PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICENTER, PHASE I TRIAL EVALUATING THE SAFETY AND PHARMACOKINETICS OF ESCALATING DOSES OF RO7297089 IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA**
PROTOCOL NUMBER:	GO41582
VERSION NUMBER:	4
EUDRACT NUMBER:	2019-003540-76
IND NUMBER:	To be determined
NCT NUMBER:	NCT04434469
TEST PRODUCT:	RO7297089 (BPCT2605S)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
10-Nov-2020 02:40:06	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on title page	—	—	—
3	18 September 2020	—	—	—
2	23 April 2020	Belgium	2	30 July 2020
		Norway	2	10 May 2020
1	25 November 2019	—	—	—

PROTOCOL AMENDMENT, VERSION 4
RATIONALE

Protocol GO41582 has been amended to add the option to implement up to three dose-escalation arms in a given dose cohort to mitigate the risk of infusion-related reactions (IRRs). These dose-escalation arms differ in the schedule of RO7297089 administration in Cycle 1. In addition, this amendment modifies eligibility criteria related to serum monoclonal protein (M-protein) levels and serum calcium levels. Changes to the protocol, along with a rationale for each change, are summarized below.

The following changes have been incorporated in Version 4:

- Section 3.1.1 has been revised to add an option for up to three dose-escalation arms in a dose cohort. These dose-escalation arms define the Cycle 1 administration schedule for RO7297089 and include a flat-dose arm (Arm A), a split-dose arm (Arm B), and a step-dose arm (Arm C). The criteria for the opening and enrollment into each of these arms are also described.
- Additional changes regarding the dose-escalation arms are as follows:
  - Section 3.1.3 has been revised to specify that RO7297089 administration for the first cycle after intrapatient dose escalation may follow any administration schedule previously evaluated in the study.
  - Section 3.1.5 has been revised to specify that the Internal Safety Committee (ISC) will make decisions in consultation with study investigators regarding opening Arm B and/or Arm C for a given dose cohort.
  - Section 3.3.2 has been revised to include rationale for the dose-escalation arms.
  - Section 4.3.2.1 has been revised to include additional dosing instructions regarding the additional dose-escalation arms.
  - Section 4.5.5 has been revised to include additional vital sign monitoring instructions regarding the additional dose-escalation arms.
  - Appendix 1 and Appendix 3 have been revised to reflect the additional timepoints and assessments regarding the additional dose-escalation arms.
- Section 4.1.1 has been revised to update the inclusion criterion for serum M-protein concentration from ≥1.0 g/dL (≥10 g/L) to ≥0.5 g/dL (≥5 g/L). This revision was made on the recommendation of investigators based on the patient population for this study. Additionally, at least three historical values for serum M-protein (or serum free light chains [SFLC], if light chain–only disease) from the end of prior therapy to the initiation of study treatment with RO7297089 will be collected if available (Section 4.5.6 and Appendix 1).

- Section 4.1.1 has been revised to update the inclusion criterion for serum calcium concentration (corrected for albumin) from a threshold of the upper limit of normal (ULN) to a threshold of ≤11.5 mg/dL (2.9 mmol/L). This new threshold is consistent with NCI CTCAE v5.0 guidelines for hypercalcemia and removes the threshold variability that occurs when local laboratory ranges are used.
- Section 4.1.2 has been revised to clarify the exclusion criterion regarding previous treatment with systemic immunosuppressive medications.
- Section 5.1.1.1 has been revised to provide recent information regarding IRR events in this study and to reiterate premedication instructions accordingly.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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TITLE:	**AN OPEN-LABEL, MULTICENTER, PHASE I TRIAL EVALUATING THE SAFETY AND PHARMACOKINETICS OF ESCALATING DOSES OF RO7297089 IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please retain a copy of the signed form as instructed by the Sponsor.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, MULTICENTER, PHASE I TRIAL EVALUATING THE SAFETY AND PHARMACOKINETICS OF ESCALATING DOSES OF RO7297089 IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA**
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IND NUMBER:	To be determined
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TEST PRODUCT:	RO7297089 (BPCT2605S)
PHASE:	I
INDICATION:	Relapsed or refractory multiple myeloma
SPONSOR:	Genentech, Inc.

OBJECTIVES AND ENDPOINTS

This study will evaluate the safety and pharmacokinetics of RO7297089 in patients with relapsed or refractory (R/R) multiple myeloma (MM) and make a preliminary assessment of anti-tumor activity. Specific objectives and corresponding endpoints for the study are outlined below.

Safety Objective (Primary Study Objective)

The safety objective for this study is to evaluate the safety of RO7297089, including estimation of the maximum tolerated dose (MTD) and characterization of dose-limiting toxicities (DLTs), on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) and the Modified Cytokine-Release Syndrome Grading System
- Change from baseline in targeted vital signs
- Change from baseline in targeted ECG parameters
- Change from baseline in targeted clinical laboratory test results
- Relationship between RO7297089 dose and safety, pharmacokinetic (PK), activity, and immunogenicity endpoints

Pharmacokinetic Objectives

The PK objective for this study is to characterize the RO7297089 PK profile on the basis of the following endpoints:

- Serum concentration of RO7297089 at specified timepoints
- PK parameters for RO7297089

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the safety and activity of RO7297089 on the basis of the following endpoints:

  - Relationship between serum concentration or PK parameters for RO7297089 and safety endpoints
  - Relationship between serum concentration or PK parameters for RO7297089 and activity endpoints
- To evaluate potential relationships between selected covariates and exposure to RO7297089 on the basis of the following endpoint:
  - Relationship between selected covariates and serum concentration or PK parameters for RO7297089

Activity Objectives

The activity objective for this study is to make a preliminary assessment of the activity of RO7297089 on the basis of the following endpoints:

- Objective response rate, defined as a stringent complete response, complete response, very good partial response, or partial response, as determined by the investigator according to International Myeloma Working Group (IMWG) Uniform Response Criteria
- Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to IMWG Uniform Response Criteria

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to RO7297089 on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and safety, PK, biomarker, or activity endpoints

Biomarker Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to RO7297089 (i.e., predictive biomarkers), are early surrogates of activity, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to RO7297089, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of RO7297089 activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in blood and tissue samples (listed in the protocol) and safety, PK, activity, immunogenicity, or other biomarker endpoints

Additional Objective

An additional objective for this study is to identify a recommended Phase II dose (RP2D) and regimen for RO7297089 on the basis of the following endpoint:

- Relationship between RO7297089 exposure and safety, PK, activity, and immunogenicity endpoints

STUDY DESIGN

Description of Study

This is a first-in-human Phase I, open-label, multicenter, global, dose-escalation study designed to evaluate the safety, tolerability, and pharmacokinetics of RO7297089 and make a preliminary assessment of anti-tumor activity in patients with R/R MM for whom no established therapy for MM is appropriate and available or who are intolerant to those established therapies. The study consists of a screening period of up to 28 days and a minimum follow-up period of 90 days after treatment. Following confirmation of eligibility, patients will receive RO7297089 by IV infusion. Patients will be enrolled in two stages: a dose-escalation stage and an expansion stage. *To mitigate the risk of infusion-related reactions (IRRs), up to three dose-escalation arms that*

differ in the RO7297089 administration schedule for Cycle 1 may be enrolled in a dose-escalation cohort. The study will enroll approximately 30–50 patients during the dose-escalation stage and approximately 30 patients during the expansion stage at approximately 12 sites globally.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients must re-sign the consent form prior to re screening. The investigator will record reasons for screen failure in the screening log.

All patients will be closely monitored for adverse events throughout the study and for at least 90 days after the final dose of study treatment. Adverse events will be graded according to the NCI CTCAE v5.0, with the exception of cytokine-release syndrome (CRS), which will be graded according to the Modified Cytokine-Release Syndrome Grading System.

Patients may continue treatment with RO7297089 until disease progression as determined by the investigator using IMWG Uniform Response Criteria, unacceptable toxicity, start of new anti-cancer therapy, or withdrawal from study participation, whichever occurs first.

Dose-Escalation Stage

Approximately 30–50 patients will be enrolled in the dose-escalation stage. The dose-escalation stage of the study will assess the safety, tolerability, and pharmacokinetics of RO7297089 administered by IV infusion. *The cycle length is 14 days.*

To mitigate the risk of IRRs, up to three dose-escalation arms may be enrolled in a given dose cohort. These arms differ in the RO7297089 administration schedule for Cycle 1:

- ***Arm A (Flat Dose-Escalation Arm).*** *Patients in Arm A will receive the Cycle 1 target dose of RO7297089 as a flat dose independent of body weight on Day 1 and Day 8. Dosing for Cycle 2 and beyond will follow the same administration schedule. The DLT assessment window for Arm A is 14 days (Cycle 1, Days 1–14).*
- ***Arm B (Split Dose-Escalation Arm).*** *Patients in Arm B will receive the first dose in Cycle 1 as a split dose. The initial target dose of RO7297089 will be divided over 2 days (Days 1 and 2), and the full target dose will be administered on Day 8.*

  Initially, the dose will be divided such that 50% of the target dose is administered on Day 1 and the remaining 50% on Day 2. If the Day 1 dose is associated with a Grade ≥ 2 IRR, the ratio may be adjusted for subsequent patients so that a smaller percentage of the dose is administered on Day 1, with the remainder of the dose administered on Day 2. For example, 25% of the target dose administered on Day 1 and the remaining 75% administered on Day 2.

  If a patient does not receive the full planned dose on Day 1 because of scheduling reasons but has received at least 75% of the intended Day 1 dose, the patient may proceed with the Day 2 infusion to receive the remainder of the full target dose.

  For Cycle 2 and beyond, RO7297089 will be administered on Day 1 and Day 8 of each 14-day cycle. The DLT assessment window for Arm B is 14 days (Cycle 1, Days 1–14).
- ***Arm C (Single-Step Dose-Escalation Arm).*** *Patients in Arm C will receive the first cycle of RO2797089 as a single-step dose escalation. The Cycle 1, Day 1 dose will be 60 mg, followed by the full target dose on Day 8. For Cycle 2 and beyond, the target dose of RO7297089 will be administered on Day 1 and Day 8 of each 14-day cycle. The DLT assessment window for Arm C is 14 days (Cycle 1, Day 8 to Cycle 2, Day 7, to allow for two target doses); the window excludes the Cycle 1, Day 1 60-mg dose, which has already cleared.*

For all arms, the target dose refers to the highest dose administered in Cycle 1; this target dose will be administered on Day 1 and Day 8 of subsequent cycles.

Enrollment in the dose-escalation arms will be managed as follows:

- *For new dose cohorts, all patients will enroll in Arm A unless criteria have been met for opening Arms B or C in a previous cohort.*

- *Arm B may open if the planned infusion time for Arm A exceeds 4 hours on Cycle 1, Day 1. Arm C may open if 2 or more patients in Arm B of that dose cohort experience any grade IRR that precludes the patient from receiving the full target dose during Cycle 1, Day 1 and Day 2.*
- *Once Arm B is open, Arm A for that dose cohort may close to further enrollment and may not open for subsequent dose cohorts. Similarly, once Arm C is open, Arm B for that dose cohort may close to further enrollment and may not open for subsequent dose cohorts.*
- *A minimum of 3 patients must complete the DLT assessment period for a given arm (Arm A, B, or C) before dose escalation for that arm may occur.*

Dose escalations will be guided by the modified continual reassessment method of escalation with overdose control (mCRM-EWOC) model (Neuenschwander et al. 2008). All cohorts will enroll a minimum of 3 patients. Enrollment of the first 2 patients in each *arm of each* dose-escalation cohort will be staggered such that the respective Cycle 1, Day 1 treatments are administered ≥72 hours apart. The maximal dose escalation increment recommended by the model will be 3-fold. In addition, the relevant demographic, adverse event, laboratory, dose administration, and available PK data will be reviewed prior to dose-escalation decisions, which will be made by an Internal Safety Committee (ISC) in consultation with the investigator.

Evidence of clinical activity at a given dose level (e.g., decrease in serum monoclonal protein [M-protein]) or PD activity (e.g., NK cell activation) may ungate backfill cohorts at doses that have already completed DLT assessment and have been found not to exceed the MTD in escalation cohorts. DLT information from patients in these back-fill cohorts will be used to inform the mCRM-EWOC model.

Patients will be closely monitored for adverse events during a DLT assessment window (14 days)*, as defined above for each arm*. Adverse events identified as DLTs, as defined below, will be reported to the Sponsor within 24 hours.

