: Amendments Harmonized with Global Protocol Amendment 9

Date	Amendment Number	Region
26 February 2024	Amendment 10 v1 (not implemented)	Global
02 August 2023	Amendment 9	Global
10 February 2023	Amendment 8 CH v1	Local China
12 July 2022	Amendment 8 NO v1	Local Norway
23 June 2022	Amendment 8 GB v1	Local United Kingdom
01 March 2022	Amendment 8	Global
25 October 2021	Amendment 7 (not implemented)	Global
16 October 2020	Amendment 6	Global
03 July 2019	Amendment 5	Global
22 October 2018	Amendment 4	Global
29 June 2018	Amendment 3	Global
07 November 2017	Amendment 2	Global
05 April 2017	Amendment 1	Global
14 December 2016	Initial protocol	Global

Protocol History: Amendments Not Harmonized with Global Protocol Amendment 9

Country	Date of Amendment	Amendment Title
France	15 July 2022	Amendment 8 FR v1
France	12 August 2022	Amendment 8 FR v2
Germany	25 August 2022	Amendment 8 DE v1
Czech Republic	04 November 2022	Amendment 8 CZ v1
Japan	31 March 2022	Amendment JP v1
Japan	12 August 2022	Amendment JP v2
Japan	20 October 2022	Amendment JP v3

Country Specific Requirements/Differences for the European Union

(Consolidation of country-specific protocol differences approved in different member states under the Directive 2001/20/EC that will transition to the Regulation [EU] No. 536/2014)

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
France v2	8.1 Study Drug Administration Section 8.6.1 Premedications	…hospitalization is required for the first [infusion] of modakafusp alfa.	Modakafusp alfa doses of 120 and 240 mg will be administered over 1 hour (±10 minutes). **Hospitalization is required for Cycle 1 Day 1 dose administration of modakafusp alfa.**
France v1	7.2 Exclusion Criteria #12	urine or or serum	Female patients who are lactating and breastfeeding or have a positive **urine or** serum pregnancy test during the screening period or a positive urine **or serum** pregnancy test on Day 1 before first dose of study drug if applicable.
France v1	9.3.9.2 Pregnancy Test	or serum urine or For women of childbearing potential, a urine or serum pregnancy test will be performed monthly on Day 1 of each cycle during treatment prior to dosing and at the EOT visit.	A urine **or serum** pregnancy test will be used during screening (within 10 to 14 days prior to start of study drug). A **urine or** serum pregnancy test must be performed at baseline (within 24 hours prior to the start of study drug). **For women of childbearing potential, a urine or serum pregnancy test will be performed monthly on Day 1 of each cycle during treatment prior to dosing and at the EOT visit.** During the study, if menstrual period is delayed, absence of pregnancy in women of childbearing potential must be confirmed by **urine or** serum pregnancy test. Pregnancy tests may also be repeated during the study as per request of IRB or if required by local regulations. At end of treatment, a urine **or serum** pregnancy test is required in women of childbearing potential.
France v1	Appendix A Part 3 Footnote *l*	or serum urine or For women of childbearing potential, a urine or serum pregnancy test will be performed monthly on Day 1 of each cycle during treatment prior to dosing.	Pregnancy test (refer to Section 9.3.9.2). • Screening: Women of childbearing potential must have 2 negative pregnancy tests prior to starting study drug. A urine **or serum** pregnancy test will be used during screening (within 10 to 14 days prior to start of study drug). A **urine or** serum pregnancy test is required at baseline.

<table>
<tr><th colspan="4">Summary of Changes</th></tr>
<tr><th>Country</th><th>Section Number</th><th>Country Specific Language</th><th>Country Specific Language in Tracked Changes against Global Protocol Language</th></tr>
<tr><td></td><td></td><td></td><td>• On treatment: For women of childbearing potential, a urine or serum pregnancy test will be performed monthly on Day 1 of each cycle during treatment prior to dosing. If menstrual period is delayed, absence of pregnancy in women of childbearing potential must be confirmed by serum pregnancy test.
• A urine or serum pregnancy test is required at EOT in women of childbearing potential.</td></tr>
<tr><td>France v1</td><td>7.1 Inclusion Criteria #8 and #9</td><td>see Table 8.e</td><td>#7
…Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Table 8.e) at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, OR

#8…
Male patients, even if surgically sterilized (ie, status postvasectomy), who:
• Agree to practice effective barrier contraception (see Table 8.e) during the entire study treatment period and through 120 days after the last dose of study drug, OR</td></tr>
<tr><td>France v1</td><td>8.7 Precautions and Restrictions</td><td>Table 8.e Highly Effective Methods of Contraception
<table><tr><td>Highly Effective Methods

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
• Oral
• Intravaginal
• Transdermal</td><td>Additional Effective (Barrier) Methods
Male or female condom with or without spermicide (female and male condoms should not be used together)</td></tr></table></td><td>Table 8.e Highly Effective Methods of Contraception
<table><tr><td>Highly Effective Methods

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
• Oral
• Intravaginal
• Transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation
• Oral</td><td>Additional Effective (Barrier) Methods
Male or female condom with or without spermicide (female and male condoms should not be used together)</td></tr></table></td></tr>
</table>

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
		Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable • Implantable Intrauterine device Cap, diaphragm, or sponge with spermicide Intrauterine hormone-releasing system Bilateral tubal occlusion Vasectomized partner Sexual abstinence	**• Injectable** **• Implantable** **Intrauterine device Cap, diaphragm, or sponge with spermicide** **Intrauterine hormone-releasing system** **Bilateral tubal occlusion** **Vasectomized partner** **Sexual abstinence**
France v1	9.3.9.4 ECGs	before and	In Part 3, all patients will have single ECGs collected and read locally at screening, **before and** at the end of the infusion (+30 minutes), or in accordance with Appendix A.
Germany	2.0 STUDY SUMMARY 6.1 Overview of Study Design 7.0 STUDY POPULATION 8.1 Study Drug Administration 9.0 STUDY CONDUCT 6.2 Number of Patients 13.2 Interim Analyses and Criteria for Early Termination	Only the Part 3 dose-extension portion of the study will be conducted in Germany.	**Only the Part 3 dose-extension portion of the study will be conducted in Germany.**

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
Germany	7.1 Inclusion Criteria #7	or 5 half-lives, whichever is longer	Patient has received the final dose of any of the following treatments/procedures within the specified minimum intervals before the first dose of modakafusp alfa. Chemotherapy, including proteasome inhibitors and IMiDs 14 days Antibody therapy (except anti-CD38 antibody as presented in exclusion criterion #4) 21 days **or 5 half-lives, whichever is longer** Corticosteroid therapy for myeloma 7 days Radiation therapy for localized bone lesions 7 days Major surgery 21 days .
Germany	7.1 Inclusion Criteria #8	7 days	Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through ~~6 months~~**7 days** after the last dose of study drug, OR – Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent through ~~6 months~~**7 days** after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.) – Agree not to donate an egg or eggs (ova) during the study and for ~~6 months~~**7 days** after the last dose of study drug.
Germany	Inclusion Criteria #9	unless for over a year 7	Male patients, ~~even if~~**unless** surgically sterilized (ie, status postvasectomy) **for over a year**, who: • Agree to practice effective barrier contraception during the entire study treatment period and through ~~120~~**7** days after the last dose of study drug, OR • Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
			the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.) • Agree not to donate sperm during the study and for ~~120~~**7** days after the last dose of study drug.
Germany	7.2 Exclusion Criteria	14. Infection with HIV: Screening for HIV infection will be performed, and patients who have a positive result will be excluded.	**14. Infection with HIV: Screening for HIV infection will be performed, and patients who have a positive result will be excluded.**
Germany	7.2 Exclusion Criteria	15. Screening for HBV and HCV infection will be performed.	Part 3: Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. **Screening for HBV and HCV infection will be performed.**
Germany	Appendix A Part 3 SOE	..and HBV, HCV, and HIV serologies)… HBV, HCV, and HIV serologies are performed at screening only and analyzed locally.	Part 3 SOE Footnote *i* Local laboratory results may be used for dosing decisions; however, **all samples (other than thyroid function tests and HBV, HCV, and HIV serologies) must still be sent to the central laboratory** until the occurrence of progression, death, the start of subsequent systemic antineoplastic therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first. Chemistry will consist of albumin, ALT, alkaline phosphatase, AST, HCO3- or CO2, blood urea nitrogen, calcium, chloride, magnesium, potassium, sodium, phosphate, creatinine, total bilirubin, LDH, urate, blood glucose (nonfasting), and standard C-reactive protein and may be collected up to 3 days prior to dosing. Thyroid function tests (TSH, T3, T4) will be performed during screening, Cycle 3, and every 3 cycles thereafter and will be analyzed locally. **HBV, HCV, and HIV serologies are performed at screening only and analyzed locally.**
Germany	9.3.9.6 Clinical Chemistry,	In all	~~Central laboratory analysis is required for~~In Part 3~~., L~~local ~~hematology and chemistry~~

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
	Hematology, and Urinalysis	(other than thyroid function tests and HBV, HCV, and HIV serologies) until the occurrence of progression, death, the start of subsequent systemic antineoplastic therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first.	laboratory results may be used for dosing decisions; however, all samples (other than thyroid function tests and HBV, HCV, and HIV serologies) must still be sent to the central laboratory ~~as well~~ until the occurrence of progression, death, the start of subsequent systemic antineoplastic therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first.
Germany	4.5.2 Clinical Safety	must	Premedications and treatment ~~should~~ **must** be provided**,** as described in Section 8.7.1.1.
Germany	8.6.1 Premedication 5.4.1.2 Part 1 Secondary Endpoints	This amendment makes premedications mandatory, as detailed in Section 8.6.1.	~~In addition, patients receiving modakafusp alfa doses ≥6 mg/kg are treatedwith additional premedication and the dose is delivered over a longer infusion time.~~ **This amendment makes premedications mandatory, as detailed in Section 8.6.1.**
Germany	8.7.1.1 Handling of IRRs	Mandatory IV and/or oral corticosteroids, methylprednisolone, acetaminophen, and/or diphenhydramine, as well as nonsteroidal anti-inflammatory drugs and H2 blockers if indicated, should be administered according to local standards and at sufficient time before the start of the modakafusp alfa infusion to allow the premedication drugs to exert their effects. Montelukast may be given to patients who are intolerant to diphenhydramine or for whom diphenhydramine is contraindicated.	It is ~~strongly recommended~~mandatory that all patients receive premedication, including corticosteroids, before modakafusp alfa dosing. P~~atients who are receiving a modakafusp alfa dose of 6 mg/kg or higher must be premedicated with dexamethasone, acetaminophen, diphenhydramine, and montelukast.~~ IV and/or oral corticosteroids, methylprednisolone, acetaminophen, and/or diphenhydramine, as well as nonsteroidal anti-inflammatory drugs and H2 blockers if indicated, should be administered according to local standards and at sufficient time before the start of the modakafusp alfa infusion to allow the premedication drugs to exert their effects. Montelukast may be given to patients who are intolerant to diphenhydramine or for whom diphenhydramine is contraindicated. Modakafusp alfa doses <6 mg/kg will be administered over 1 hour (~~±10 minutes~~). ~~Modakafusp alfa doses ≥6 mg kg will be administered over 2 hours~~ (±10 minutes). Any decrease in infusion duration must be discussed with and agreed upon by the sponsor.

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
Germany	Appendix A Schedules of Events, Tables 12 and 13, Part 3 Extension Schedule of Events.	It is mandatory that all patients receive premedication, including corticosteroids, before modakafusp alfa dosing.	Footnote *f* **It is mandatory that all patients receive premedication, including corticosteroids, before modakafusp alfa dosing.** In case of an IRR, the following samples should be collected: serum sample for circulating biomarkers and serum sample for immunogenicity.
Germany	6.3.4.1 Closure of the Study (new section)	6.3.4.1 Closure of the Study Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Takeda, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Takeda by the terminating party. Circumstances that may warrant termination include, but are not limited to: • Determination of unexpected, significant, or unacceptable risk to patients. • Failure to enter patients at an acceptable rate. • Insufficient adherence to protocol requirements. • Insufficient, incomplete, and/or unevaluable data. • Determination of efficacy based on an IA. • Plans to modify, suspend, or discontinue the development of the study drug. Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. Any	6.3.4.1 Closure of the Study Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Takeda, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Takeda by the terminating party. Circumstances that may warrant termination include, but are not limited to: • Determination of unexpected, significant, or unacceptable risk to patients. • Failure to enter patients at an acceptable rate. • Insufficient adherence to protocol requirements. • Insufficient, incomplete, and/or unevaluable data. • Determination of efficacy based on an IA. • Plans to modify, suspend, or discontinue the development of the study drug. Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. Any devices provided to access the EDC application will be returned to Takeda once the site's participation in the study has concluded. Takeda must notify the competent authorities and IECs of any member state where the study is being conducted within 15 days of premature study closure and provide the reasons for study closure. Within 90 days of ending the study, the sponsor will notify the competent authorities and the IECs in all member states where the study was

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
		devices provided to access the EDC application will be returned to Takeda once the site's participation in the study has concluded. Takeda must notify the competent authorities and IECs of any member state where the study is being conducted within 15 days of premature study closure and provide the reasons for study closure. Within 90 days of ending the study, the sponsor will notify the competent authorities and the IECs in all member states where the study was being carried out. Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.	being carried out. Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.
Germany	8.1.1 Administration of Dexamethasone in Modakafusp Alfa Plus Dexamethasone Cohort(s)	In Part 2 expansion only,	**In Part 2 expansion only,** ~~D~~**d**examethasone will be added to the selected MTD/OBD of one or more schedule(s) as additional cohort(s).
Germany	8.1 Study Drug Administration	*Deletion only.*	~~Modakafusp alfa doses <6 mg/kg will be administered over 1 hour (±10 minutes). Modakafusp alfa doses ≥6 mg/kg will be administered over >2 hours (±10 minutes).~~ Any decrease in infusion duration must be discussed with and agreed upon by the sponsor.
Germany	8.6.1 Premedication	*Deletion only.*	Montelukast (10 mg PO) may be given to patients who are intolerant to diphenhydramine or for whom diphenhydramine is ineffective. ~~Patients who are receiving a modakafusp alfa dose of 6 mg/kg or higher must be premedicated with dexamethasone,~~

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
			~~acetaminophen, diphenhydramine, and montelukast, and it is recommended that the dose will be administered over >2 hours (±10 minutes). Any decrease in infusion duration must be discussed with and agreed upon by the sponsor.~~
Germany	9.3.9.2 Pregnancy Test Appendix A Part 3 SOE	Participants or serum urine or reproductively During the study, participants of childbearing potential must have a negative urine or serum pregnancy test result within 72 hours before dosing on Day 1 of each cycle.	~~Women~~**Participants** of childbearing potential must have 2 negative pregnancy tests **results** prior to starting study drug. A urine **or serum** pregnancy test will be used during screening (within 10 to 14 days prior to start of study drug). A **urine or** serum pregnancy test must be performed at baseline (within 24 hours prior to the start of study drug). A ~~woman~~ **participant** of childbearing potential is a sexually mature **reproductively** female **participant** who: **(**1) has not undergone a hysterectomy or bilateral oophorectomy; or **(**2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). **During the study, participants of childbearing potential must have a negative urine or serum pregnancy test result within 72 hours before dosing on Day 1 of each cycle.** During the study, if menstrual period is delayed, absence of pregnancy in ~~women~~ **participants** of childbearing potential must be confirmed by serum pregnancy test. Pregnancy tests may also be repeated during the study as per request of IRB or if required by local regulations. At end of treatment, a urine **or serum** pregnancy test is required in ~~women~~ **participants** of childbearing potential.
Germany	Appendix C PK Sampling Schedules, Table 9, Parts 1 and 2 Schedule D (Q4W) PK	*New table* **Appendix C Table 9 Parts 1 and 2 Schedule D (Q4W) PK Sampling: Cycle 3 and Beyond**	**Appendix C Table 9 Parts 1 and 2 Schedule D (Q4W) PK Sampling: Cycle 3 and Beyond Schedule D PK Sampling: Cycle 3 and Beyond** **Time Points**

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
	Sampling: Cycle 3 and Beyond	**Schedule D PK Sampling: Cycle 3 and Beyond** **Time Points** **Cycle 3 and Beyond** **Day 1 a** **Predose (within 30 min prior to start of infusion) X** **End of infusion X** **2 to 4 hours after end of infusion (±30 min) X** **PK: pharmacokinetic; Q4W: every 4 weeks.** **a TAK-573 infusion. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous infusion visits.**	**Cycle 3 and Beyond** **Day 1 a** **Predose (within 30 min prior to start of infusion) X** **End of infusion X** **2 to 4 hours after end of infusion (±30 min) X** **PK: pharmacokinetic; Q4W: every 4 weeks.** **a TAK-573 infusion. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous infusion visits.**
Czech Republic	4.4.2 Toxicology Studies	Sexually immature nonhuman primates were used in the repeat dose toxicity studies, and thus no data on fertility are available from these general toxicity studies. Based on the development of antidrug antibodies (ADA) by Day 15 in all cynomolgus monkeys, which was associated with substantial loss of exposure and neutralization of pharmacologic activity by Day 22, the duration of meaningful exposure is considered too short to conduct reproductive (embryo/fetal development) toxicity studies. In addition, since rodents are not a relevant species for modakafusp alfa, they cannot be used for reproductive toxicity testing. In accordance with regulatory guidelines (ICH Guidances S6(R1) 2011, and S9, 2009), a weight-of-evidence approach is used to assess the risk of reproductive toxicity of modakafusp alfa. While there are no direct nonclinical data to support a lack of teratogenicity or	~~As described in International Conference on Harmonisation (ICH) Guidance S6 (R1), the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals. ICH Guidance S9, Nonclinical Evaluation for Anticancer Pharmaceuticals, also states that genotoxicity studies are not considered essential to support clinical trials for therapeutics intended to treat patients with advanced cancer. Therefore, genotoxicity studies have not been conducted with modakafusp alfa.~~ **Sexually immature nonhuman primates were used in the repeat dose toxicity studies, and thus no data on fertility are available from these general toxicity studies. Based on the development of antidrug antibodies (ADA) by Day 15 in all cynomolgus monkeys, which was associated with substantial loss of exposure and neutralization of pharmacologic activity by Day 22, the duration of meaningful exposure is considered too short to conduct reproductive (embryo/fetal development) toxicity studies. In addition, since rodents are not a relevant species for modakafusp alfa, they cannot be used for reproductive**

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
		embryo-fetal lethality effects with modakafusp alfa, genotoxicity assessments are not required for biologics due to a lack of demonstrable interaction with DNA and accepted low risk from health authorities. Based on these considerations, modakafusp alfa is considered nongenotoxic and falls into the category of possible human teratogenicity/fetal toxicity based on a lack of data. United States (US) Food and Drug Administration (FDA) guidelines for nongenotoxic biologic pharmaceuticals with a potential for teratogenicity or embryo-fetal lethality recommend a contraception period of 5 half-lives after the last dose for females and no additional duration after the last dose for males. The half-life of modakafusp alfa is less than 24 hours. Similarly, for therapeutics with these characteristics, the Clinical Trial Facilitation Group (CTFG) recommends contraception in females for the duration of systemic exposure plus 1 month and no contraception in males. The lack of contraception requirements in males for biologics is due to a low likelihood of exposure to childbearing partners (lack of semen accumulation, limited absorption, and likely proteolytic degradation by vaginal/cervical enzymes) (Scialli et al. 2015). Based on the current lack of reproductive toxicity data with modakafusp alfa, the duration of contraception was extended over that recommended by guidance	**toxicity testing. In accordance with regulatory guidelines (ICH Guidances S6(R1) 2011, and S9, 2009), a weight-of-evidence approach is used to assess the risk of reproductive toxicity of modakafusp alfa. While there are no direct nonclinical data to support a lack of teratogenicity or embryo-fetal lethality effects with modakafusp alfa, genotoxicity assessments are not required for biologics due to a lack of demonstrable interaction with DNA and accepted low risk from health authorities.** **Based on these considerations, modakafusp alfa is considered nongenotoxic and falls into the category of possible human teratogenicity/fetal toxicity based on a lack of data. United States (US) Food and Drug Administration (FDA) guidelines for nongenotoxic biologic pharmaceuticals with a potential for teratogenicity or embryo-fetal lethality recommend a contraception period of 5 half-lives after the last dose for females and no additional duration after the last dose for males. The half-life of modakafusp alfa is less than 24 hours. Similarly, for therapeutics with these characteristics, the Clinical Trial Facilitation Group (CTFG) recommends contraception in females for the duration of systemic exposure plus 1 month and no contraception in males. The lack of contraception requirements in males for biologics is due to a low likelihood of exposure to childbearing partners (lack of semen accumulation, limited absorption, and likely proteolytic degradation by vaginal/cervical enzymes) (Scialli et al. 2015).** **Based on the current lack of reproductive toxicity data with modakafusp alfa, the duration of contraception was extended over that recommended by guidance from the FDA and the CTFG. The duration of contraception after the last dose of modakafusp alfa of 6 months after the last dose for females and 120 days after the last**