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD assessments and will be replaced by an additional patient at that same dose level. Patients must receive two *planned target* doses of RO7297089 during the DLT assessment window to be considered DLT-evaluable. Treatment delays during the first cycle of RO7297089 will be allowed if they are less than one cycle (i.e., <14 days); under these circumstances, the DLT assessment window may be extended up to *an additional 7* days in order to capture two *planned target* doses of treatment. Patients who receive supportive care during the DLT assessment window that confounds the evaluation of DLTs (not including supportive care described below as part of the DLT definition) may be replaced at the discretion of the Medical Monitor.

As described below, the ISC will additionally review cumulative safety data and make recommendations regarding overall study conduct to ensure patient safety while receiving study treatment. These recommendations include suspending patient enrollment based on the overall benefit-risk profile of RO7297089 during dose escalation.

Definition of Dose-Limiting Toxicity

All adverse events, including DLTs, will be reported according to instructions in the protocol and graded according to the NCI CTCAE v5.0, with the exception of CRS, which will be graded according to the Modified Cytokine-Release Syndrome Grading System. DLTs will be treated according to clinical practice and will be monitored through their resolution. Any one of the following events will be considered a DLT if it occurs during the DLT assessment window (Days 1–14 of Cycle 1 *for Arms A and B; Cycle 1, Day 8 to Cycle 2, Day 7 for Arm C*) unless clearly attributed to another identified etiology by the investigator (e.g., cancer progression):

- Any Grade 4 or 5 adverse event
- Grade 3 febrile neutropenia lasting >3 days

- Grade 3 elevation of serum hepatic transaminase (ALT or AST) lasting >7 days

  Any Grade 3 AST or ALT elevation that occurs in the context of Grade ≤ 2 CRS (as defined by the criteria established by Lee et al. [2019]) and resolves to Grade ≤ 1 within <3 days will not be considered a DLT.
- Grade 3 elevation of serum bilirubin (total)
- Any increase in hepatic transaminase (ALT or AST) $>3\times$ baseline in combination with either an increase in direct bilirubin $>2\times$ upper limit of normal (ULN) or clinical jaundice, in the absence of cholestasis or other contributory factors (e.g., concomitant exposure to known hepatotoxic agent, or documented infectious etiology)

  This is suggestive of potential drug-induced liver injury (according to Hy's Law).
- Grade 3 non-hematologic, non-hepatic major organ adverse event, with the following exceptions:
  - Grade 3 nausea, vomiting, or diarrhea that improves to Grade ≤ 2 with standard-of-care therapy in ≤ 3 days will not be considered a DLT.

    Grade 3 nausea or vomiting that requires total parenteral nutrition or hospitalization is not excluded and should be considered a DLT.
  - Grade 3 fatigue that improves to Grade ≤ 2 within 7 days will not be considered a DLT.
  - Grade 3 infection that resolves within 7 days to Grade ≤ 2 and does not require intensive care unit will not be considered a DLT.
  - Grade 3 fever (as defined by >40ºC) for ≤ 48 hours will not be considered a DLT.
  - Grade 3 laboratory abnormalities that are asymptomatic, resolve to Grade ≤ 1 or baseline within 7 days, and are considered by the investigator not to be clinically significant will not be considered a DLT.
  - Fractures of any grade at site of lytic bone disease will not be considered a DLT.
  - Grade 3 IRRs will not be considered a DLT, as generally IRRs are not considered to be dose-related events on the basis of experience with monoclonal antibodies. Precautions will be taken if IRRs Grade ≥ 2 occur.

    Grade ≥ 4 IRRs or re-occurrence of an IRR event in a patient that precluded the administration of the full dose or the administration of the next scheduled dose of study drug will be considered a DLT.

Anemia, neutropenia, lymphopenia, leukopenia, and thrombocytopenia are anticipated in the study population due to the extensive prior therapy and myeloma involvement in the R/R MM population. Investigator assessment of causality and change from pre-treatment baseline will be important to characterize the effect of RO7297089 on cytopenias. In addition, infection is a common occurrence in R/R MM due to prior therapy and hypogammaglobulinemia. Hence, infection that recovers as expected with appropriate therapy (as per above) will not be considered a DLT.

Dose-Escalation Rules

The starting dose of RO7297089 will be 60 mg, administered IV weekly for Cohort 1.

Dose escalations will be guided by the mCRM-EWOC model. The MTD is defined as the dose that maximizes the probability of a DLT being in the targeted toxicity interval in the range of 20%–35%, subject to the probability of the DLT being in the excessive toxicity interval in the range of 35%–100% being $<25\%$. For each cohort, patients will be followed through a 14-day DLT assessment window. At each dose-escalation step, the dose can be escalated or de-escalated and/or an additional cohort at that same dose level could be enrolled.

If MTD is not reached, the RP2D will be determined based on the totality of data including clinical activity, safety, PK, and pharmacodynamics biomarkers. Once the MTD or is RP2D determined, all patients in dose-escalation will be eligible to receive the RP2D, based upon ISC decision.

In addition, different dosing regimens (e.g., every 2 weeks) may be explored in parallel, if warranted, on the basis of the safety and PK profile of RO7297089, with DLT periods specific for each regimen and starting dose not exceeding the weekly MTD. Any evaluation of a different administration schedule will be based on the recommendation of the ISC and reviewed with study investigators. Addition of different dosing regimens will require a protocol amendment. For this new regimen, the mCRM-EWOC model and priors as defined in the protocol, as well as the simulations, will be reviewed and possibly modified and the DLT assessment period will be extended to 21 days to ensure that patients have received at least two doses of study drug.

Continued Dosing Beyond the Dose-Limiting Toxicity Observation Period (Cycles ≥2)

Nonclinical toxicology data supports RO7297089 treatment every 7 days. The ethical conduct of a clinical study of cancer requires that patients have the opportunity to continue study treatment provided that the treatment is active and tolerable and patients comply with protocol requirements. Therefore, dosing beyond Cycle 1 for patients with R/R MM will be allowed in the absence of unacceptable toxicity or objective evidence of disease progression as assessed by the treating study investigator and following a careful assessment and discussion of the potential risks and benefits with the patient. Patients will *continue study treatment* until objective disease progression is documented or unacceptable toxicity, whichever occurs first.

RO7297089 administration will be interrupted in patients who experience a DLT during the DLT assessment window. Patients who experience a DLT during the first cycle and whose toxicity returns to baseline within 14 days may be restarted at a dose level tolerated by the prior cohort following discussion with the Medical Monitor. A treatment delay beyond 14 days may be acceptable upon discussion with the Medical Monitor.

Intrapatient Dose Escalation

To maximize the collection of information at relevant doses and minimize the exposure of patients to sub-optimal doses of RO7297089, intrapatient dose escalation may be permitted. Within each assigned dose-escalation cohort, the dose of RO7297089 for an individual patient may be increased to the highest cleared dose level that is tolerated by completed cohorts through *the DLT window*. Patients may be able to undergo intrapatient dose escalation after completing at least two cycles at their originally assigned dose level. Subsequent intrapatient dose escalations may occur after at least one cycle of any subsequently higher cleared dose level without any adverse event that meets the definition of a DLT or necessitates post-administration hospitalization. Once the MTD is declared and the RP2D is determined, intrapatient dose escalation directly to the RP2D is permitted for patients who remain on study and continue to tolerate RO7297089.

At the discretion of the investigator and in consultation with the Medical Monitor, the RO7297089 administration schedule for the first cycle after intrapatient dose escalation may follow any administration schedule previously evaluated in the study.

Expansion Stage

After dose escalation has been completed, approximately 30 patients will be enrolled in the expansion stage. Patients will be treated at the RP2D (at or below the MTD) to obtain additional safety, tolerability, and PK data, as well as preliminary evidence of clinical activity. The ISC will assess all safety data on an ongoing basis. At no time will the dose administered in the expansion stage exceed the highest dose level that qualified as an MTD in the dose escalation stage.

Internal Safety Committee

Given that this is a first-in-human trial, an ISC will be utilized during the study to make recommendations regarding study conduct on the basis of trial safety data to ensure enhanced patient safety monitoring while receiving study treatment. The ISC will be formed before the first patient is enrolled into the study.

The ISC will include at a minimum the Medical Monitor, study Safety Scientist, study Biostatistician, and a Sponsor Medical Monitor not associated with the study. Representatives from other Sponsor functional areas may be included as ad hoc members.

In addition to the ongoing assessment of the incidence and nature of DLTs, adverse events, serious adverse events, adverse events of special interest, and laboratory abnormalities by the investigator and the Medical Monitor, the ISC will review cumulative data at regular intervals during the study. This committee will make decisions in consultation with study investigators regarding *opening Arm B and/or Arm C for a given dose cohort as well as* dose escalations based on the plan described in the protocol. The ISC, in consultation with study investigators, will also review the cumulative data from dose escalation prior to opening the dose expansion portion of the study and review data from the dose expansion at routine intervals. In addition, the ISC will meet regularly and as needed at the request of the study Medical Monitor (e.g., based on unexpected safety signals). The ISC may further make recommendations regarding study conduct, including, but not limited to, the following: performing additional safety analyses, amending the study protocol, holding patient enrollment pending further safety evaluations, enrolling additional patients at a specific dose level and schedule to obtain additional safety data, holding/discontinuing study treatment, or terminating the study.

Number of Patients

The study will enroll approximately 30–50 patients during the dose-escalation stage and approximately 30 patients during the expansion stage.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1

  ECOG Performance Status of 2 due to MM may be eligible after discussion with the Medical Monitor.
- Life expectancy of at least 12 weeks
- Patients must have R/R MM for which no established therapy for MM is appropriate and available or be intolerant to those established therapies
- Agreement to provide bone marrow biopsy and aspirate samples as detailed in the protocol
- Adverse events from prior anti-cancer therapy resolved to Grade ≤ 1, with the following exceptions:
  - Any grade alopecia
  - Peripheral sensory or motor neuropathy that has resolved to Grade ≤ 2
- Measurable disease, defined as at least one of the following:
  - Serum monoclonal protein (M-protein) ≥ *0.5* g/dL (≥ *5* g/L)
  - Urine M-protein ≥ 200 mg/24 hr
  - Serum free light chain (SFLC) assay: Involved SFLC ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal SFLC ratio (<0.26 or >1.65)
- Laboratory values as follows:
  - Hepatic function:
    - AST and ALT ≤ 3 × ULN
    - Total bilirubin ≤ 1.5 × ULN

      Patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
  - Hematologic function:
    - Platelet count ≥ 50,000/mm^3 without transfusion within 7 days of assessment

- ANC $\geq$1000/mm^3
- Total hemoglobin $\geq$8 g/dL without transfusion within 14 days of assessment

  Patients who do not meet criteria for hematologic function because of MM related cytopenias (e.g., due to extensive marrow involvement by MM) may be enrolled into the study after discussion with the Medical Monitor.

- Creatinine clearance $\geq$30 mL/min (either calculated using a modified Cockcroft-Gault calculation or per 24-hour urine collection; inulin or radionuclide-based methods may be used after discussion with Medical Monitor)
- Serum calcium (corrected for albumin) level $\leq 11.5\ mg/dL\ (2.9\ mmol/L)$

  Treatment of hypercalcemia is allowed and patient may enroll if hypercalcemia returns to normal with standard treatment.

- For women of childbearing potential: agreement to remain completely abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 28 days after the final dose of RO7297089. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, or copper intrauterine devices.

  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug and is consistent with the usual lifestyle of the patient. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain completely abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom with spermicide during the treatment period and for 28 days after the final dose of RO7297089 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the final dose of study drug

Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

- Prior use of any monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate for the treatment of cancer within 4 weeks before first RO7297089 infusion
- Prior treatment with systemic immunotherapeutic agents, including, but not limited to, cytokine therapy and anti-CTLA4, anti−PD-1, and anti−PD-L1 therapeutic antibodies, within 12 weeks or 5 half-lives of the drug, whichever is shorter, before first RO7297089 infusion
- Prior treatment with CAR-T therapy within 90 days before first study drug administration
- Treatment with any chemotherapeutic agent, or treatment with any other anti-cancer agent (investigational or otherwise) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to first RO7297089 infusion
- Autologous stem cell transplantation within 100 days prior to first RO7297089 infusion
- Allogeneic stem cell transplantation within 180 days prior to first RO7297089 infusion or requiring immunosuppression for treatment or prophylaxis of graft versus host disease
- Primary or secondary plasma cell leukemia as defined by an absolute plasma cell count exceeding 2000/μL or 20% of the peripheral blood white cells
- Known cardiac amyloidosis
- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins) or any of the components of the RO7297089 drug product
- Significant active pulmonary disease (e.g., chronic obstructive pulmonary disease with known forced expiratory volume in 1 second of less than 50% of predicted normal, severe persistent asthma) that may limit a patient's ability to adequately respond to an IRR event in the investigator's assessment
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the following exceptions:
  - Patients with history of curatively basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix
  - Localized prostate cancer Gleason Grade ≤6 AND with stable prostate-specific antigen levels off treatment
  - Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission for ≥2 years prior to first RO7297089 infusion.
- Acute or chronic hepatitis C virus (HCV) infection

  Patients who are positive for the HCV antibody must be negative for HCV by PCR to be eligible for study participation.
- Positive serologic or PCR test result for acute or chronic hepatitis B virus (HBV) infection

  Patients whose HBV infection status cannot be determined by serologic test results must be negative for HBV by PCR to be eligible for study participation.

  Antiviral prophylaxis for patients at risk of HBV reactivation is permitted.
- Known HIV infection unless the patient meets all the following criteria:
  - CD4 count ≥350 cells/μL prior to enrollment
  - No history of AIDS-defining illness in the last 12 months prior to study enrollment
  - Must be on established antiretroviral therapy for at least 4 weeks and have an HIV viral load <400 copies/mL prior to enrollment
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV anti-microbial therapy within 14 days prior to first RO7297089 infusion

- Administration of a live, attenuated vaccine within 4 weeks before first RO7297089 infusion or anticipation that such a live, attenuated vaccine will be required during the study

  Influenza vaccine should be given during influenza season (approximately October to May in the Northern Hemisphere; approximately May to October in the Southern Hemisphere). Patients must not receive live, attenuated influenza vaccine at any time during the study period.

  Investigators should review the vaccination status of potential study patients being considered for this study and follow the local guidelines for adult vaccination with any other non-live vaccines intended to prevent infectious diseases prior to study.

- Received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) *within 2 weeks prior to the first dose of RO7297089,* with the *following* exception*s*:

  Patients who received acute, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea*, prophylactic corticosteroids to prevent allergic reaction to CT contrast*) may be enrolled in the study after discussion with the Medical Monitor.

  The use of corticosteroids for anti-cancer treatment is permitted prior to the first dose of RO7297089; washout requirements for anti-cancer therapies are defined above.

  The use of corticosteroid treatment of ≤10 mg/day prednisone or equivalent is permitted.

  The use of inhaled corticosteroids is permitted.

  The use of mineralocorticoids for management of orthostatic hypotension is permitted.

  The use of physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.

- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Significant cardiovascular disease (such as, but not limited to, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina)
- Current CNS involvement by MM

  Patients with a history of CNS involvement must have at least 6 months of remission in the CNS without interval CNS directed therapies prior to first RO7297089 infusion.

  Patients with a history of CNS involvement must have a magnetic resonance imaging of the brain and lumbar puncture during screening to confirm that CNS is clear.

- Recent major surgery within 4 weeks prior to first RO7297089 infusion or anticipation of need for a major surgical procedure during the course of the study

  Protocol-mandated procedures (e.g., tumor biopsies and bone marrow biopsies) and superficial lymph node biopsies for diagnosis are permitted.

  Prophylactic orthopedic intervention to long bones to prevent fracture is permitted within 2 weeks prior to first RO7297089 infusion.

- Uncontrolled tumor-related pain

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment.

Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 1 year after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3 years.

INVESTIGATIONAL MEDICINAL PRODUCT

The investigational medicinal product for this study is RO7297089 (BPCT2605S). Dosing independent of body weight will be used for RO7297089. The dose of RO7297089 for each patient will depend on the dose level assignment as detailed in the protocol. Patients will receive RO7297089 by IV infusion.

STATISTICAL METHODS

Primary Analysis

The safety analysis population will consist of all patients who received at least one dose of study drug. Statistical summaries will be descriptive in nature (e.g., incidence rates, means, and percentiles).

Primary Safety Model (mCRM-EWOC)

An mCRM-EWOC model will be utilized to inform decision-making about the dose of RO7297089. All patients will be followed through the DLT window (2 weeks) and be enrolled in a sequential manner. Patients within a cohort will be sequentially enrolled in cohorts of three patients each, which, if required, can be expanded with additional patients.

The dose-toxicity relationship will be described by a two-parameter logistic regression model, which can be updated anytime by incorporating available information from all patients. A minimal informative prior will be used.

The Sponsor and Investigators will evaluate the next dose recommended by the mCRM-EWOC design and agree on the dose for the subsequent cohort. At each dose-escalation step, the dose can be escalated, de-escalated, or an additional cohort at that same dose level could be enrolled.

The mCRM will continue until a maximum of approximately 40 patients, or all rules in a pre-defined set of MTD precision criteria, have been reached; or if it is concluded that the RP2D has been defined, using multiple parameters of safety, PD, and efficacy data.

The set of MTD precision criteria is:

- At least 9 patients have accrued overall;
- At least 6 patients have been accrued near the MTD dose where “near” is defined as being within 20% of the MTD;
- The probability that the MTD lies within the target toxicity interval is above 40%.

After the dose-escalation phase, a tentative RP2D, which will guide the recommended dose in expansion, will be defined. The final RP2D will be estimated based on the DLT occurrence rate in all patients evaluable for DLTs in the dose-escalation and dose-expansion parts of the study. The model will be implemented by R and Jags software.

All patients from the safety analysis population who follow the protocol-specified dose regimen within the DLT observation period and have undergone the scheduled safety evaluations, or who discontinued earlier due to a DLT, will be included in the MTD-determined analysis.

Clinical judgment can always override the Bayesian adaptive design recommendations in the dose-selection process.

Analyses of Exposure, Adverse Event, Laboratory, and Vital Sign Data

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

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

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

Determination of Sample Size

Sample size of the dose-escalation study is based on the mCRM-EWOC design and not based on statistical power calculations. A minimum of 9 evaluable patients and approximately 30–50 evaluable patients will be enrolled for dose-escalation. A simulation study has been conducted to evaluate the sample size. Approximately 30 patients may be enrolled in the expansion cohort to better characterize PK, PD, and preliminary activity signals at the presumed RP2D.

A sample size of thirty patients is a reasonable size for the expansion cohort in order to obtain an estimate of the response rate; with a sample size of 30 and an observed response rate of 20%, the 90% confidence interval for the true response rate is (8%, 32%), corresponding with 2 and 10 responses, and the expected number of responses is 6.

Interim Analyses

Continuous safety monitoring and interim analyses will be performed for the expansion portion of the study to guide potential early stopping of enrollment in the event of unacceptable toxicity or a lower than expected response rate.

A Bayesian posterior probability approach (Thall and Simon 1994) with a uniform prior will be used to evaluate toxicity, including the rate of DLTs. If at any time in the expansion cohort, the number of observed DLTs indicates that there is an approximately 80% chance that the true DLT rate is $\geq$20% (e.g., DLTs observed in 2/5, 3/10, 4/15, 5/20 patients), accrual to the cohort may be paused and the ISC will meet to determine whether further enrollment in the cohort should be halted taking into account feedback from study investigators.

A similar approach will be used to assess the response rate. Specifically, after approximately 15 patients in the expansion cohort have completed their first tumor assessment, an interim analysis will be conducted to inform potential early stopping of enrollment if observed response rates are lower than expected. Using the Bayesian posterior probability approach with a uniform prior, the cohort may be stopped if the objective response rate is less or equal to 25% with a probability greater or equal to 60%. This would be the case for example if 2 or fewer out of the first 15 patients have an objective response. At each interim analysis, the ISC will review the response data and decide whether to recommend an early decision to stop enrollment in the subgroup due to futility. Additional futility analyses may be conducted in periodic review of efficacy data. In all cases, decisions to stop enrollment into the expansion cohort will be made in consultation with study investigators.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AUC	area under the concentration–time curve
BCMA	B-cell maturation antigen
CAR-T	chimeric antigen receptor T cell
C_{max}	maximum concentration observed
C_{min}	minimum concentration observed
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
EOI	*end of infusion*
EWOC	escalation with overdose control
FACS	fluorescence-activated cell sorting
Fc	fragment crystallizable
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
ICH	International Council for Harmonisation
IFN-γ	interferon-γ
IL	interleukin
IMiD	immunomodulatory drug
IMP	investigational medicinal product
IMWG	International Myeloma Working Group
IND	Investigational New Drug (Application)

Abbreviation	Definition
IRB	Institutional Review Board
IRR	infusion-related reaction
ISC	Internal Safety Committee
IVIg	intravenous immunoglobulin
IxRS	interactive voice or web-based response system
MAS	macrophage activation syndrome
mCRM	modified continual reassessment method
MM	multiple myeloma
MMC	multiple myeloma cell
M-protein	monoclonal protein
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NK	natural killer (cell)
NOAEL	no observed adverse-effect level
ORR	objective response rate
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
PR	partial response
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RP2D	recommended Phase II dose
R/R	relapsed or refractory
sBCMA	soluble B-cell maturation antigen
sCR	stringent complete response
SFLC	serum free light chain
SIFE	serum protein electrophoresis
SPEP	serum protein electrophoresis
t_{max}	time to maximum concentration observed
TLS	tumor lysis syndrome
TNF-α	tumor necrosis factor-α
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	serum protein electrophoresis
USM	*Urgent Safety Measure*
USPI	U.S. Package Insert

Abbreviation	Definition
VGPR	very good partial response
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE MYELOMA

Multiple myeloma (MM) is a neoplasm characterized by the proliferation and accumulation of malignant plasma cells. Worldwide, approximately 160,000 people are diagnosed with MM annually (Bray et al. 2018). End-organ damage resulting from MM includes hypercalcemia, renal insufficiency, anemia, and lytic bone lesions. MM remains incurable despite advances in treatment, with an estimated median survival of 8–10 years for standard-risk myeloma and 2–3 years for high-risk disease, despite receipt of an autologous stem-cell transplant (Mikhael et al. 2013). Increased survival has been achieved with the introduction of proteasome inhibitors such as bortezomib (Velcade® U.S. Package Insert [USPI] and Summary of Product Characteristics [SmPC]), immunomodulatory drugs (IMiDs) such as lenalidomide (Revlimid® USPI and SmPC), and monoclonal antibodies such as daratumumab (Darzalex® USPI and SmPC). The successful use of monoclonal antibodies in MM (e.g., daratumumab and elotuzumab) provides evidence that antibody-dependent cell-mediated cytotoxicity (ADCC) is an important therapeutic mechanism for MM. Nevertheless, most patients (if not all) eventually relapse, and the outcome of patients with MM after they become refractory, or ineligible to receive a proteasome inhibitor or an IMiD, is quite poor, with survival less than 1 year (Usmani et al. 2016). Therefore, relapsed or refractory (R/R) MM continues to constitute a significant unmet medical need, and novel therapeutic agents are still necessary.

1.2 BACKGROUND ON RO7297089

RO7297089 (BPCT2605S) is a bispecific, tetravalent antibody targeting B-cell maturation antigen (BCMA) and CD16a. The molecule consists of a humanized anti-BCMA antibody with two identical light and heavy chains of human IgG1 isotype and two anti-CD16a single chain variable fragments derived from light and heavy variable domains of human origin fused to the C-terminal end of the IgG1 heavy chain. The bispecific antibody also contains amino acid changes in the fragment crystallizable (Fc) region to impair its binding to human Fc gamma-receptors (FcγRs) and thus attenuates normal Fc-mediated effector functions (Lund et al. 1996; Borrok et al. 2017; RO7297089 Investigator's Brochure).

BCMA is exclusively expressed on plasmablasts and plasma cells, but it is absent on cells in earlier stages of B-cell development (e.g., pro- and pre-B cells, naive and memory B cells, as well as resting and activated B cells) and other normal tissues (Cho et al. 2019). BCMA is essential for the survival of long-lived bone marrow plasma cells, is over-expressed in malignant plasma cells in patients with MM, and its expression level is reported to be associated with disease progression (Lee et al. 2016; Seckinger et al. 2017; Tai and Anderson 2019). CD16a, also known as FcγRIIIa, is expressed on macrophages, natural killer (NK) cells, and monocyte subsets as a transmembrane receptor (Ravetch and Perussia 1989; Wong et al. 2011). Engagement of BCMA and CD16a by RO7297089 results in the target-specific killing of BCMA-positive tumor plasma cells by CD16a-positive immune effector cells such as NK cells and macrophages. Therefore, RO7297089 is a potential therapeutic treatment for MM.