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
		from the FDA and the CTFG. The duration of contraception after the last dose of modakafusp alfa of 6 months after the last dose for females and 120 days after the last dose for males is considered a very conservative approach.	**dose for males is considered a very conservative approach.**
Czech Republic	7.1 Inclusion Criteria #7	Live vaccine 30 days	Chemotherapy, including proteasome inhibitors and IMiDs 14 days Antibody therapy (except anti-CD38 antibody as presented in exclusion criterion #4) 21 days Corticosteroid therapy for myeloma7 days Radiation therapy for localized bone lesions 7 days Major surgery 21 days **Live vaccine 30 days**
Czech Republic	8.5 Excluded Concomitant Medications and Procedures	Patients may not receive a live vaccine during the study and within 90 days after completion of study treatment.	**Patients may not receive a live vaccine during the study and within 90 days after completion of study treatment.**
Czech Republic	7.2 Exclusion Criteria #14	Known history of human immunodeficiency virus (HIV). Infection with Screening for will be performed, and patients who have a positive result will be excluded. Screening for HBV and HCV infection will be performed. Patients with HBV or HCV infection, or who are are excluded	14. ~~12.~~ Parts 1 and 2: Known chronic hepatitis C and/or positive serology (unless due to vaccination or passive immunization due to Ig therapy) for chronic hepatitis B. **Known history of human immunodeficiency virus (HIV).** Part 3: ~~Hepatitis B virus (~~**Infection with** HB**I**V~~) or hepatitis C virus (~~**: Screening for** HC**I**V~~)~~ infection~~.~~ **will be performed, and patients who have a positive result will be excluded. Screening for HBV and HCV infection will be performed. Patients with HBV or HCV infection, or who are** ~~S~~seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]**) are excluded**. Participants with resolved infection (that is, participants who are HBsAg-negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
			HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of HBV DNA levels. Those who are PCR positive will be excluded.
Czech Republic	9.3.9.6 Clinical Chemistry, Hematology, and Urinalysis	In all other than thyroid function tests and HBV, HCV, and HIV serologies)	~~Central laboratory analysis is required for~~**In** Part 3., ~~L~~local h~~ematology and chemistry~~ laboratory results may be used for dosing decisions; however, **all** samples (**other than thyroid function tests and HBV, HCV, and HIV serologies)** must still be sent to the central laboratory ~~as well~~.
Czech Republic	9.3.9.2 Pregnancy Test Appendix A Part 3 SOE	Participants or serum urine or reproductively During the study, participants of childbearing potential must have a negative urine or serum pregnancy test result within 72 hours before dosing on Day 1 of each cycle.	~~Women~~**Participants** of childbearing potential must have 2 negative pregnancy tests **results** prior to starting study drug. A urine **or serum** pregnancy test will be used during screening (within 10 to 14 days prior to start of study drug). A **urine or** serum pregnancy test must be performed at baseline (within 24 hours prior to the start of study drug). A ~~woman~~ **participant** of childbearing potential is a sexually mature **reproductively** female **participant** who: **(**1) has not undergone a hysterectomy or bilateral oophorectomy; or **(**2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). **During the study, participants of childbearing potential must have a negative urine or serum pregnancy test result within 72 hours before dosing on Day 1 of each cycle.** During the study, if menstrual period is delayed, absence of pregnancy in ~~women~~ **participants** of childbearing potential must be confirmed by serum pregnancy test. Pregnancy tests may also be repeated during the study as per request of IRB or if required by local regulations. At end of treatment, a urine **or serum** pregnancy test is required in ~~women~~ **participants** of childbearing potential.

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
Czech Republic	Appendix A Part 3 Footnote *l*	or serum urine or For women of childbearing potential, a urine or serum pregnancy test will be performed monthly on Day 1 of each cycle during treatment prior to dosing.	Pregnancy test (refer to Section 9.3.9.2). • Screening: Women of childbearing potential must have 2 negative pregnancy tests prior to starting study drug. A urine **or serum** pregnancy test will be used during screening (within 10 to 14 days prior to start of study drug). A **urine or** serum pregnancy test is required at baseline. • On treatment: **For women of childbearing potential, a urine or serum pregnancy test will be performed monthly on Day 1 of each cycle during treatment prior to dosing.** If menstrual period is delayed, absence of pregnancy in women of childbearing potential must be confirmed by serum pregnancy test. • A urine **or serum** pregnancy test is required at EOT in women of childbearing potential.
Czech Republic	9.4.1 Discontinuation of Treatment With Study Drug and Patient Replacement	**Confirmed pregnancy in a study patient.**	Study drug must be permanently discontinued for patients meeting any of the following criteria: • Patient experiences an AE or other medical condition that indicates to the investigator that continued participation is not in the best interest of the patient. • **Confirmed pregnancy in a study patient….** • ~~Female patient has confirmed pregnancy.~~ • ~~Lost to follow-up.~~
Czech Republic	Appendix C PK Sampling Schedules, Table 9, Parts 1 and 2 Schedule D (Q4W) PK Sampling: Cycle 3 and Beyond	*New table* **Appendix C Table 9 Parts 1 and 2 Schedule D (Q4W) PK Sampling: Cycle 3 and Beyond** **Schedule D PK Sampling: Cycle 3 and Beyond** **Time Points** **Cycle 3 and Beyond** **Day 1 a** **Predose (within 30 min prior to start of infusion) X** **End of infusion X** **2 to 4 hours after end of infusion (±30 min) X**	**Appendix C Table 9 Parts 1 and 2 Schedule D (Q4W) PK Sampling: Cycle 3 and Beyond Schedule D PK Sampling: Cycle 3 and Beyond** **Time Points** **Cycle 3 and Beyond** **Day 1 a** **Predose (within 30 min prior to start of infusion) X** **End of infusion X** **2 to 4 hours after end of infusion (±30 min) X** **PK: pharmacokinetic; Q4W: every 4 weeks. a TAK-573 infusion. The timing of the**

Summary of Changes			
Country	**Section Number**	**Country Specific Language**	**Country Specific Language in Tracked Changes against Global Protocol Language**
		PK: pharmacokinetic; Q4W: every 4 weeks. **a TAK-573 infusion. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous infusion visits.**	**morning visits should occur at approximately the same time as the morning infusion times on previous infusion visits.**

Global Amendments Summary of Changes

Protocol Amendment 10 v1 Summary of Changes (Not Implemented)

This section describes the changes to the protocol incorporating Amendment 10 v1 (not implemented). The primary reasons for this amendment were to change the primary objective of the Part 3 Dose Extension portion of the study from IRC-assessed objective response rate (ORR) to investigator-assessed ORR and change the primary analysis time point to utilize an earlier data cutoff date due to the sponsor decision to discontinue the development of modakafusp alfa.

In light of the decision to discontinue the development of modakafusp alfa, the sponsor has decided to change the primary analysis time point to utilize an earlier data cutoff date as of the implementation of Protocol Amendment 10 v1. Following the implementation of Protocol Amendment 10 v1, the majority of study assessments will be discontinued to ease the burden of protocol-mandated assessments on patients. Modakafusp alfa will continue to be provided for patients who continue to derive benefit.

Upon implementation of Protocol Amendment 10 v1, activities will be limited to dosing of study drug and any modifications to administration and data collection requirements will be limited to the following safety assessments: all serious adverse events (SAEs) (regardless of causality, including all deaths), any adverse event (AE) leading to dose modification or discontinuation of study drug, Grade ≥3 AEs, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). All other study assessments are no longer required. Given what is already known regarding the safety profile of modakafusp alfa based upon all previous data collection, further collection and reporting of Grade ≤2 AEs is not expected to result in a change to patient management. Treating physicians will monitor and manage patients according to standard of care, in order to ensure overall patient safety.