No clinical studies have been conducted with RO7297089 to date. Nonclinical in vivo safety and pharmacokinetic (PK)/pharmacodynamic (PD) studies with RO7297089 were conducted in cynomolgus monkeys. No in vivo efficacy studies have been performed due to lack of any relevant efficacy model in rodents or other species.

Nonclinical characterization of RO7297089 activity to confirm its mechanism of action was performed. In vitro pharmacological activity of RO7297089 requires binding to both CD16a-positive immune cells and BCMA-positive tumor cells. Simultaneous binding results in target-dependent NK cell activation, potent killing of target cells (MM cell lines and normal plasma cells), without any significant NK cell fratricide. RO7297089 was shown to induce both ADCC and antibody-dependent cellular phagocytosis (ADCP) with the use of peripheral blood mononuclear cells (PBMCs) and macrophages, respectively, as effector cells in BCMA-positive MM cell lines.

An in vitro cytokine release assay was performed to evaluate the potential for acute cytokine-release syndrome (CRS) following RO7297089 administration to patients. RO7297089 led to minimal increases in TNFα and IFN-γ levels, and no change in the 15 other cytokines tested, including IL-6. Importantly, in vitro cytokine release was comparable between RO7297089 and daratumumab at the same concentrations; daratumumab has not been associated with CRS in patients, therefore risk of RO7297089-induced CRS in patients is considered to be low. Published results for similar in vitro cytokine assays conducted for a CD3 bispecific molecule show robust increase in cytokines consistent with mechanism of action and known clinical effect of T-cell engaging molecules (Li et al. 2019). Results with RO7297089 suggest low risk for CRS and are consistent with a mechanism of action of engaging CD16a-positive immune cells (e.g., NK cells).

RO7297089 has high affinities for recombinant cynomolgus monkey CD16 and BCMA as well as recombinant human CD16a and BCMA, but does not bind to recombinant mouse CD16. RO7297089 functionally activates cynomolgus or human PBMCs, resulting in killing of cynomolgus or human cell lines.

Therefore, cynomolgus monkey was selected as the relevant animal species to assess the PK, toxicokinetic, PD, and safety profiles of RO7297089. The nonclinical toxicology program consisted of a single-dose IV toxicity study and a 4-week repeat-dose, IV, Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys, including a core battery of safety pharmacology (cardiovascular and neurological) endpoints. RO7297089 was well tolerated in cynomolgus monkeys at doses of up to 50 mg/kg IV (5 weekly doses), and there were no RO7297089-related adverse findings. Cytokines were also monitored in the toxicity studies. There were no RO7297089-related changes in cytokines observed at up to 50 mg/kg in monkeys. Minimal non-adverse decreases in blood pressures were observed at 50 mg/kg following the fifth administered dose. The no observed adverse-effect level (NOAEL) was assessed as 50 mg/kg. Increases in soluble BCMA (due to binding to RO7297089) and monocytes along with decreases in IgM and mRNA levels of plasma cell markers were notable changes in cynomolgus monkeys. These changes were considered evidence of pharmacological activity of RO7297089 and they were seen at both the 15 mg/kg and 50 mg/kg dose levels.

The totality of in vitro and in vivo data with RO7297089 support that the potential for CRS is low. This is consistent with the mechanism of action of engaging CD16a-immune cells (e.g., NK cells, monocytes) and differentiated from data seen with T-cell engaging molecules. Additionally, the lack of CRS seen in the Phase I study with AFM13 (anti-CD30/CD16a) in Hodgkin lymphoma (Rothe et al. 2015) supports a low potential for CRS with RO7297089.

The recommended safe starting dose in patients is 60 mg RO7297089, which was determined based on an integrated analysis of the nonclinical data including the in vitro cytokine release assay and the repeat-dose GLP toxicity study in cynomolgus monkeys (see Section 3.3.2).

Collectively, the data from the nonclinical program with RO7297089 provide a scientific basis for investigating RO7297089 for the treatment of MM and support the proposed first-in-human Phase I trial.

Refer to the RO7297089 Investigator's Brochure for details on nonclinical studies and starting dose rationale.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

MM that is R/R to standard-of-care therapies, including intensive induction/stem cell transplant, proteasome inhibitors, and IMiDs, represents an indication with a significant unmet clinical need. Clinical activity seen with antibodies, such as daratumumab and elotuzumab, provides strong evidence that ADCC is an important therapeutic mechanism for treating MM. NK cells are cytotoxic effector cells that play a potent role in ADCC by binding to FcγRIIIA (CD16a). BCMA has been demonstrated to be a validated target in MM with compelling early clinical activity reported from BCMA-specific chimeric antigen receptor T cells (CAR-Ts) (Raje et al. 2019), BCMA antibody-drug

conjugate (Trudel et al. 2018), and BCMA-CD3 bispecific T-cell engager (Topp et al. 2019). Promising early clinical data from these agents support that BCMA is a valid target for immune-based therapies in MM. However, significant toxicities related to cytokine release in T cell–based therapies and ocular toxicities related to cytotoxic payload in antibody-drug conjugates have been noted with other agents. Targeting BCMA with a different mechanism of action may provide clinical benefit with an improved safety profile.

A bispecific anti-CD30/CD16a antibody construct, AFM13, has shown early promising data in R/R Hodgkin lymphoma and demonstrates superior cytotoxicity to other CD30-targeting antibodies in vitro (Rothe et al. 2015). In the Phase I dose-escalation study, 28 patients were treated at doses of 0.01 to 7 mg/kg body weight. Treatment with this agent was generally well-tolerated and the maximum tolerated dose (MTD) was not reached. Most adverse events were Grades 1 and 2 and largely related to infusion-related reactions (IRRs), which were managed through standard supportive care, without the need for premedication in the single-agent Phase I study. CRS was not reported. PD markers in the clinical study included dose-dependent transient decrease of circulating NK cells, likely due to margination and dose-dependent increases in the proportion of NK cells expressing the activation marker CD69. Quantifiable serum cytokine levels could only be measured for IL-6, IL-8, IL-10, and TNF-α. Data on cytokine release were inconclusive regarding a correlation with dose or activity of AFM13.

While there are no clinical data available with NK cell–engaging agents in R/R MM, the data in R/R Hodgkin lymphoma with AFM13 is encouraging for further development of these agents with different antigen targets in other malignancies. Given the poor prognosis of patients with R/R MM who have failed standard-of-care therapies, prior clinical studies demonstrating the efficacy and tolerability of the NK cell–engaging agent in Hodgkin lymphoma, and the favorable nonclinical toxicity profile observed with RO7297089 treatment, the anticipated benefit–risk balance of a clinical study of RO7297089 is proposed to be acceptable. Based on the mechanism of action and the nonclinical safety profile of RO7297089, the anticipated potential safety risks of RO7297089 include IRR/CRS, immunogenicity, infection, tumor lysis syndrome (TLS), lymphopenia, and blood pressure decrease (see Section 5.1.1). The study safety monitoring and mitigation plan will be implemented to manage and mitigate these potential toxicities (see Section 5.1).

Patients with R/R MM who have failed standard-of-care therapies have a poor prognosis, with survival less than 1 year (Usmani et al. 2016; Gandhi et al. 2019). The nonclinical studies conducted in support of the clinical trial application of RO7297089 demonstrate biologically effective activity and a favorable toxicity profile for the clinical dose level. The available clinical data with other BCMA-directed therapies in MM provide a supporting rationale for the clinical development of RO7297089 based on validation of BCMA as a target in MM. In addition, strong clinical benefit and tolerability

demonstrated in combination studies with approved monoclonal antibodies (e.g., daratumumab and elotuzumab) with proteasome inhibitors and in combination with IMiDs suggest that a future combination of RO7297089 and a proteasome inhibitor or an IMiD may provide additional treatment options for patients. Preclinical data exists for the role of IMiDs in augmenting NK cell cytotoxicity (Hayashi et al. 2005). Novel combinations with immune agents that enhance or augment NK function may also offer opportunities to enhance the activity of RO7297089.

RO7297089 may provide a potential therapeutic option, either alone or in combination with other therapies, in R/R MM, which continues to constitute a significant unmet need. RO7297089 has not been studied in humans, and therefore its clinical benefit or safety profile as a single agent or in combination is unknown.

This Phase I study will enroll patients with R/R MM to assess safety, tolerability, and pharmacokinetics and to make a preliminary assessment of anti-tumor activity of RO7297089. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for early-stage trials of novel therapeutic candidates, and the benefit–risk ratio of a clinical study of RO7297089 is considered acceptable.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety and pharmacokinetics of RO7297089 in patients with R/R MM and make a preliminary assessment of anti-tumor activity. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVE (PRIMARY STUDY OBJECTIVE)

The safety objective for this study is to evaluate the safety of RO7297089, including estimation of the MTD and characterization of dose-limiting toxicities (DLTs), on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) and the Modified Cytokine-Release Syndrome Grading System (Appendix 9)
- Change from baseline in targeted vital signs
- Change from baseline in targeted ECG parameters
- Change from baseline in targeted clinical laboratory test results
- Relationship between RO7297089 dose and safety, PK, activity, and immunogenicity endpoints

2.2 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to characterize the RO7297089 PK profile on the basis of the following endpoints:

- Serum concentration of RO7297089 at specified timepoints
- PK parameters for RO7297089

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the safety and activity of RO7297089 on the basis of the following endpoints:

  Relationship between serum concentration or PK parameters for RO7297089 and safety endpoints

  Relationship between serum concentration or PK parameters for RO7297089 and activity endpoints

- To evaluate potential relationships between selected covariates and exposure to RO7297089 on the basis of the following endpoint:

  Relationship between selected covariates and serum concentration or PK parameters for RO7297089

2.3 ACTIVITY OBJECTIVES

The activity objective for this study is to make a preliminary assessment of the activity of RO7297089 on the basis of the following endpoints:

- Objective response rate (ORR), defined as a stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR), as determined by the investigator according to International Myeloma Working Group (IMWG) Uniform Response Criteria (Appendix 5)
- Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to IMWG Uniform Response Criteria

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to RO7297089 on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and safety, PK, biomarker, or activity endpoints

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to RO7297089 (i.e., predictive biomarkers), are early surrogates of activity, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to RO7297089, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of RO7297089 activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in blood and tissue samples (listed in Section 4.5.7) and safety, PK, activity, immunogenicity, or other biomarker endpoints

2.6 ADDITIONAL OBJECTIVE

An additional objective for this study is to identify a RP2D and regimen for RO7297089 on the basis of the following endpoint:

- Relationship between RO7297089 exposure and safety, PK, activity, and immunogenicity endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a first-in-human Phase I, open-label, multicenter, global, dose-escalation study designed to evaluate the safety, tolerability, and pharmacokinetics of RO7297089 and make a preliminary assessment of anti-tumor activity in patients with R/R MM for whom no established therapy for MM is appropriate and available or who are intolerant to those established therapies. The study consists of a screening period of up to 28 days and a minimum follow-up period of 90 days after treatment. Following confirmation of eligibility, patients will receive RO7297089 by IV infusion. Patients will be enrolled in two stages: a dose-escalation stage and an expansion stage. *To mitigate the risk of IRRs, up to three dose-escalation arms that differ in the RO7297089 administration schedule for Cycle 1 may be enrolled in a dose-escalation cohort.* The study will enroll approximately 30–50 patients during the dose-escalation stage and approximately 30 patients during the expansion stage at approximately 12 sites globally. Figure 1 presents an overview of the study design.