All central laboratory and investigator assessments of response and progression for protocol purposes will be discontinued. Patients will not be followed for the progression-free survival (PFS) or overall survival (OS) follow-up periods, as PFS and OS will no longer be collected. Quality of Life (QOL), pharmacokinetic (PK), immunogenicity, biomarker, and pharmacodynamic assessments will no longer be performed or recorded. Patients should otherwise be treated by the investigator according to local standard of care, including local laboratory assessments. Further, recording of AEs in the electronic case report form (eCRF) will be limited to AEs leading to dose modification or discontinuation of study drug and local laboratory assessments and symptom-directed physical examination data will only be recorded in the eCRF in the event that they are needed to evaluate an AE. See the updated Schedule of Events—Protocol Amendment 10 v1 and Beyond (Appendix A Table 1) for more detailed information.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	2.0 STUDY SUMMARY	The purpose and rationale for the implementation of Protocol Amendment 10 was added.	Clarification.
2.	2.0 STUDY SUMMARY 5.3.1 Part 3 Primary Objective 5.4.3.1 Part 3 Primary Endpoint 6.1 Overview of Study Design	Changed the Primary Objective and Endpoint for the Part 3 Dose Extension part of the study to investigator-assessed ORR. Removed independent review committee (IRC) assessment of objective response rate (ORR).	Clinical updates.
3.	2.0 STUDY SUMMARY 5.3.2 Part 3 Secondary Objectives 5.4.3.2 Part 3 Secondary Endpoints 5.3.3 Part 3 Exploratory Objectives 5.4.3.3 Part 3 Exploratory Endpoints	"Following the implementation of Protocol Amendment 10 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the Part 3 Dose Extension Secondary and Exploratory Objectives and Endpoints for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:…" was added before the text characterizing the Part 3 Dose Extension Secondary and Exploratory Objectives and Endpoints for use prior to implementation of Protocol Amendment 10. Removed ORR as assessed by the investigator from the Part 3 Dose Extension Secondary Objectives and Endpoints because it was changed to the Part 3 Dose Extension Primary Objective and Endpoint. Removed IRC assessment of disease control rate (DCR), clinical benefit rate (CBR), and duration of response (DOR).	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
4.	3.3 Committees in Part 3 Dose Extension 13.1.3 Efficacy Analysis	The text regarding the IRC was removed from the protocol.	Clinical update and statistical update.
5.	3.3.1 Independent Data Monitoring Committee	"Following the implementation of Protocol Amendment 10, no further IDMC reviews of safety and efficacy data will take place for patients still receiving study therapy. The sponsor will continue to monitor safety endpoints as indicated in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the description of the independent data monitoring committee (IDMC) information for use after the implementation of Protocol Amendment 10.	Clinical update.
6.	4.6.1 Rationale for the Part 1 Starting Dose of Modakafusp Alfa 4.6.3 Changes to Modakafusp Alfa Infusion 8.6.1 Premedication	Previous amendments are referred to as "Protocol Amendment" and their respective number.	Clarification.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7.	6.1 Overview of Study Design	The purpose and rationale for the implementation of Protocol Amendment 10 was added. "Prior to Implementation of Protocol Amendment 10:…" was added before the text characterizing Overview of Study Design for use prior to implementation of Protocol Amendment 10. "Following the implementation of Protocol Amendment 10 (see Section 1.3), activities will be limited to dosing of study drug and any modifications to administration and data collection requirements will be limited to ease the burden of protocol-mandated assessments on patients as outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the Part 3 Dose Extension Overview of Study Design for use after the implementation of Protocol Amendment 10.	Clarification and clinical updates.
8.	6.3.1 Duration of an Individual Patient's Study Participation	"Following the implementation of Protocol Amendment 10 (see Section 1.3), the majority of study assessments will be discontinued to ease the burden of protocol-mandated assessments on patients as outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the Duration of an Individual Patient's Study Participation for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:…" was added before the text characterizing Duration of an Individual Patient's Study Participation for use prior to implementation of Protocol Amendment 10.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
9.	6.3.2 End of Study/Study Completion Definition and Planned Reporting	"Following the implementation of Protocol Amendment 10, patients will not be followed for the PFS or OS follow-up periods, as PFS and OS will no longer be collected as outlined in Section 1.3." was added to the End of Study/Study Completion Definition and Planned Reporting for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:…" was added before the text characterizing Duration of an End of Study/Study Completion Definition and Planned Reporting for use prior to implementation of Protocol Amendment 10.	

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
10.	6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures	"Following the implementation of Protocol Amendment 10 (see Section 1.3), the primary objective of the Part 3 Dose Extension portion of the study is investigator-assessed ORR and data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the Timeframes for Primary and Secondary Endpoints to Support Disclosures for use after the implementation of Protocol Amendment 10. Table 6.a was updated to remove ORR as assessed by the IRC as a Part 3 Dose Extension Primary Endpoint. Table 6.a was updated to indicate that ORR as assessed by the investigator was the Part 3 Dose Extension Primary Endpoint. "This has been updated to align with the primary objective of the Part 3 Dose Extension portion of the study utilized following the implementation of Protocol Amendment 10 (see Section 1.3)." was added to the Table 6.a Part 3 Dose Extension Primary Endpoint row.	Clinical updates.
11.	6.3.4 Total Study Duration	"Following the implementation of Protocol Amendment 10, patients will not be followed for the PFS or OS follow-up periods, as PFS and OS will no longer be collected as outlined in Section 1.3" was added to the Total Study Duration for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:…" was added before the text characterizing the Total Study Duration for use prior to implementation of Protocol Amendment 10.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
12.	9.0 STUDY CONDUCT	"Following the implementation of Protocol Amendment 10 (see Section 1.3), activities will be limited to dosing of study drug and any modifications to administration and data collection requirements will be limited to ease the burden of protocol-mandated assessments on patients as outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the description of the Study Conduct for use after the implementation of Protocol Amendment 10. Clarification was added that "At all time points," this study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.	Clinical updates and clarification.
13.	9.3 Study Procedures	"Following the implementation Protocol Amendment 10, the SOE has been simplified to apply to the remainder of the study for ease of study conduct as outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the Study Procedures for use after the implementation of Protocol Amendment 10. "Prior to the implementation of Protocol Amendment 10, the SOEs utilized can be found in the remainder of the Tables presented in Appendix A, Appendix B, and Appendix C." was added before the text characterizing the Study Procedures for use prior to implementation of Protocol Amendment 10.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
14.	9.3.9 Safety Evaluations	Added the following text: "Data collection requirements will be limited to the following safety assessments: all SAEs (regardless of causality, including all deaths), any AE leading to dose modification or discontinuation of study drug, Grade ≥3 AEs, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). All other study assessments are no longer required for protocol purposes."	Clinical update.
15.	9.3.4 Physical Examination 9.3.7 ECOG Performance Status 9.3.8 Concomitant Medications and Procedures 9.3.9 Safety Evaluations 9.3.9.1 Vital Signs 9.3.9.2 Pregnancy Testing 9.3.9.3 TEAEs 9.3.9.4 ECGs 9.3.9.5 Clinical Laboratory Evaluations 9.3.9.6 Clinical Chemistry, Hematology, and Urinalysis 9.3.9.7 β_2-Microglobulin	"Following the implementation of Protocol Amendment 10 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the relevant Study Procedure section for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:" was added before the text characterizing the relevant Study Procedure section for use prior to implementation of Protocol Amendment 10.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
16.	9.3.9.5 Clinical Laboratory Evaluations	Indicated that with the implementation of Protocol Amendment 10: - "…centralized clinical laboratory evaluations of efficacy and safety will no longer be performed." - "Local laboratory evaluations should be entered into the eCRF only if required to document a TEAE." - "For dosing decisions, response assessment, and all other safety assessments for the patient, local hematology and clinical chemistry laboratory results should be used and do not need to be entered into the eCRF." - "Local laboratory evaluations may be performed according to local standard of care (ie, for acute management of TEAEs), per the investigator's judgment of standard of care."	Clinical updates.
17.	9.3.9.6 Clinical Chemistry, Hematology, and Urinalysis 9.3.9.7 β_2-Microglobulin	"All laboratory assessments will be done locally." was added to clarify that no central assessments were to be performed with the implementation of Protocol Amendment 10.	Clinical update.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
18.	9.3.10 Disease Assessment 9.3.10.1 Extramedullary Disease Imaging 9.3.10.2 Bone Imaging 9.3.10.3 Quantification of Immunoglobulins 9.3.10.4 Quantification of M-Protein in Serum and Urine 9.3.10.5 Serum FLC Assay 9.3.10.6 Immunofixation of Serum and Urine 9.3.10.7 Interference Assay 9.3.10.8 Bone Marrow Aspiration 9.3.10.8.1 Bone Marrow Central Laboratory Evaluations 9.3.10.8.2.1 Disease Assessment 9.3.10.8.2.2 Cytogenetics 9.3.10.8.2.3 Bone Marrow Morphology	"Following the implementation of Protocol Amendment 10 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)…" was added to the relevant Disease Assessment section for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:" was added before the text characterizing the relevant Disease Assessment section for use prior to implementation of Protocol Amendment 10.	Clinical updates.
19.	9.3.10 Disease Assessment	Indicated that with the implementation of Protocol Amendment 10: - All assessments will be done locally, and disease assessments will <u>not</u> be recorded in the eCRF." - "Disease assessment will be performed and assessed by the investigator according to standard of care treatment."	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
20.	9.3.11 PK, Immunogenicity, Biomarker, and Pharmacodynamic Samples 9.3.11.1 Primary Specimen Collection for PK, Immunology, and Biomarker Assessments 9.3.11.2 PK Measurements 9.3.11.3 Biomarkers and Pharmacodynamic Measurements 9.3.11.3.1 Biomarker Measurements 9.3.11.3.2.1 Fresh BMA Samples for Pharmacodynamics (Parts 1 and 2 Only) Fresh BMA Samples for Pharmacodynamics (Parts 1 and 2 Only) 9.3.11.3.2.2 Fresh BMA for Cytogenetics/Fresh BMA (Part 3 Only) 9.3.11.3.2.3 Fresh BMA Samples for MRD 9.3.11.3.2.4 Fresh BMA Samples for RNA (Parts 1 and 2 Only) 9.3.11.3.2.5 Blood Sample for Flow Cytometry 9.3.11.3.2.6 Blood Sample for RNA 9.3.11.3.2.7 Blood Sample for Receptor Sequencing 9.3.11.4 DNA Measurements 9.3.11.5 Immunogenicity Measurements	"Following the implementation of Protocol Amendment 10 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the relevant PK, Immunogenicity, Biomarker, and Pharmacodynamic Samples section for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:" was added before the text characterizing the relevant PK, Immunogenicity, Biomarker, and Pharmacodynamic Samples section for use prior to implementation of Protocol Amendment 10.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
21.	9.3.11 PK, Immunogenicity, Biomarker, and Pharmacodynamic Samples	"All PK, immunogenicity, biomarker, and pharmacodynamic assessments will no longer be performed." was added for use after the implementation of Protocol Amendment 10.	Clinical update.
22.	9.3.11.1 Primary Specimen Collection for PK, Immunology, and Biomarker Assessments	"As noted above, following the implementation of Protocol Amendment 10, blood and serum samples for PK, immunogenicity, biomarker, and pharmacodynamic assessments will no longer be collected." was added prior to the presentation of Table 9.c. Table 9.cwas updated so the caption indicates that the table is not applicable for use following the implementation of Protocol Amendment 10.	Clinical updates.
23.	9.3.12 PRO Assessments 9.3.12.1 *EORTC QLQ-MY20* 9.3.12.2 EQ-5D-5L	"Following the implementation of Protocol Amendment 10 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the relevant PRO Assessments section for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:" was added before the text characterizing the relevant PRO Assessments section for use prior to implementation of Protocol Amendment 10.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
24.	9.3.13 Healthcare Resource Utilization	"Following the implementation of Protocol Amendment 10 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the relevant Healthcare Resource Utilization section for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:" was added before the text characterizing the relevant Healthcare Resource Utilization section for use prior to implementation of Protocol Amendment 10.	Clinical updates.
25.	9.4 Completion of Study Treatment (for Individual Patients) 9.4.1 Discontinuation of Treatment with Study Drug and Patient Replacement 9.4.2 Withdrawal of Patients From Study	"Following the implementation of Protocol Amendment 10 (see Section 1.3), the majority of study assessments will be discontinued to ease the burden of protocol-mandated assessments on patients as outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the relevant Completion of Study Treatment (for Individual Patients) section for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:" was added before the text characterizing the relevant Completion of Study Treatment (for Individual Patients) section for use prior to implementation of Protocol Amendment 10.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
26.	9.5 Posttreatment Follow-up Assessments	"Following the implementation of Protocol Amendment 10 (see Section 1.3), the majority of study assessments will be discontinued to ease the burden of protocol-mandated assessments on patients as outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the relevant Posttreatment Follow-up Assessments section for use after the implementation of Protocol Amendment 10. "Prior to Implementation of Protocol Amendment 10:" was added before the text characterizing the relevant Posttreatment Follow-up Assessments section for use prior to implementation of Protocol Amendment 10.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
27.	10.2 Procedures for Recording and Reporting AEs and SAEs	"Following the implementation of Protocol Amendment 10 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the Procedures for Recording and Reporting AEs and SAEs section for use after the implementation of Protocol Amendment 10. "If the EDC is not available, then the SAE form should be faxed or emailed within 24 hours after becoming aware of the event." was added to the Procedures for Recording and Reporting AEs and SAEs section for use after the implementation of Protocol Amendment 10. "Please note that while the types of AEs recorded and reported may differ dependent upon the implementation of Protocol Amendment 10, procedures for reporting AEs and SAEs will remain the same as stipulated here in Section 10.2." was added to the Procedures for Recording and Reporting AEs and SAEs section for use after the implementation of Protocol Amendment 10. Indicated that the SAE Form can be emailed (in addition to faxed). Updated the SAE Reporting Contact Information with the fax number for the United States and Canada, fax number for the Rest of the World, and the email address.	Clinical updates and clarifications.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
28.	10.2.1 Monitoring and Reporting IRRs	"Following the implementation of Protocol Amendment 10 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the Monitoring and Reporting IRRs section for use after the implementation of Protocol Amendment 10. "Please note that while the types of AEs recorded and reported may differ dependent upon the implementation of Protocol Amendment 10, procedures for reporting IRRa will remain the same as stipulated here in Section 10.2.1." was added to the Monitoring and Reporting IRRs section for use after the implementation of Protocol Amendment 10.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
29.	10.3 Monitoring of AEs and Period of Observation	"Following the implementation of Protocol Amendment 10 (see Section 1.3), the majority of study assessments will be discontinued to ease the burden of protocol-mandated assessments on patients as outlined in the updated Schedule of Events—Protocol Amendment 10 and Beyond (Appendix A Table 1)." was added to the Monitoring of AEs and Period of Observation section for use after the implementation of Protocol Amendment 10. "Only SAEs (regardless of causality, including all deaths), any AE leading to dose modification or discontinuation of study drug, Grade ≥3 AEs, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose) are to be reported." was indicated. "Prior to Implementation of Protocol Amendment 10:" was added before the text characterizing the Monitoring of AEs and Period of Observation section for use prior to implementation of Protocol Amendment 10.	Clinical updates.
30.	10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Indicated that the Pregnancy Form can be emailed (in addition to faxed).	Clarification.
31.	13.1 Statistical and Analytical Plans	Added "…or at a time determined by the sponsor if the study is terminated early." to the description of the timing for the analysis of the primary endpoint.	Statistical update.
32.	13.1.1 Analysis Sets	Added "…and PRO compliance" to the description of the Full Analysis Set.	Statistical update.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
33.	13.1.3 Efficacy Analysis	Removed ORR as assessed by the investigator from the Part 3 Dose Extension Secondary Objectives and Endpoints because it was changed to the Part 3 Dose Extension Primary Objective and Endpoint. Removed IRC assessment of disease control rate (DCR), clinical benefit rate (CBR), and duration of response (DOR).	Statistical update.
34.	13.1.4 PK Analysis	Added "…or sponsor decision" to the description of PK parameter determination in Parts 1 and 2 and in Chinese Patients with the intensive PK schedule in Part 3.	Statistical update.
35.	13.1.6 PRO Analyses	Removed "The difference between baseline scores and scores over may be also explored using linear mixed models."	Statistical update.
36.	13.1.8 Safety Analysis	Removed "Listings of laboratory test results and vital signs will be generated."	Statistical update.
37.	14.1 Study-Site Monitoring Visits	Added "Details can be found in the monitoring plan." Changed "will be" to "may be" regarding source document verification of data recorded on the eCRFs.	Clarification.
38.	Appendix A Schedule of Events	Provided rationale for the implementation of the Updated Schedule of Events—Protocol Amendment 10 and Beyond. Added a new schedule of events for use with the implementation of Protocol Amendment 10 (Appendix A Table 1) and updated all other Schedules of Events for use prior to the implementation of Protocol Amendment 10 (Appendix A Table 2 through Appendix A Table 14). Updated the titles for the Schedules of Events (Appendix A Table 2 through Appendix A Table 14) to be used Prior to Protocol Amendment 10 with text indicating as such.	Clinical updates.

Protocol Amendment 10 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
39.	Appendix A Table 13	Provided text to indicate that "The full Schedule of Events for the Part 3 Dose Extension of the study is no longer in effect, as of the implementation of Protocol Amendment 10 (see Section 1.3). See Appendix A Table 1 for the Schedule of Events to be used after the implementation of Protocol Amendment 10." for Appendix A Table 13 and Appendix A Table 14	Clinical updates and clarifications.
40.	Appendix B Bone Marrow Collection and Assessment Schedules (Part 1 and Part 2)	Provided text to indicate that "IMPORTANT NOTE: Bone marrow sample collection and assessment are no longer required as of the implementation of Protocol Amendment 10. Refer to Section 1.3 for a description of the changes to study conduct as a result of the implementation of Protocol Amendment 10."	Clinical updates and clarifications.
41.	Appendix C PK Sampling Schedules	Provided text to indicate that "IMPORTANT NOTE: Pharmacokinetic sample collection and assessment are no longer required as of the implementation of Protocol Amendment 10. Refer to Section 1.3for a description of the changes to study conduct as a result of the implementation of Protocol Amendment 10."	Clinical updates and clarifications.

Protocol Amendment 9 Summary of Changes

This section describes the changes to the protocol incorporating Amendment 9. The primary reasons for this amendment were to add the Investigational New Drug No., add neutralizing antibodies (NAb) as a secondary endpoint, simplify text about the study design of Part 1, clarify Part 3 inclusion criteria, update serious adverse event (SAE) and product complaint reporting procedures, and clarify hepatitis testing requirements.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 9			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Cover page.	IND No. added. Abbreviated European Union Drug Regulating Authorities Clinical Trials (EUDRACT) number added.	Administrative update.
2.	2.0 STUDY SUMMARY 9.3.11 PK, Immunogenicity, Biomarker, and Pharmacodynamic Samples	"Immunogenicity" was added to description of assessments.	Clarification.
3.	2.0 STUDY SUMMARY 6.1 Overview of Study Design 6.2 Number of Patients 13.3 Determination of Sample Size	The purpose, enrollment plan, and number of patients for the China cohort were described.	Country-specific update.
4.	2.0 STUDY SUMMARY 5.3.3 Part 3 Exploratory Objectives 5.4.3.3 Part 3 Exploratory Endpoints 9.3.12 PRO Assessments 13.1.6 PRO Analyses Appendix A Schedule of Events	The description of health-related quality of life instrument collection as an exploratory objective and endpoint in Part 3 was clarified, including that paper PROs may no longer be used and the instruction to sites to remind patients to complete PROs at each cycle,	Clarification.
5.	2.0 STUDY SUMMARY 7.1 Inclusion Criteria	Serum creatinine was removed as an inclusion criterion.	Clinical update.
6.	2.0 STUDY SUMMARY 6.3.1 Duration of an Individual Patient's Study Participation	Patients may be treated after disease progression if the investigator considers it in the best interest of the patient and with approval by the sponsor.	Clinical update.

Protocol Amendment 9			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7.	6.3.2 End of Study/Study Completion Definition and Planned Reporting	"…or have transitioned to posttrial access (Section 6.3.5)" was added to the end of study definition.	Administrative update.
8.	2.0 STUDY SUMMARY 7.1 Inclusion Criteria	Inclusion Criterion #1 for Part 3 was revised to include patients with disease progression during or after their last therapy.	Clinical update.
9.	2.0 STUDY SUMMARY 5.4.1.2 Part 1 Secondary Endpoints 5.2.2 Part 2 Secondary Objectives 5.4.2.2 Part 2 Secondary Endpoints Table 6.a Primary and Secondary Endpoints for Disclosures 9.3.11 PK, Immunogenicity, Biomarker, and Pharmacodynamic Samples 9.3.11.3 Biomarkers and Pharmacodynamic Measurements 13.1.7 Immunogenicity Analyses Appendix A Schedule of Events	Evaluation of neutralizing antibodies was added to antidrug antibody assessments and endpoints in Parts 1 and 2 endpoints.	Clinical update.
10.	2.0 STUDY SUMMARY 5.3.2 Part 3 Secondary Objectives 5.4.3.2 Part 3 Secondary Endpoints Table 6.a Primary and Secondary Endpoints for Disclosures 13.1.4 PK Analysis Appendix C PK Sampling Schedules	Intensive pharmacokinetic (PK) sampling endpoints for the China cohort were added to Part 3 Secondary Objectives and Part 3 Secondary Endpoints, along with a corresponding PK table in the appendix.	Country-specific update.