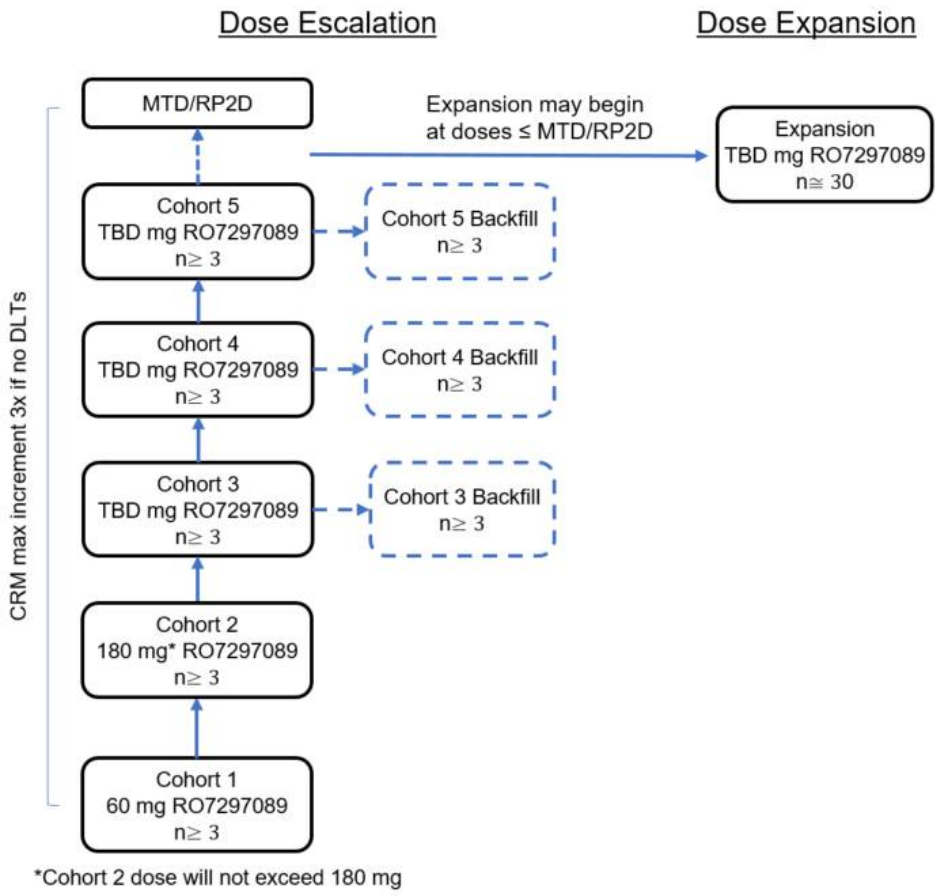
Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

All patients will be closely monitored for adverse events throughout the study and for at least 90 days after the final dose of study treatment. Adverse events will be graded according to the NCI CTCAE v5.0, with the exception of CRS, which will be graded according to the Modified Cytokine-Release Syndrome Grading System (Appendix 9).

Patients may continue treatment with RO7297089 until disease progression as determined by the investigator using IMWG Uniform Response Criteria (Appendix 5), unacceptable toxicity, start of new anti-cancer therapy, or withdrawal from study participation, whichever occurs first.

A schedule of activities is provided in Appendix 1 and Appendix 2. To characterize the PK properties of RO7297089, blood samples will be taken at various timepoints before and after dosing (see Appendix 3).

Figure 1 Study Design



Notes:
RO7297089 is administered by IV infusion*, with a cycle length of 14 days. The Cycle 1 administration schedule is dependent on the assigned treatment arm (see Figure 2). From Cycle 2 onwards, RO7297089 is administered* on Days 1 and 8 of each cycle.

Cohort must clear the DLT assessment window to open next cohort. The DLT assessment window is *14 days (see Figure 2)*.

Backfill cohorts are ungated based on evidence of clinical activity (e.g., decrease in M-protein) and/or PD activity (e.g., NK cell activation). Dose-escalation decisions are based on totality of data (clinical, safety, PK, biomarker). Dose recommended will not exceed dose recommended by the mCRM-EWOC model.

DLT = dose-limiting toxicity; mCRM-EWOC = modified continual reassessment method of escalation with overdose control; MTD = maximum tolerated dose; NK = natural killer; RP2D = recommended Phase II dose; PD = pharmacodynamic; PK = pharmacokinetic; TBD = to be determined.

3.1.1 Dose-Escalation Stage

Approximately 30–50 patients will be enrolled in the dose-escalation stage.

The dose-escalation stage of the study will assess the safety, tolerability, and pharmacokinetics of RO7297089 administered by IV infusion. *The cycle length is 14 days.*

To mitigate the risk of IRRs, up to three dose-escalation arms may be enrolled in a given dose cohort (see Figure 2). These arms differ in the RO7297089 administration schedule for Cycle 1:

- ***Arm A (Flat Dose-Escalation Arm).*** *Patients in Arm A will receive the Cycle 1 target dose of RO7297089 as a flat dose independent of body weight on Day 1 and Day 8. Dosing for Cycle 2 and beyond will follow the same administration schedule. The DLT assessment window for Arm A is 14 days (Cycle 1, Days 1–14).*
- ***Arm B (Split Dose-Escalation Arm).*** *Patients in Arm B will receive the first dose in Cycle 1 as a split dose. The initial target dose of RO7297089 will be divided over 2 days (Days 1 and 2), and the full target dose will be administered on Day 8.*

  Initially, the dose will be divided such that 50% of the target dose is administered on Day 1 and the remaining 50% on Day 2. If the Day 1 dose is associated with a Grade ≥ 2 IRR, the ratio may be adjusted for subsequent patients so that a smaller percentage of the dose is administered on Day 1, with the remainder of the dose administered on Day 2. For example, 25% of the target dose administered on Day 1 and the remaining 75% administered on Day 2.

  If a patient does not receive the full planned dose on Day 1 because of scheduling reasons but has received at least 75% of the intended Day 1 dose, the patient may proceed with the Day 2 infusion to receive the remainder of the full target dose.

  For Cycle 2 and beyond, RO7297089 will be administered on Day 1 and Day 8 of each 14-day cycle. The DLT assessment window for Arm B is 14 days (Cycle 1, Days 1–14).
- ***Arm C (Single-Step Dose-Escalation Arm).*** *Patients in Arm C will receive the first cycle of RO2797089 as a single-step dose escalation. The Cycle 1, Day 1 dose will be 60 mg, followed by the full target dose on Day 8. For Cycle 2 and beyond, the target dose of RO7297089 will be administered on Day 1 and Day 8 of each 14-day cycle. The DLT assessment window for Arm C is 14 days (Cycle 1, Day 8 to Cycle 2, Day 7, to allow for two target doses); the window excludes the Cycle 1, Day 1 60-mg dose, which has already cleared.*

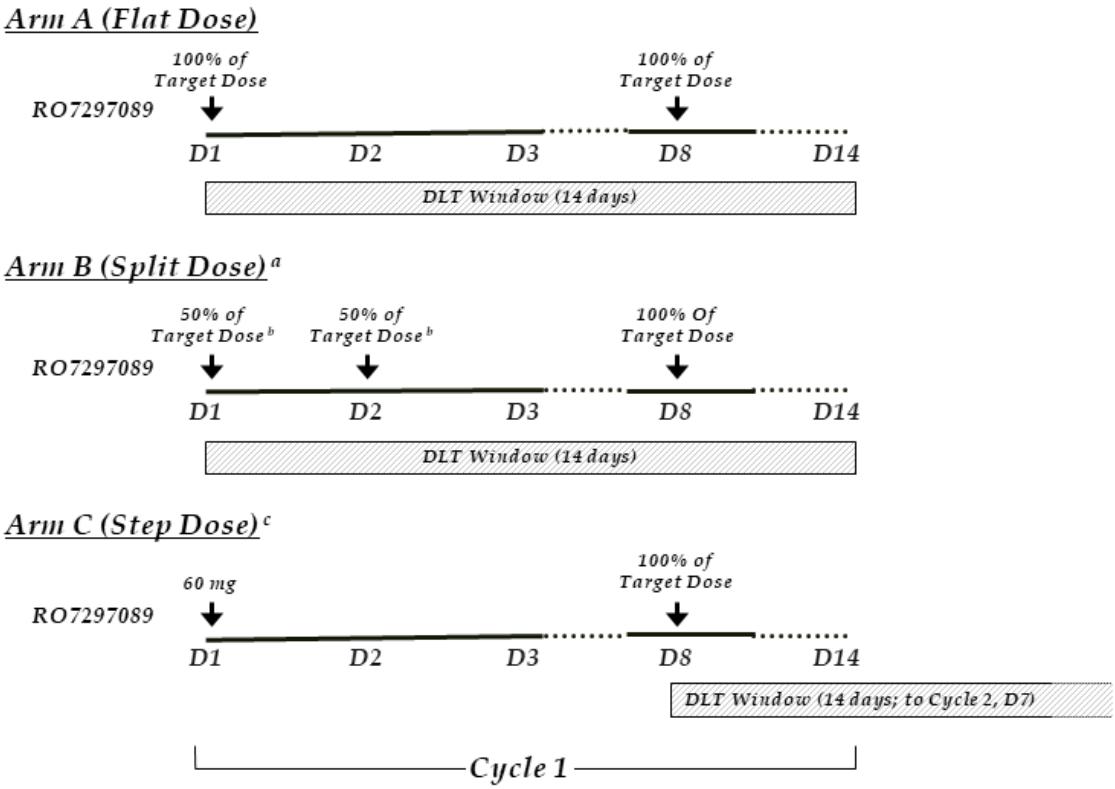
For all arms, the target dose refers to the highest dose administered in Cycle 1; this target dose will be administered on Day 1 and Day 8 of subsequent cycles.

Enrollment in the dose-escalation arms will be managed as follows:

- *For new dose cohorts, all patients will enroll in Arm A unless criteria have been met for opening Arms B or C in a previous cohort.*
- *Arm B may open if the planned infusion time for Arm A exceeds 4 hours on Cycle 1, Day 1. Arm C may open if 2 or more patients in Arm B of that dose cohort experience any grade IRR that precludes the patient from receiving the full target dose during Cycle 1, Day 1 and Day 2.*

- *Once Arm B is open, Arm A for that dose cohort may close to further enrollment and may not open for subsequent dose cohorts. Similarly, once Arm C is open, Arm B for that dose cohort may close to further enrollment and may not open for subsequent dose cohorts.*
- *A minimum of 3 patients must complete the DLT assessment period for a given arm (Arm A, B, or C) before dose escalation for that arm may occur.*

Figure 2 Dose-Escalation Arms: Study Drug Administration for Cycle 1



D =day; DLT =dose-limiting toxicity; IRR =infusion-related reaction.

Notes: One treatment cycle is 14 days. Target dose is the highest dose administered in Cycle 1. DLT window is 14 days.

[a] *Arm B may open if the planned infusion time exceeds 4 hours on Cycle 1, Day 1.*

[b] *If the Day 1 dose is associated with Grade ≥ 2 IRR, the ratio may be adjusted so that a smaller percentage of the dose is administered on Day 1, with the remainder of the dose administered on Day 2.*

[c] *Arm C may open if more than one patient in Arm B of that dose cohort experiences an IRR that precludes the patient from receiving the full target dose during Cycle 1, Day 1 and Day 2.*

Dose escalations will be guided by the modified continual reassessment method of escalation with overdose control (mCRM-EWOC) model (Neuenschwander et al. 2008; Appendix 11). All cohorts will enroll a minimum of 3 patients. Enrollment of the first 2 patients in each *arm of each* dose-escalation cohort will be staggered such that the respective Cycle 1, Day 1 treatments are administered ≥72 hours apart. The maximal

dose escalation increment recommended by the model will be 3-fold. In addition, the relevant demographic, adverse event, laboratory, dose administration, and available PK data will be reviewed prior to dose-escalation decisions, which will be made by an Internal Safety Committee (ISC) in consultation with the investigator (see Section 3.1.5 for more information about the ISC).

Evidence of clinical activity at a given dose level (e.g., decrease in serum monoclonal protein [M-protein]) or PD activity (e.g., NK cell activation) may ungate backfill cohorts at doses that have already completed DLT assessment and have been found not to exceed the MTD in escalation cohorts. DLT information from patients in these back-fill cohorts will be used to inform the mCRM-EWOC model.

Patients will be closely monitored for adverse events during a DLT assessment window (14 days)*, as defined above for each arm*. Adverse events identified as DLTs, as defined below (see Section 3.1.1.1), will be reported to the Sponsor within 24 hours.

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD assessments and will be replaced by an additional patient at that same dose level. Patients must receive two *planned target* doses of RO7297089 during the DLT assessment window to be considered DLT-evaluable. Treatment delays during the first cycle of RO7297089 will be allowed if they are less than one cycle (i.e., <14 days); under these circumstances, the DLT assessment window may be extended up to *an additional 7* days in order to capture two *planned target* doses of treatment. Patients who receive supportive care during the DLT assessment window that confounds the evaluation of DLTs (not including supportive care described below as part of the DLT definition) may be replaced at the discretion of the Medical Monitor.