Protocol Amendment 9			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
11.	4.5.2 Clinical Safety 8.7 Precautions and Restrictions	Text regarding potential interference of modakafusp alfa with serologic testing based on daratumumab characteristics was removed, and the potential interference of modakafusp alfa with serologic testing is described in Section 8.7.	The potential interference of modakafusp alfa with serologic testing is now better understood and is described in Section 8.7.
12.	2.0 STUDY SUMMARY 6.1 Overview of Study Design 8.3 Part 1 Dose Escalation Rules 8.4.1 Part 1 Dose Escalation	Text detailing Part 1 dose escalation was streamlined.	Part 1 dose escalation has concluded.
13.	6.1 Overview of Study Design 8.3 Part 1 Dose Escalation Rules	Sites are referred to the Site Operations Manual for guidance about rescreening patients.	Administrative update.
14.	6.1 Overview of Study Design	Text added stating that the sponsor may decide to discontinuation 1 arm if the interim analysis reveals an unfavorable risk-benefit profile.	Clinical update.
15.	6.3.1 Duration of an Individual Patient's Study Participation 8.4.5 Criteria for Discontinuing Modakafusp Alfa	The duration of a patient's participation was clarified to include an end-of-treatment (EOT) evaluation 30 days after the last modakafusp alfa dose.	Administrative update.
16.	7.1 Inclusion Criteria 7.2 Exclusion Criteria	A table specifying restrictions on certain treatments and procedures before study enrollment was moved from inclusion to exclusion criteria.	Clarification.
17.	7.1 Inclusion Criteria 8.7 Precautions and Restrictions Appendix A Schedule of Events	The time period for contraception use and egg/sperm donation was lowered to 7 days.	Clinical update.
18.	7.2 Exclusion Criteria Appendix A Schedule of Events	The exclusion criterion for hepatitis infection was revised, and hepatitis testing for the Japan safety lead-in Part 3 was added.	Clinical update.
19.	7.2 Exclusion Criteria	Previous treatment with modakafusp alfa was added as an exclusion criterion.	Clinical update.

Protocol Amendment 9			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
20.	8.12 Packaging and Labeling	Description of modakafusp alfa drug product revised.	Clinical update.
21.	8.13 Storage, Handling, and Accountability	Sites are referred to the Pharmacy Manual regarding any discrepancies in storage conditions.	Administrative update.
22.	8.4.4 Part 3 8.4.5 Criteria for Discontinuing Modakafusp Alfa	Dose modifications and potential discontinuation of modakafusp alfa treatment in Part 3 are to be discussed with the sponsor or CRO before implementation.	Clinical update.
23.	8.7.1.1 Handling of IRRs	Recommendations for managing infusion-related reactions (IRRs) were updated.	Clinical update.
24.	9.5 Posttreatment Follow-up Assessments Appendix A Schedule of Events	Subsequent anticancer therapy will be recorded for study patients, including response status.	Clinical update.
25.	9.3.9.1 Vital Signs	Patients must be observed after the end of every modakafusp alfa infusion.	Clinical update.
26.	9.3.9.2 Pregnancy Testing Appendix A Schedule of Events	Timing and type of pregnancy tests required are detailed.	Clinical update.
27.	9.3.9.6 Clinical Chemistry, Hematology, and Urinalysis Appendix A Schedule of Events	Thyroid function tests consist of thyroid stimulating hormone, free or total T3, and free or total T4.	Clinical update.
28.	9.3.9.6 Clinical Chemistry, Hematology, and Urinalysis Appendix A Schedule of Events	Prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen, and D-dimer tests are to be collected if a patient exhibits significant bleeding.	Clinical update.
29.	9.3.10 Disease Assessment Appendix A Schedule of Events	Serum M-protein and serum free light chain samples are to be collected if a cycle is delayed.	Clinical update.

Protocol Amendment 9			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
30.	9.3.10.8.1 Bone Marrow Central Laboratory Evaluations 9.3.11.1 Primary Specimen Collection for PK, Immunology, and Biomarker Assessments 9.3.11.3.2.3 Fresh BMA Samples for MRD Appendix A Schedule of Events	Screening minimal residual disease samples will be obtained in China based on the acceptability of the method chosen.	Regulatory update.
31.	9.3.11.4 DNA Measurements	Circulating tumor DNA is to be collected in Part 3 as permitted by country regulations.	Regulatory update.
32.	9.3.13 Healthcare Resource Utilization	Collection of healthcare resource utilization forms is required. ut PRO collection in Part 3 were added, and electronic forms must be used.	Clinical update.
33.	9.4.2 Withdrawal of Patients From Study	Withdrawal is required, not optional, if any of the criteria listed occur.	Clinical update.
34.	10.2 Procedures for Recording and Reporting AEs and SAEs	Procedures for reporting SAEs were updated.	Administrative update.
35.	10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	Procedures for reporting product complaints and medication errors were clarified.	Clarification.
36.	12.1 eCRFs	Investigators are not to review PRO data.	Administrative update.
37.	13.1.5 Biomarker and Pharmacodynamic Analysis	Biomarker and pharmacodynamic analysis was revised.	Clinical update.
38.	13.1.7 Immunogenicity Analyses	Immunogenicity analysis was revised.	Statistical update.
39.	Appendix C PK Sampling Schedules	The Schedule D Cycles 3 and Beyond PK table, which had been inadvertently omitted, was included.	Correction.
40.	Appendix F IMWG Definition of MM (Kumar et al. 2016)	International Myeloma Working Group (IMWG) criteria were updated to 2016 version.	Clinical update.

Protocol Amendment 8 Summary of Changes

This section describes the changes to the global protocol incorporating Amendment 8.

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	STUDY SUMMARY 6.2 Number of Patients	The number of planned study sites was increased to 100.	Update.
2.	STUDY SUMMARY 5.3.1 Part 3 Primary Objective 7.1 Inclusion Criteria	Revised eligibility criteria regarding disease characteristics required for Part 3.	Clarification.
3.	7.1 Inclusion Criteria 8.7 Precautions and Restrictions	Postmenopausal status requirement for female patients aligned in all sections as 2 years.	Clarification.
4.	STUDY SUMMARY 6.1 Overview of Study Design 6.4 Randomization in Phase 2 Part 3 Extension	Stratification criteria revised to (IgA vs other).	Update.
5.	STUDY SUMMARY 5.3.3 Part 3 Exploratory Objectives	Deleted 2 Part 3 exploratory objectives.	Update.
6.	STUDY SUMMARY 5.4.1.2 Part 1 Secondary Endpoints	Clarified the definition of duration of response (DOR).	Clarification.
7.	STUDY SUMMARY 6.1 Overview of Study Design 13.2.2 Part 3 Extension Appendix H Operating Characteristics of the Futility Stopping Rules Appendix I Statistical Guidance on Unacceptable Toxicity and Treatment Related Death	Added a second interim analysis for Part 3.	Update.
8.	4.6.2 Rationale for Part 3	The rationale for Part 3 was updated based on current clinical data.	Update.
9.	4.6.2.1 Rationale for Fixed Dosing	The rationale for fixed dosing was updated based on current clinical data.	Update.
10.	7.1 Inclusion Criteria	Contraceptive guidelines (inclusion criterion #8) were clarified.	Clarification.
11.	7.2 Exclusion Criteria	Hepatitis exclusion criterion (#15) was clarified.	Clarification.
12.	8.4.4 Part 3	Dose modification guidelines for Part 3 were revised.	Update.

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13.	9.3.14 PRO Assessments	Administration of patient-reported outcomes (PRO) instruments was clarified.	Clarification.
14.	9.4.1 Discontinuation of Treatment with Study Drug and Patient Replacement	Complete response (CR) was removed as a reason for discontinuation (already covered under "other).	Clarification.
15.	13.2.2.2 Part 3 Continuous Safety Monitoring Plan and Stopping Rules	Sentence added clarifying that regulatory agencies and investigators will be informed if the study is stopped or paused for unacceptable toxicity or death.	Clarification.
16.	14.1 Study-Site Monitoring Visits	Study monitoring guidelines were updated to allow for COVID-19 circumstances.	Update.
17.	Appendix A	The schedules of events for Part 3 were updated.	Update.

Protocol Amendment 7 Summary of Changes (Not Implemented)

This section describes the changes in reference to the protocol incorporating Amendment 7 (not implemented). The primary reasons for this amendment are to update the drug name from TAK-573 to modakafusp alfa throughout, add a Part 3 dose extension component, and add patient-reported outcome (PRO) assessments.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 7 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Throughout protocol	TAK-573 was changed to modakafusp alfa.	Update.
2.	Title	"Relapsed" was added.	Update.
3.	2.0 STUDY SUMMARY	Efficacy was added to the study design.	Update.
4.	2.0 STUDY SUMMARY 6.0 Study Design	Schedule A (Part 1) was noted to be no longer under evaluation.	Update.

Protocol Amendment 7 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5.	2.0 STUDY SUMMARY 4.6.2 Rationale for Part 3 5.3 Part 3 Dose Extension Objectives 5.4.3 Part 3 Extension Endpoints 6.0 Study Design 6.4 Randomization in Phase 2 Part 3 Extension 7.0 Study Population 8.0 Study Drug 9.3 Study Procedures 9.4 Completion of Study Treatment (for Individual Patients) 11.0 STUDY-SPECIFIC COMMITTEES 13.0 STATISTICAL METHODS Appendix A Appendix B Appendix C	Part 3 extension and corresponding eligibility requirements, assessments, objectives, and endpoints were added to the study.	Update.
6.	2.0 STUDY SUMMARY 5.1.3 Part 1 Exploratory Objectives 5.4.1.3 Part 1 Exploratory Endpoints 6.0 Study Design	Part 1 Escalation exploratory objectives and endpoints were clarified.	Update.
7.	2.0 STUDY SUMMARY 5.4.2.2 Part 2 Secondary Endpoints 5.2.2 Part 2 Secondary Objectives 6.0 Study Design	Part 2 Expansion secondary objectives and endpoints were clarified.	Update.
8.	2.0 STUDY SUMMARY 5.2.3 Part 2 Exploratory Objectives 5.4.2.3 Part 2 Exploratory Endpoints 6.0 Study Design	Part 2 Expansion exploratory objectives and endpoints were clarified.	Update.
9.	2.0 STUDY SUMMARY 6.0 Study Design 13.0 STATISTICAL METHODS	Sample size and statistical considerations were revised to include Part 3.	Update.
10.	2.0 STUDY SUMMARY 13.0 STATISTICAL METHODS	The number of study sites and projected patient enrollment were increased.	Update.