As described in Section 3.1.5, the ISC will additionally review cumulative safety data and make recommendations regarding overall study conduct to ensure patient safety while receiving study treatment. These recommendations include suspending patient enrollment based on the overall benefit-risk profile of RO7297089 during dose escalation.

3.1.1.1 Definition of Dose-Limiting Toxicity

All adverse events, including DLTs, will be reported according to instructions in Section 5.3.5 and graded according to the NCI CTCAE v5.0, with the exception of CRS, which will be graded according to the Modified Cytokine-Release Syndrome Grading System (Appendix 9). DLTs will be treated according to clinical practice and will be monitored through their resolution. Any one of the following events will be considered a DLT if it occurs during the DLT assessment window (Days 1–14 of Cycle 1

for Arms A and B; Cycle 1, Day 8 to Cycle 2, Day 7 for Arm C) unless clearly attributed to another identified etiology by the investigator (e.g., cancer progression):

- Any Grade 4 or 5 adverse event
- Grade 3 febrile neutropenia lasting > 3 days
- Grade 3 elevation of serum hepatic transaminase (ALT or AST) lasting >7 days

  Any Grade 3 AST or ALT elevation that occurs in the context of Grade ≤ 2 CRS (as defined by the criteria established by Lee et al. [2019]; see Appendix 9) and resolves to Grade ≤ 1 within < 3 days will not be considered a DLT.
- Grade 3 elevation of serum bilirubin (total)
- Any increase in hepatic transaminase (ALT or AST) $>3\times$ baseline in combination with either an increase in direct bilirubin $>2\times$ upper limit of normal (ULN) or clinical jaundice, in the absence of cholestasis or other contributory factors (e.g., concomitant exposure to known hepatotoxic agent, or documented infectious etiology)

  This is suggestive of potential drug-induced liver injury (according to Hy's Law).
- Grade 3 non-hematologic, non-hepatic major organ adverse event, with the following exceptions:
  - Grade 3 nausea, vomiting, or diarrhea that improves to Grade ≤ 2 with standard-of-care therapy in ≤ 3 days will not be considered a DLT.

    Grade 3 nausea or vomiting that requires total parenteral nutrition or hospitalization is not excluded and should be considered a DLT.
  - Grade 3 fatigue that improves to Grade ≤ 2 within 7 days will not be considered a DLT.
  - Grade 3 infection that resolves within 7 days to Grade ≤ 2 and does not require intensive care unit will not be considered a DLT.
  - Grade 3 fever (as defined by >40ºC) for ≤ 48 hours will not be considered a DLT.
  - Grade 3 laboratory abnormalities that are asymptomatic, resolve to Grade ≤ 1 or baseline within 7 days, and are considered by the investigator not to be clinically significant will not be considered a DLT.
  - Fractures of any grade at site of lytic bone disease will not be considered a DLT.
  - Grade 3 IRRs will not be considered a DLT, as generally IRRs are not considered to be dose-related events on the basis of experience with monoclonal antibodies. Precautions will be taken if IRRs Grade ≥ 2 occur (see Section 5.1.2.2).

    Grade ≥ 4 IRRs or re-occurrence of an IRR event in a patient that precluded the administration of the full dose or the administration of the next scheduled dose of study drug will be considered a DLT.

Anemia, neutropenia, lymphopenia, leukopenia, and thrombocytopenia are anticipated in the study population due to the extensive prior therapy and myeloma involvement in the R/R MM population (see Section 4.1). Investigator assessment of causality and change from pre-treatment baseline will be important to characterize the effect of RO7297089 on cytopenias. In addition, infection is a common occurrence in R/R MM due to prior therapy and hypogammaglobulinemia. Hence, infection that recovers as expected with appropriate therapy (as per above) will not be considered a DLT.

3.1.1.2 Dose-Escalation Rules

The starting dose of RO7297089 will be 60 mg, administered IV weekly for Cohort 1.

Dose escalations will be guided by the mCRM-EWOC model (Appendix 11). The MTD is defined as the dose that maximizes the probability of a DLT being in the targeted toxicity interval in the range of 20%–35%, subject to the probability of the DLT being in the excessive toxicity interval in the range of 35%–100% being $<$25%. For each cohort, patients will be followed through a 14-day DLT assessment window. At each dose-escalation step, the dose can be escalated or de-escalated and/or an additional cohort at that same dose level could be enrolled. Refer to Section 3.1.1 for additional information. If MTD is not reached, the RP2D will be determined based on the totality of data including clinical activity, safety, PK, and pharmacodynamics biomarkers. Once the MTD or is RP2D determined, all patients in dose-escalation will be eligible to receive the RP2D, based upon ISC decision.

In addition, different dosing regimens (e.g., every 2 weeks) may be explored in parallel, if warranted, on the basis of the safety and PK profile of RO7297089, with DLT periods specific for each regimen and starting dose not exceeding the weekly MTD. Any evaluation of a different administration schedule will be based on the recommendation of the ISC and reviewed with study investigators. Addition of different dosing regimens will require a protocol amendment. For this new regimen, the mCRM-EWOC model and priors as defined in Appendix 11, as well as the simulations, will be reviewed and possibly modified and the DLT assessment period will be extended to 21 days to ensure that patients have received at least two doses of study drug.

3.1.2 Continued Dosing Beyond the Dose-Limiting Toxicity Observation Period (Cycles ≥2)

Nonclinical toxicology data supports RO7297089 treatment every 7 days. The ethical conduct of a clinical study of cancer requires that patients have the opportunity to continue study treatment provided that the treatment is active and tolerable and patients comply with protocol requirements. Therefore, dosing beyond Cycle 1 for patients with R/R MM will be allowed in the absence of unacceptable toxicity or objective evidence of disease progression as assessed by the treating study investigator and following a careful assessment and discussion of the potential risks and benefits with the patient. Patients will *continue study treatment* until objective disease progression is documented or unacceptable toxicity, whichever occurs first.

RO7297089 administration will be interrupted in patients who experience a DLT during the DLT assessment window (Section 3.1.1). Patients who experience a DLT during the first cycle and whose toxicity returns to baseline within 14 days may be restarted at a dose level tolerated by the prior cohort following discussion with the Medical Monitor. A treatment delay beyond 14 days may be acceptable upon discussion with the Medical Monitor (see Section 5.1.2).

3.1.3 Intrapatient Dose Escalation

To maximize the collection of information at relevant doses and minimize the exposure of patients to sub-optimal doses of RO7297089, intrapatient dose escalation may be permitted. Within each assigned dose-escalation cohort, the dose of RO7297089 for an individual patient may be increased to the highest cleared dose level that is tolerated by completed cohorts through *the DLT window*. Patients may be able to undergo intrapatient dose escalation after completing at least two cycles at their originally assigned dose level.

Subsequent intrapatient dose escalations may occur after at least one cycle of any subsequently higher cleared dose level without any adverse event that meets the definition of a DLT or necessitates post-administration hospitalization (Section 3.1.1.1). Once the MTD is declared and the RP2D is determined, intrapatient dose escalation directly to the RP2D is permitted for patients who remain on study and continue to tolerate RO7297089.

At the discretion of the investigator and in consultation with the Medical Monitor, the RO7297089 administration schedule for the first cycle after intrapatient dose escalation may follow any administration schedule previously evaluated in the study.

3.1.4 Expansion Stage

After dose escalation has been completed, approximately 30 patients will be enrolled in the expansion stage. Patients will be treated at the RP2D (at or below the MTD) to obtain additional safety, tolerability, and PK data, as well as preliminary evidence of clinical activity. The ISC will assess all safety data on an ongoing basis. At no time will the dose administered in the expansion stage exceed the highest dose level that qualified as an MTD in the dose-escalation stage.

3.1.5 Internal Safety Committee

Given that this is a first-in-human trial, an ISC will be utilized during the study to make recommendations regarding study conduct on the basis of trial safety data to ensure enhanced patient safety monitoring while receiving study treatment. The ISC will be formed before the first patient is enrolled into the study.

The ISC will include at a minimum the Medical Monitor, study Safety Scientist, study Biostatistician, and a Sponsor Medical Monitor not associated with the study.

Representatives from other Sponsor functional areas may be included as ad hoc members.

In addition to the ongoing assessment of the incidence and nature of DLTs, adverse events, serious adverse events, adverse events of special interest, and laboratory abnormalities by the investigator and the Medical Monitor, the ISC will review cumulative data at regular intervals during the study. This committee will make decisions in consultation with study investigators regarding *opening Arm B and/or Arm C for a given dose cohort as well as* dose escalations based on the plan described in Section 3.1.1. The ISC, in consultation with study investigators, will also review the cumulative data from dose escalation prior to opening the dose expansion portion of the study and review data from the dose expansion at routine intervals. In addition, the ISC will meet regularly and as needed at the request of the study Medical Monitor (e.g., based on unexpected safety signals). The ISC may further make recommendations regarding study conduct, including, but not limited to, the following: performing additional safety analyses, amending the study protocol, holding patient enrollment pending further safety evaluations, enrolling additional patients at a specific dose level and schedule to obtain additional safety data, holding/discontinuing study treatment, or terminating the study.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 1 year after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

This study will enroll patients with a history of R/R MM who meet the inclusion and exclusion criteria as outlined in Sections 4.1.1 and 4.1.2. Confirmation of BCMA expression will not be required during eligibility screening prior to enrollment, but it will be evaluated retrospectively, based on the following rationale:

- Nonclinical studies have demonstrated that RO7297089 is potent in cell killing in multiple human MM cell lines and primary human MM plasma cells with a wide range of BCMA expression levels, including cells with minimal BCMA expression, suggesting that even very low levels of BCMA expression may be sufficient for clinical activity (RO7297089 Investigator's Brochure).

- BCMA is a cell surface antigen whose expression is restricted to plasma cells. It is expressed in all MM samples tested to date (Carpenter et al. 2013; Seckinger et al. 2017).

Bone marrow samples obtained from all patients will be retrospectively analyzed for BCMA expression with validated assays (e.g., quantitative reverse transcription-PCR, immunohistochemistry, and quantitative flow cytometry). These data will be used to inform how best to utilize BCMA expression screening in subsequent studies.

Patients with prior BCMA therapy exposure will be permitted to enroll in the study. Based on experience with BCMA CAR-T treated patients, BCMA expression increases at time of disease progression (Cohen et al. 2019b). In addition, limited data exists for successful sequencing of BCMA therapies (Cohen et al. 2019a).

Eligibility criteria for this Phase I study additionally consider the totality of nonclinical toxicology studies of RO7297089, clinical safety data from agents targeting BCMA (e.g., GSK2857916, bb2121), and published clinical safety data from AFM13 (anti-CD30/CD16a).

3.3.2 Rationale for RO7297089 Dose and Schedule

The recommended first-in-human starting dose of 60 mg IV is based on an integrated approach using both in vivo data from the repeat-dose toxicity study in cynomolgus monkeys and in vitro data from the cytokine assay.

RO7297089 showed minimal increase of cytokines in in vitro assays with human BCMA-positive cell lines and PBMCs at concentrations up to 50 μg/mL (250 nM). There were no RO7297089-related toxicity findings in the single-dose and repeat-dose toxicology studies in cynomolgus monkeys, while clear pharmacologic activity (reflected by reduction of IgM and decreased expression of BCMA and J-chain mRNA) was observed in a repeat-dose GLP safety study at both 15 m/kg and 50 mg/kg. These observations, in combination with the mechanism of action of RO7297089, which is similar to ADCC and ADCP, suggest that RO7297089 has a low likelihood of CRS in the clinic. This is supported further with AFM13 clinical data, where no CRS was detected in doses of up to 7 mg/kg (Rothe et al. 2015).

The recommended first-in-human starting dose of 60 mg IV is based on an integrated approach using both in vivo and in vitro data. The dose of 60 mg is predicted to have exposure (C_{max} and AUC) ≥10-fold lower than the exposure at 15 mg/kg in cynomolgus monkeys (lowest dose at which RO7297089 demonstrated clear pharmacological changes) and also achieves a projected C_{max} of 19 μg/mL that is approximately 2.5-fold lower than the highest concentration of 50 μg/mL tested in the in vitro cytokine assay (where only minimal cytokine increases were observed). Overall, the proposed first-in-human dose of 60 mg has >40 safety margin (based on C_{max}, AUC, and dose)

when compared to cynomolgus monkey NOAEL (50 mg/kg). Based on the totality of the nonclinical data, the recommended starting dose is expected to be safe.

A weekly dosing frequency is proposed based on the in vivo PK properties of RO7297089 and the clinical experience of other therapeutics for the treatment of MM (e.g., daratumumab). RO7297089 is proposed to be administered via IV infusion, a commonly used route of administration for large molecule anti-cancer therapeutics.

Dedicated dose-escalation arms have been added to evaluate split-dose and step-dose administration schedules with regard to mitigating the risk of IRRs. While the impact of these alternate dose administration schedules on the frequency and severity of IRR is unknown for RO7297089, similar interventions have been successful with other monoclonal antibody therapies.

Details of nonclinical studies described above, starting dose rationale, and human equivalent dose calculation can be found in RO7297089 Investigator's Brochure.

3.3.3 Rationale for Dose-Escalation Plan

The mCRM-EWOC model will be used to guide dose escalation to determine the MTD. mCRM-EWOC has many favorable characteristics compared with a conventional 3+3 design. Such an adaptive Bayesian model-based design is one of the key elements of the U.S. Food and Drug Administration (FDA)'s Critical Path Initiative. The key advantages of the mCRM-EWOC design are as follows:

It adaptively fits a DLT dose-response curve by incorporating toxicity data from eligible patients among different cohorts. Thus, dose recommendations for the next cohort are decisions made according to multiple cohorts instead of a single cohort in context of a 3+3 design, and preclinical information is contributable by building an informative/minimal informative prior distribution of the statistical model.

It locates the MTD efficiently without pre-specifying dose levels in each cohort. Dose selections are made based on the DLT dose-response curve measured by a two-parameter logistic model over the dose range, subject to clinical judgment and mandated safety constraints that limit the size of dose-increments. It has been suggested in multiple reports that the method exposes fewer patients to sub-therapeutic doses than the traditional 3+3 design (Le Tourneau et al. 2009).

It greatly reduces risks of exposing patients to overly toxic doses by utilizing the escalation with overdose control algorithm. The design will never recommend a dose with more than 25% likelihood of being in the excessive toxicity interval in which the DLT rate is above 35% according to the present DLT information.

The maximal increment for escalation is 3-fold. Nonclinical data for RO7297089 and published clinical safety data for AFM13 (described in Section 1.3) supports this

approach (see Section 1.2 for a summary of nonclinical data and Section 5.1.1 for potential risks).

Decision making with respect to patient dosing and dose-escalation is described in Section 3.1. Furthermore, DLT criteria, stopping rules, monitoring and management guidelines of all potential toxicities and dose delay rules are included in this protocol (Sections 3.1 and 5.1.2).

3.3.4 Rationale for PK Sampling Schedule

The PK sampling schedule that follows RO7297089 administration is designed to capture data at a sufficient number of timepoints to inform the concentration-time curve and enable characterization of key PK parameters, including maximum serum concentration observed (C_{max}), minimum serum concentration observed (C_{min}), area under the concentration-time curve (AUC), time to maximum concentration observed (t_{max}), total clearance, volume of distribution at steady state, and half-life, as appropriate. These data will also be used to understand the relationship between dose, pharmacokinetics, safety, and activity to inform clinical dose selection.

Exploratory PK samples are collected using a sparse sampling schedule to allow exploratory assessment of potential presence of drug fragments and in relative ratio to intact molecules.

3.3.5 Rationale for Biomarker Assessments

Understanding the mechanism of action of RO7297089 and identifying prognostic and predictive biomarkers for safety and clinical activity in patients with R/R MM forms the underlying rationale for their assessment in this study.

The biomarker sampling schedule (from peripheral blood, and bone marrow biopsies and aspirates) following RO7297089 administration is designed to provide a detailed profile of the following:

- Expression of phenotypic markers of NK cell and T-cell function and potential markers of resistance to RO7297089 therapy

  Examples of these include, but are not limited to, markers of NK/T-cell activation and proliferation as well as expression of T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and other inhibitory molecules on NK cells.
- Dynamic quantitative changes in NK cell, T-cell, and B-cell counts
- Assessments of cytokine levels as clinically indicated in relation to RO7297089 pharmacokinetics and clinical safety during and beyond the DLT assessment period

  These assessments will permit correlations with any chronic safety signals observed with RO7297089 treatment.
- Monitoring for minimal residual disease (MRD) by next-generation sequencing and establishing correlations with objective response

In addition to biomarker sampling (as outlined in Appendix 3), bone marrow biopsies and aspirates will be obtained as detailed in Appendix 1. Evaluating changes to the tumor immune microenvironment is important in understanding the mechanism of action of RO7297089, understanding potential mechanisms of RO7297089 resistance, and providing biologic rationale for combinations of RO7297089 with other anti-cancer therapies. The sampling schedule is therefore designed to capture quantitative and functional changes in the immune cell infiltrate as well as changes to disease biology using both phenotypic and gene expression assays.

Contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body (Section 4.5.9), tissue samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or whole exome sequencing (WES). The aim of these analyses is to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 60–80 patients with R/R MM will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1

  ECOG Performance Status of 2 due to MM may be eligible after discussion with the Medical Monitor.
- Life expectancy of at least 12 weeks
- Patients must have R/R MM for which no established therapy for MM is appropriate and available or be intolerant to those established therapies
- Agreement to provide bone marrow biopsy and aspirate samples as detailed in Appendix 1
- Adverse events from prior anti-cancer therapy resolved to Grade ≤ 1, with the following exceptions:
  - Any grade alopecia
  - Peripheral sensory or motor neuropathy that has resolved to Grade ≤ 2
- Measurable disease, defined as at least one of the following:
  - Serum monoclonal protein (M-protein) ≥ 0.5 g/dL (≥ 5 g/L)
  - Urine M-protein ≥ 200 mg/24 hr
  - Serum free light chain (SFLC) assay: Involved SFLC ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal SFLC ratio (<0.26 or >1.65)
- Laboratory values as follows:
  - Hepatic function:
    - AST and ALT ≤ 3 × ULN
    - Total bilirubin ≤ 1.5 × ULN

      Patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
  - Hematologic function:
    - Platelet count ≥ 50,000/mm^3 without transfusion within 7 days of assessment
    - ANC ≥ 1000/mm^3
    - Total hemoglobin ≥ 8 g/dL without transfusion within 14 days of assessment

Patients who do not meet criteria for hematologic function because of MM related cytopenias (e.g., due to extensive marrow involvement by MM) may be enrolled into the study after discussion with the Medical Monitor.

- Creatinine clearance (CrCl) $\geq$30 mL/min (either calculated using a modified Cockcroft-Gault calculation or per 24-hour urine collection; inulin or radionuclide-based methods may be used after discussion with Medical Monitor)
- Serum calcium (corrected for albumin) level $\leq 11.5\ mg/dL\ (2.9\ mmol/L)$

  Treatment of hypercalcemia is allowed and patient may enroll if hypercalcemia returns to normal with standard treatment.

- For women of childbearing potential: agreement to remain completely abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 28 days after the final dose of RO7297089. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, or copper intrauterine devices.

  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug and is consistent with the usual lifestyle of the patient. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain completely abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom with spermicide during the treatment

period and for 28 days after the final dose of RO7297089 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the final dose of study drug

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Prior use of any monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate for the treatment of cancer within 4 weeks before first RO7297089 infusion
- Prior treatment with systemic immunotherapeutic agents, including, but not limited to, cytokine therapy and anti-CTLA4, anti–PD-1, and anti–PD-L1 therapeutic antibodies, within 12 weeks or 5 half-lives of the drug, whichever is shorter, before first RO7297089 infusion
- Prior treatment with CAR-T therapy within 90 days before first study drug administration
- Treatment with any chemotherapeutic agent, or treatment with any other anti-cancer agent (investigational or otherwise) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to first RO7297089 infusion
- Autologous stem cell transplantation within 100 days prior to first RO7297089 infusion
- Allogeneic stem cell transplantation within 180 days prior to first RO7297089 infusion or requiring immunosuppression for treatment or prophylaxis of graft versus host disease
- Primary or secondary plasma cell leukemia as defined by an absolute plasma cell count exceeding 2000/μL or 20% of the peripheral blood white cells
- Known cardiac amyloidosis
- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins) or any of the components of the RO7297089 drug product
- Significant active pulmonary disease (e.g., chronic obstructive pulmonary disease with known forced expiratory volume in 1 second of less than 50% of predicted

normal, severe persistent asthma) that may limit a patient's ability to adequately respond to an IRR event in the investigator's assessment

- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the following exceptions:
  - Patients with history of curatively basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix
  - Localized prostate cancer Gleason Grade ≤ 6 AND with stable prostate-specific antigen levels off treatment
  - Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission for ≥ 2 years prior to first RO7297089 infusion.
- Acute or chronic hepatitis C virus (HCV) infection

  Patients who are positive for the HCV antibody must be negative for HCV by PCR to be eligible for study participation.
- Positive serologic or PCR test result for acute or chronic hepatitis B virus (HBV) infection

  Patients whose HBV infection status cannot be determined by serologic test results must be negative for HBV by PCR to be eligible for study participation.

  Antiviral prophylaxis for patients at risk of HBV reactivation is permitted.
- Known HIV infection unless the patient meets all the following criteria:
  - CD4 count ≥ 350 cells/μL prior to enrollment
  - No history of AIDS-defining illness in the last 12 months prior to study enrollment (see Appendix 13 for a list of AIDS-defining illnesses)
  - Must be on established antiretroviral therapy for at least 4 weeks and have an HIV viral load < 400 copies/mL prior to enrollment
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV anti-microbial therapy within 14 days prior to first RO7297089 infusion
- Administration of a live, attenuated vaccine within 4 weeks before first RO7297089 infusion or anticipation that such a live, attenuated vaccine will be required during the study

  Influenza vaccine should be given during influenza season (approximately October to May in the Northern Hemisphere; approximately May to October in the Southern Hemisphere). Patients must not receive live, attenuated influenza vaccine at any time during the study period.

  Investigators should review the vaccination status of potential study patients being considered for this study and follow the local guidelines for adult vaccination with any other non-live vaccines intended to prevent infectious diseases prior to study.

- Received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) *within 2 weeks prior to the first dose of RO7297089,* with the *following* exception*s:*

  Patients who received acute, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea*, prophylactic corticosteroids to prevent allergic reaction to CT contrast*) may be enrolled in the study after discussion with the Medical Monitor.

  The use of corticosteroids for anti-cancer treatment is permitted prior to the first dose of RO7297089; washout requirements for anti-cancer therapies are defined above.

  The use of corticosteroid treatment of ≤10 mg/day prednisone or equivalent is permitted.

  The use of inhaled corticosteroids is permitted.

  The use of mineralocorticoids for management of orthostatic hypotension is permitted.

  The use of physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.

- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Significant cardiovascular disease (such as, but not limited to, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina)
- Current CNS involvement by MM

  Patients with a history of CNS involvement must have at least 6 months of remission in the CNS without interval CNS directed therapies prior to first RO7297089 infusion.

  Patients with a history of CNS involvement must have a magnetic resonance imaging (MRI) of the brain and lumbar puncture during screening to confirm that CNS is clear.

- Recent major surgery within 4 weeks prior to first RO7297089 infusion or anticipation of need for a major surgical procedure during the course of the study

  Protocol-mandated procedures (e.g., tumor biopsies and bone marrow biopsies) and superficial lymph node biopsies for diagnosis are permitted.

  Prophylactic orthopedic intervention to long bones to prevent fracture is permitted within 2 weeks prior to first RO7297089 infusion.

- Uncontrolled tumor-related pain

Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment.

Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.

4.2 METHOD OF TREATMENT ASSIGNMENT

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

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is RO7297089 (BPCT2605S).

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 RO7297089

RO7297089 (BPCT2605S) will be supplied by the Sponsor (Genentech). For information on the formulation, packaging and handling of RO7297089, refer to the pharmacy manual and the RO7297089 Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.1.

4.3.2.1 RO7297089

Dosing independent of body weight will be used for RO7297089. The dose of RO7297089 for each patient will depend on the dose level assignment as detailed in the protocol.