Protocol Amendment 7 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
11.	3.3 Committees in Part 3 Dose Extension	An independent review committee and independent data monitoring committee were added for Part 3.	Update.
12.	3.3.2 Independent Data Monitoring Committee	Interim futility analysis was added.	Update.
13.	4.4.2 Toxicology Studies	Toxicology data was removed and a statement regarding genotoxicity was added.	Update.
14.	4.5.1 Nonclinical Safety Summary	Nonclinical data and details were removed and the reader referred to the investigator's brochure (IB).	Update.
15.	4.5.2 Clinical Safety	Clinical data and details were removed and the reader referred to the IB.	Update.
16.	8.4 Dose Modification Guidelines	Dose modification guidelines were clarified.	Update.
17.	8.13 Storage, Handling, and Accountability	Drug storage and usage instructions were updated.	Update.
18.	2.0 STUDY SUMMARY 7.0 Study Population	Wash-out periods were defined.	Update.
19.	2.0 STUDY SUMMARY 9.3.14 PRO Assessments 13.1.6 PRO Analyses Appendix A	PRO assessments were added for Part 3.	Update.
20.	2.0 STUDY SUMMARY 4.6.2 Rationale for Part 3	Flat dosing will be used for Part 3.	Update.
21.	4.5.2 Clinical Safety	Safety information was updated.	Update
22.	2.0 STUDY SUMMARY 4.5.2 Clinical Safety 8.0 Study Drug 10.0 ADVERSE EVENTS	Updated CTCAE to Version 5.0.	Update.
23.	7.1 Inclusion Criteria	ECOG criteria was modified to ≤2.	Update.

Protocol Amendment 7 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
24.	8.6.1 Premedication	Guidance for premedications in second paragraph was changed to "should."	Update.
25.	8.7.1.1 Handling of IRRs	Premedication guidelines were revised.	Update.
26.	9.3.10.1 Extramedullary Disease Imaging	Heading title was revised and text added describing Part 3 assessments.	Update.
27.	9.3.10.2 Bone Imaging	Heading title was revised and text added describing Part 3 assessments.	Update.
28.	9.3.10.4 Quantification of M-Protein in Serum and Urine	Urine collection for the different parts of the study was clarified.	Update.
29.	9.3.10.8.1 Bone Marrow Central Laboratory Evaluations	Sample collection and analysis requirements were clarified	Update.
30.	Table 9.c Primary Specimen Collection	Specimen collection table was updated to include Part 3 assessments.	Update.

Protocol Amendment 6 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 6. The primary reasons for this amendment are to maintain patient safety, confidentiality, and study integrity in the context of healthcare challenges presented by the coronavirus disease 2019 (COVID-19) public health emergency. This amendment allows investigators and study personnel to conduct visits remotely and electronic informed consent if these comply with national and local laws and regulations, use local laboratory and imaging results if patients are unable to travel to the investigative site, and remotely access patient records for data monitoring as necessary during the COVID-19 public health emergency.

Additionally, safety data, premedication requirements for doses of 6 mg/kg or greater and recommendations for all dose levels were updated, secondary endpoints and the sample size were revised, the criteria for early termination were expanded, clinical chemistry parameters were revised, and blood samples were added for pharmacokinetic (PK) and pharmacodynamic assessments.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 1.2 Approval	Updated study personnel	To reflect change in Takeda representatives.
Section 4.5.1.3 Potential Effects Based on Nonclinical and Clinical Studies	Added new safety data	To include additional safety data now available.
Section 4.6.2 Changes to TAK-573 Infusion Over the Course of the Study Section 8.6.1 Premedication Section 8.6.2 Postinfusion Medication	Clarified use of premedication requirements and recommendations prior to the dosing of TAK-573	To update guidance to include additional clinical experience.
Section 2.0 STUDY SUMMARY Section 5.2.2 Phase 1 Secondary Endpoints Section 5.2.3 Phase 2 Primary Endpoints Section 6.1 Overview of Study Design Section 13.1.3 Efficacy Analysis	Added clinical benefit rate and disease control rate as a secondary endpoint for phase 1 and as a primary endpoint for phase 2	To adjust endpoints to be more relevant in this early-phase study.
Section 2.0 STUDY SUMMARY Section 5.2.2 Phase 1 Secondary Endpoints Section 5.2.3 Phase 2 Primary Endpoints Section 6.3.1 Duration of an Individual Patient's Study Participation Section 6.3.4 Total Study Duration Section 9.8 Posttreatment Follow-up Assessments (PFS) Appendix A	Removed overall survival as a secondary endpoint	To reflect determination that the endpoint of overall survival is not informative without a comparator group.
Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 8.1 Study Drug Administration Section 8.8.1 Handling of IRRs Appendix A	Added further dosing instructions	To update guidance to reflect additional clinical experience.
Section 2.0 STUDY SUMMARY Section 6.2 Number of Patients	Changed number of sites and expected study duration	To reflect current expectations for number of sites and predicted duration of study.
Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting	Revised end-of-study criteria	To clarify conditions for study completion.
Section 8.8.1 Handling of IRRs Section 10.2.1 Monitoring and Reporting IRRs Appendix A	Defined infusion-related reaction (IRR) and treatment of IRRs	To include additional safety data now available.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.3 Study Procedures Section 9.3.1 Informed Consent Section 9.3.4 Physical Examination Section 9.3.13 Clinical Laboratory Evaluations Section 9.3.14 Disease Assessment	Clarified exceptions for site visits and procedural adjustments during unforeseen situations, like the COVID-19 public health emergency	To maintain patient safety, confidentiality, and study integrity in the context of health care challenges presented by the COVID-19 public health emergency.
Section 9.3.8 Vital Signs Appendix A	Added oxygen saturation as a vital sign	To clarify this information, which is routinely clinically assessed, should be collected and documented.
Section 9.3.13.1 Clinical Chemistry, Hematology, and Urinalysis	Removed coagulation, activated partial thromboplastin time, and prothrombin time from hematology panel	To eliminate tests determined not to be necessary given further experience with TAK-573.
Section 9.3.17 Immunogenicity Sample Collection	Added text to “strongly suggest” sample collection	To clarify recommendations for sample collection.
Section 9.4 Completion of Study Treatment (for individual patients) Appendix A	Revised content regarding completion of study treatment	To clarify criteria for completion of study treatment.
Section 10.1.3 AESIs Section 10.2.1 Monitoring and Reporting IRRs	Added definition of adverse events of special interest (AESI)	To clarify the definition and reporting of adverse events that should be classified as special interest, highlighting that IRRs would be designated as AESIs in studies of this compound.
Section 13.1.1 Analysis Sets	Added response-evaluable analysis set	To align statistical content with change in study endpoints.
Section 13.2 Criteria for Early Termination	Added criteria for early termination	To clarify conditions for early termination and clarify that no interim analysis is planned.
Section 13.3 Determination of Sample Size	Changed planned sample size for phase 2	To align sample size with change in study endpoints.

Protocol Amendment 6		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Appendix A Table 6 Schedule C (Q3W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 Appendix A Table 9 Schedule D (Q4W) Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 Appendix A Table 10 Schedule D (Q4W) Schedule of Events, Continued: Cycle 3 to Cycle 13 and Beyond	Addition of time points for blood sample for flow cytometry (CD38 occupancy in PBMCs), blood sample for flow cytometry (immunoprofiling), serum sample for PK, circulating biomarkers, and blood sample for RNA	To generate data evaluating a longer duration of CD38 receptor occupancy and how it relates to subsequent pharmacodynamic biomarkers as we continue to dose escalate. To characterize PK for a longer duration on Cycles 1 and 2 as dose escalates to greater than 6 mg/kg, and to collect Day 2 PK for limited visits beyond Cycle 2 to further characterize potential impact of ADA on PK.
Appendix A Table 11 Schedules A, B, C and D: End of Treatment and Follow-up	Removal of collection of subsequent therapy	Data on subsequent therapy is not needed since OS is no longer an endpoint.
Appendix C Table 8 Schedule D (Q4W) PK Sampling: Cycle 1 and Cycle 2	Addition of time point "end of infusion (+/- 5 min)" on Day 1 Removal of time point "1 hour after end of infusion (+/- 15 min)" on Day 1 Addition of time point on "504 hours after end of infusion (+/-1 hour)" on Day 22, strongly recommended for > 6 mg/kg only.	To characterize PK for a longer duration as dose escalates to greater than 6 mg/kg.
Appendix C Table 9 Schedule D (Q4W) PK Sampling: Cycle 3 and Beyond	Addition of time point for Day 2 of Cycle 3, 7, and 11 only	Collect Day 2 PK for limited visits beyond Cycle 2 to further characterize potential impact of ADA on PK.

Protocol Amendment 5 Summary and Rationale

This document describes the changes in reference to the protocol incorporating Amendment No. 05. The primary reasons for this amendment are to reduce infusion time for TAK-573 (Section 4.6.2), to remove the requirement for pre- and postinfusion medication, to add combination cohort(s) with dexamethasone during phase 2 expansion phase, and to update the expected number of cohorts and patients for phase 2. Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific descriptions of text changes, rationales for the changes, and where the changes are located, see Appendix H.

Changes in Amendment 5

1. Global changes:
    i. Changed phase 2a to phase 2 throughout protocol.
    ii. For consistency of terminology, replaced "monotherapy" with "single agent" throughout protocol.
    iii. Added "relapsed" to description of study population (eg, patients with relapsed/refractory MM) throughout protocol.
2. Updated Introduction for consistency with recently updated Investigator's Brochure (Edition 2).
3. Added Clinical Safety section.
4. Updated and reorganized Potential Effects Based on Nonclinical and Clinical Studies section to include clinical data.
5. Updated study rationale section, which includes reduction in study drug infusion time and removal of requirement for pre- and postinfusion medications.
6. Updated phase 2 primary and secondary objectives to reflect addition of dexamethasone combination cohort.
7. Included description of dexamethasone combination arm in study design section and study design figure.
8. Added definition of "DLT-like."
9. Updated expected number of patients.
10. Added guidance regarding discontinuation of dexamethasone for combination arm.
11. Revised end of study description.
12. Increased frequency of PFS follow-up to 4 weeks for patients who discontinue for reasons other than progressive disease.
13. Added Posttrial Access section.
14. Updated inclusion criterion for females of childbearing potential and male patients.
15. Revised exclusion criterion regarding severe allergic or anaphylactic reactions.
16. Revised Study Drug Administration section to change infusion time, remove unnecessary detail, remove pre- and postinfusion medications, and add Administration of Dexamethasone section.
17. Clarified Dose Escalation Rules.
18. Clarified Dose Modification Guidelines and added Dexamethasone Dose Modification section.

19. Updated Excluded Concomitant Medications and Procedures to address treatment of thrombocytopenia and tumor flare.
20. Moved Premedication section from Study Drug Administration section to Permitted Concomitant Medications and Procedures section.
21. Moved Postinfusion Medication subsection from Study Drug Administration section to Permitted Concomitant Medications and Procedures section and added guidance regarding Grade ≥2 IRRs.
22. Clarified guidance in Other Permitted Concomitant Medications and Procedures section.
23. Provided additional guidance regarding Handling of IRRs (Table 8.b and Table 8.c).
24. Provided additional guidance regarding Handling of Low Platelet Counts.
25. Added guidance regarding procurement and sourcing of dexamethasone.
26. Added antiplatelet antibody testing to table for Clinical Chemistry and Hematology Tests (Table 9.a).
27. Added Bone Marrow Morphology subsection to Bone Marrow Aspiration.
28. Corrected sentence regarding serum PK samples.
29. Added blood sample for T-lymphocyte, B-lymphocyte, and natural killer cells (TBMK).
30. Provided additional reason for withdrawal of patient from study.
31. Provided additional guidance for posttreatment imaging of patients with extramedullary disease.
32. Revised list of analysis sets and efficacy analyses in statistical plans section.
33. Updated Determination of Sample Size for phase 2.
34. Revised Schedule of Events (Appendix A) as follows:
    - Revised visit days for Schedules C and D: C1D4 changed to C1D3; C2D4 changed to C2D3.
    - Removed the following visits:
        - Schedule B: C1D4, C1D18, C2D4
        - Schedule C: C3D15
        - Schedule D: C3D15.
    - Added parentheses to crosses (indicating that tests are only to be performed under certain circumstances as indicated in footnotes) throughout SOE for 24-hour urine protein.
    - Revised SOE to make collection of the following tests consistent and, where previously missing at C1D1, added footnote k and parentheses to crosses (indicating

that tests are only to be performed under certain circumstances as indicated in footnote) for the following tests:

- Serum M-protein
- 24-hour urine M-protein (also, throughout SOE, added parentheses to all crosses)
- Serum FLC assay
- Immunofixation – serum and urine
- Quantification of Ig.

- Added blood sample for TBNK assay (*local analysis if available*) (also see Change 29).
- Removed triplicate 12-lead ECGs from Schedule B visits on C1D8 and C2D8.
- Clarified screening visit for Skeletal Survey rows, added visit time points, and, where missing, added parentheses to time points.
- Added PET-CT to CT or MRI rows and, where missing, added parentheses to time points.
- Added PET-CT to CT or MRI rows.
- Added anti-platelet antibody testing rows.
- Added time points to Immunofixation–serum and urine rows.
- Added investigator assessment of disease response/status rows.
- Added time points to quantification of Ig rows.
- Added time points to serum FLC assay rows.
- Clarified screening visit for Immunofixation-serum and urine rows.
- End of Treatment and Follow-up: changed PFS follow-up visit from 12 to 4 weeks.

35. Revised Schedule of Events footnotes to:

- Clarify note regarding crosses in parentheses (X).
- Clarify footnote c regarding collection of ECG(s).
- Clarify footnote f regarding patients who have a complete skeletal survey at screening and regarding posttreatment follow-up of patients with extramedullary disease.
- Revise footnotes k, m, and x.
- Add footnotes aa, bb, cc and dd.

36. Revised Appendix B Bone Marrow Collection and Assessment Schedules.
    - Changed PFS follow-up from every 12 to every 4 weeks.
    - Added bone marrow morphology to row for disease assessment and added time points.
    - Added footnote e.
37. Revised Appendix C Pharmacokinetic Sampling Schedules: Table 4 through Table 9 for Schedules B (Q2W), C (Q3W) and D (Q4W).
    - Revised column headings for visit days.
    - Revised descriptions of time points.
    - Removed/revised certain visits or visit days.
    - Revised footnotes pertaining to timeframe of eating and drinking in relation to ECGs and PK.

Protocol Amendment 4 Summary and Rationale

This document describes the changes in reference to the protocol incorporating Amendment No. 04. Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific descriptions of text changes, rationales for the changes, and where the changes are located, see Appendix H.

Changes in Amendment 4

1. Added 3 schedules (Schedule B, C and D) to the original schedule (Schedule A) to be evaluated during the dose escalation phase.
2. Modified hematologic TEAEs to be considered DLTs.
3. Modified criteria for beginning or delaying a subsequent treatment cycle.
4. Modified triplicate 12-lead ECGs as a separate procedure from safety 12-lead ECGs.
5. Added coagulation tests and removed “serum” from categorization of chemistry tests.
6. Modified bone marrow aspirate sample collection time points.
7. Added subsequent anticancer therapy to AE and SAE reporting timelines.
8. Modified details of patients who withdraw or miss doses for reasons other than a DLT.
9. Added option for eligible patients for intrapatient dose escalation to continue in a different schedule.
10. Miscellaneous changes.

Protocol Amendment 3 Summary and Rationale

This document describes the changes in reference to the protocol incorporating Amendment No. 03.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes, rationales for the changes, and where the changes are located, see Appendix H.

Changes in Amendment 3

1. Removed test dose.
2. Reduced number of dose escalation levels to remove possible subtherapeutic doses.
3. Removed baseline visit (Day -1) associated with test dose administration.
4. Revised enrollment staggering to allow concurrent enrollment of second and third patients within a cohort.
5. Removed measurement of soluble CD38 in serum.
6. Clarified collection of bone marrow aspirates and added collection time points during screening and on-treatment.
7. Clarified inclusion criterion for hepatitis.
8. Clarified definition of excluded corticosteroid treatment.
9. Clarified observation time for vital signs after TAK-573 infusion.
10. Clarified that serum samples collected for pharmacokinetic (PK) analysis may also be used for exploration of pharmacodynamic markers.
11. Clarified that blood samples will be collected in case of an infusion-related reaction.
12. Added statement that treatment with TAK-573 may be continued after progressive disease under certain circumstances.
13. Revised the number of sampling time points for serum biomarkers.
14. Added predose sampling for baseline reference on C1D1 for serum biomarkers, serum immunogenicity, blood flow immunoprofiling and blood flow receptor occupancy.
15. Added Cycle 1 Day 15 and Cycle 2 Day 15 serum M-protein for modeling purposes and immunoprofiling.
16. Added electrocardiogram (ECG) assessments and clarified that triplicate ECG readings can be used for purposes of local safety ECG evaluation.
17. Added the possibility of defining an optimal biologic dose (OBD) based on pharmacodynamic endpoints as an alternative to the maximum tolerated dose (MTD) based on dose-limiting toxicities DLTs as a possible dose for future studies.
18. Revised PK sample collection schedule.

19. Modified Schedule of Events.
20. Changed the ECOG performance status requirement from 0-2 to 0-1.

Protocol Amendment 2 Summary and Rationale

This document describes the changes in reference to the protocol incorporating Amendment No. 02. The primary reason for this amendment is to update the original protocol to comply with Takeda standards and standard operating procedures.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix H.

Changes in Amendment 2

1. Edited so that testing is not limited to antibody drug conjugates.
2. Toxicology section updated with more recent data.
3. Clarified central versus local ECG analysis.
4. Added detail regarding study drug infusion.
5. Corrected description of postinfusion medication.
6. Clarified method and type of laboratory testing (central versus local laboratories).
7. Changed definition of complement analysis.
8. Clarified the collection and usage of clinical samples (blood and bone marrow) for pharmacodynamic analysis and sample utilization.
9. Provided additional detail regarding biomarker measurement.
10. Clarified description of serum samples for immunogenicity testing.
11. Removed text regarding antidrug neutralizing antibodies.
12. Deleted mention of Day 29 assessment from sample size section.
13. Changed at time of “enrollment” and “randomization” to “first dose”.
14. Study conduct sections were added for patient weight and ECOG performance status.
15. End-of-treatment language was standardized.
16. Clarified definition of disease assessment.
17. Modified triplicate ECG measurement time points.
18. Deleted Appendix F.
19. Clarified timing when concomitant medications will be recorded.
20. Clarified handling procedures for TAK-573.
21. Removed enrollment section.

22. Reduced the number of time points for immunofixation of serum and urine.
23. Modified Schedule of Events.
24. Measurement of IgD and IgE no longer a requirement for all patients at baseline.

Protocol Amendment 1 Summary and Rationale

This document describes the changes in reference to the protocol incorporating Amendment No. 01. The primary reason for this amendment is to update the original protocol to comply with Takeda standards and standard operating procedures.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix I.

Changes in Amendment 1

Global Changes

1. Change the compound name from TEV-48573 to TAK-573.
2. Change the protocol study number from TV48573-ONC-10128 to TAK-573-1501.

Study Objectives and Endpoints

3. Clarify the Phase 1 and 2A study objectives.
4. Clarify the Phase 1 and 2A study endpoints.

Study Design

5. Update the Overall Study Schematic diagram.
6. Revise the number of patients in the Phase 1 and 2a portions of the study.
7. Clarify the duration of the study.

Study Population

8. Clarify the inclusion criteria.
9. Clarify the exclusion criteria.

Study Drug

10. Clarify the definition of dose-limiting toxicity.
11. Clarify the dose modifications.
12. Clarify the handling of patients who experience infusion-related reactions.

Study Procedures

13. Clarify the primary specimen collection for pharmacokinetics (PK) and biomarker assessments.

14. Update the definition of PK, biomarker, and pharmacodynamics measurements.

Schedule of Events

15. Update the Schedule of Events to reflect changes in Protocol Amendment 1.

Signature Page for TAK-573-1501 Protocol Amend 10 v2 2024-04-03
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