In this study, RO7297089 will be administered to patients by IV infusion using standard syringes and syringe pumps or IV bags where applicable. The drug product will be delivered by syringe pump via an IV infusion set or IV bag with a final RO7297089 volume determined by the dose. The specific RO7297089 dose will determine the appropriate dosing concentrations, volumes, and infusion times, and will also dictate the specific, appropriate, administration apparatus (i.e., peripheral catheter vs. syringe pump vs. IV bags) to be used. Premedication with oral acetaminophen or paracetamol (e.g., 500–1000 mg), an antihistamine (25–50 mg diphenhydramine or equivalent), and a corticosteroid (minimum equivalent of 80 mg IV methylprednisolone) will be administered as prophylaxis for IRR prior to first administration of RO7297089 *for Arms A and B, and prior to the first two doses of RO7297089 for Arm C*, unless contraindicated. *Administering premedication on the day prior to infusion may also be considered and/or implemented to mitigate IRR.* Premedication may be given prior to subsequent infusions at the discretion of the investigator. All RO7297089 doses should be administered to well-hydrated patients.

Recommended management of IRR is detailed in Section 5.1.2.2.

Infusion of RO7297089 will be administered as per Table 1, but no higher than 14 mg per kg of body weight per hour (≤ 14 mg/kg/hr). The reason for the restriction in infusion time is due to the use of sucrose as a protein stabilizing agent in the drug product. Sucrose is used as a protein stabilizer in many IV formulations of therapeutics and is generally excreted unchanged in the urine with no detrimental effect to humans. It was commonly used as a stabilizer in various formulations of intravenous Ig (IVIg); however, in 1999, the U.S. FDA issued a “Dear Doctor Letter” noting several cases of renal dysfunction and renal failure with IVIg, and a disproportionate number of cases correlated with sucrose containing formulations of IVIg. The FDA recommended that infusions of IVIg containing sucrose not exceed 3 mg of sucrose/kg/min to avoid renal complications. While this correlation was seen in IVIg formulations, this infusion rate has been extrapolated to any IV product containing sucrose. The amount of sucrose present in the formulated RO7297089 drug product is approximately 61.56 mg of sucrose per milliliter of drug product. Thus, to keep the sucrose infusion rates ≤ 3 mg/kg/min, RO7297089 will be infused at a rate no higher than 14 mg/kg/hr. Please refer to the pharmacy manual for additional details on administering RO7297089.

Initially, RO7297089 will be administered over a minimum of 2 hours or longer depending on the patient’s body weight. *The minimum infusion time may be increased if needed to mitigate IRRs.* The infusion may be slowed or interrupted for patients experiencing IRRs (see Section 5.1.2.2). Patients will be observed at least 240 minutes (4 hours) for fever, chills, rigors, hypotension, nausea, or other signs and symptoms of IRRs after the first RO7297089 infusion. *For Arm B (split dose), patients will be observed at least 240 minutes (4 hours) after the Day 1 infusion and for at least 120 minutes (2 hours) after the Day 2 infusion.* At the discretion of the investigator, patients may be hospitalized overnight to *accommodate a longer infusion or* extend the

observation period (see Sections 5.3.3 and 5.3.5.11 regarding the reporting requirements for such events). Patients who experience any sign or symptom of an IRR during the first infusion or at any time during the observation period that does not resolve to Grade ≤1 by the end of the observation period should be observed for at least 24 hours in a hospital setting. In the absence of IRRs, the infusion time of RO7297089 for subsequent infusions *may be reduced as described in Table 1*, to a minimum of 30 minutes. Both of these infusion times will also be dependent on patient's body weight to meet the 14 mg/kg/hr infusion rate limit. *If the first full dose was tolerated,* the observation period may also be reduced for subsequent infusions *as described in Table 1*.

Patients who undergo intrapatient dose escalation (see Section 3.1.3) should receive the first higher dose of RO7297089 over a minimum of 2 hours and be observed for at least 240 minutes (4 hours) for fever, chills, rigors, hypotension, nausea, or other signs and symptoms of IRR.

Management of IRRs and guidelines for dosage and schedule modification and treatment interruption or discontinuation are provided in Section 5.1.2.

Table 1 Administration of First and Subsequent Infusions of RO7297089

RO7297089	Cycle 1, Day 1	*Cycle 1, Day 2*	Cycle 1, Day 8	Cycle 2, Day 1 and Beyond
Arm A (flat dose)				
Minimum infusion time	120 min	*N/A*	60 min	30 min
Monitoring window	240 min	*N/A*	60 min	30 min
Arm B (split dose)				
Minimum infusion time	*120 min*	*120 min*	*120 min*	*30 min*
Monitoring window	*240 min*	*120 min*	*120 min*	*30 min*
Arm C (step up dose)				
Minimum infusion time	*120 min*	*N/A*	*240 min*	*60 min* [a]
Monitoring window	*240 min*	*N/A*	*240 min*	*30 min*

N/A =not applicable.

Notes: These infusion and observation times may be longer to meet the 14 mg/kg/hr infusion limit. In addition, these times assume that no infusion-related adverse events occurred during or within 24 hours after the prior infusion. For patients who develop infusion-related adverse events, see Section 5.1.2 for management guidelines.

[a] *After Cycle 2, Day 1, the minimum infusion time may be reduced to 30 minutes provided the previous infusions were tolerated.*

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor, by returning the

appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to RO7297089

The Sponsor (Genentech, a member of the Roche Group) will offer continued access to Genentech IMP RO7297089 free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Genentech IMP RO7297089 after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Genentech IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive Genentech IMP RO7297089 after completing the study if any of the following conditions are met:

- The Genentech IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for MM.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for MM.
- Provision of the Genentech IMP is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the end-of-treatment visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy may continue their use.

Concomitant use granulocyte colony-stimulating factor (G-CSF) (filgrastim, pegfilgrastim), hematopoietic growth factors such as erythropoietin, granulocyte/macrophage colony-stimulating factor (sargramostim), or thrombopoietin (oprelvekin, eltrombopag) is permitted. Transfusion of red blood cells and platelets are permitted.

Anti-infective prophylaxis for viral, fungal, bacterial, or pneumocystis infections is permitted and should be instituted per institutional practice. Immunoglobulin therapy is permitted.

Patients who experience RO7297089 infusion-related symptoms may be treated symptomatically as described in Section 5.1.2.2.

Palliative radiotherapy is permitted. Study drug treatment may be continued during palliative radiotherapy. Bisphosphonates and denosumab are permitted.

Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of lesions may still be eligible to continue study treatment, at the discretion of the investigator and after discussion with the Medical Monitor.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), corticosteroids, or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists). Refer to Section 5.1.2.2 for further guidance for management of IRRs.

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

The transient release of cytokines may be observed with RO7297089 which may suppress CYP450 enzymes and cause drug–drug interactions. This risk is anticipated to be low based on nonclinical data but will be informed by clinical data during this Phase I study. Patients receiving concomitant medications that are CYP450 substrates and have a narrow therapeutic index (see Appendix 8) may have the highest risk of a drug–drug interaction.

The list of medications in Appendix 8 is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator with Medical Monitor approval.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2) and during study treatment
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, immunotherapy, radiotherapy, and herbal therapy) for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.4.1 for details)
- Hormone therapy for the treatment of cancer, whether approved by local regulatory authorities or investigational

  Adjuvant endocrine therapy for non-metastatic prostate cancer and non-metastatic, hormone-receptor positive breast cancer is permitted.
- Biologic agents other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts
- Any therapies intended for the treatment of MM, whether approved by local regulatory authorities or investigational

- Live, attenuated vaccines

Patients who require the use of any of these agents will be discontinued from treatment with RO7297089. Patients who are discontinued from study treatment will be followed for safety outcomes for 90 days following the patient's final dose of RO7297089 or until the patient receives another anti-cancer therapy, whichever occurs first.

The above list of medications is not necessarily comprehensive. The investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Screening and pretreatment tests and evaluations will be performed within 28 days preceding the first dose of RO7297089 with the following exceptions:

- Pregnancy test must be done within 7 days of first dose of study drug (Cycle 1, Day 1)
- Hematology and chemistry panels must be done within 14 days of first dose of study drug

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within appropriate window prior to Cycle 1, Day 1 may be used; these tests do not need to be repeated for screening.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. With the exception of the pretreatment bone marrow biopsy material, results of all screening evaluations must be submitted to the Genentech Medical Monitor before a patient may be enrolled in the study. The pretreatment bone marrow biopsy may be performed after the patient has been cleared for enrollment into the study. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and reproductive status will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded (see Appendix 2).

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed during screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems (including evaluation of mental status, cranial nerves, strength, sensation, and coordination) and should be documented in the patient chart. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), targeted symptom-directed physical examinations should be performed. Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, neurologic, and any system that might be associated with tumor assessment [e.g., those systems associated with symptoms], or potential drug-related toxicity; see Section 5.1.1). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 ECOG Performance Status

Performance status will be measured using the ECOG Performance Status Scale (Appendix 15).

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Every effort should be made to ensure that vital signs are obtained from patients in a consistent manner/position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital signs for patients should be obtained according to the schedule of activities in Appendix 1. Details of the frequency of vital sign monitoring are provided in Table 2 below. Additional vital sign monitoring should be performed if clinically indicated or if symptoms occurred during the prior infusion.

Table 2 Vital Sign Monitoring

Arm A (flat)	**Cycle 1, Day 1** [a]	**Cycle 1, Day 8**	**Cycle 2, Day 1 and Beyond** [b]
Pre-infusion	Once	Once	Once
During infusion	Every 30 min (±10 min)	Every 30 min (±10 min)	Once
End of infusion	Once	Once	Once
Post-infusion	Every 60 min (±10 min) for 240 min	Once 60 min after end of infusion	Once 30 min after end of infusion
Arm B (split)	***Cycle 1, Day 1 and Day 2*** [a]	***Cycle 1, Day 8***	***Cycle 2, Day 1 and Beyond*** [b]
Pre-infusion	*Once*	*Once*	*Once*
During infusion	*Every 30 min (±10 min)*	*Every 30 min (±10 min)*	*Once*
End of infusion	*Once*	*Once*	*Once*
Post-infusion	*Every 60 min (±10 min) during observation*	*Once 60 min after end of infusion*	*Once 30 min after end of infusion*
Arm C (step)	***Cycle 1, Day 1*** [a]	***Cycle 1, Day 8***	***Cycle 2, Day 1 and Beyond***
Pre-infusion	*Once*	*Once*	*Once*
During infusion	*Every 30 min (±10 min)*	*Every 30 min (±10 min)*	*Once*
End of infusion	*Once*	*Once*	*Once*
Post-infusion	*Every 60 min (±10 min) for 240 min*	*Every 60 min (±10 min) for 240 min*	*Once 30 min after end of infusion*

[a] For any patient undergoing intrapatient dose escalation, the first infusion at a higher dose requires the same vital sign monitoring as Cycle 1, Day 1 *(or Cycle 1, Day 1 and Day 2 for Arm B)*.

[b] Except for any first infusion of a higher dose for patients undergoing intrapatient dose escalation (as per above).

4.5.6 Disease-Specific Assessments

Patients will be evaluated for disease response and progression according to the IMWG Uniform Response Criteria (Appendix 5) during each cycle at timepoints identified in the schedules of activities (Appendix 1 and Appendix 2).

A bone marrow biopsy and aspirate are required prior to Cycle 1, Day 1 dosing, between Cycle 2, Day 8 and Cycle 3, Day 1, and at the time of confirmation of CR or at disease

progression. The bone marrow sample scheduled prior to Cycle 1, Day 1 may be obtained after the patient's other screening procedures have been completed and enrollment of the patient has been confirmed by the Medical Monitor.

Patients who are re-screened after an initial screen failure (see Section 3.1) do not need to undergo a repeat bone marrow biopsy and aspirate if these assessments were completed during the initial screening period.

At least three historical values for M-protein (or SFLC if light chain–only disease) from the end of prior therapy to the initiation of study treatment with RO7297089 will be collected if available.

The following myeloma-specific tests will be at the beginning of every odd cycle and processed by the Sponsor or the Sponsor's contracted specialty bioanalytical laboratories for analysis, starting with Cycle 1, Day 1:

- Serum protein electrophoresis (SPEP) with serum immunofixation electrophoresis (SIFE)
- SFLCs

If SPEP/SIFE and SFLC analyses are additionally performed locally at sites, the results of these analyses should be provided to the Sponsor.

Quantitative Ig levels should be performed locally.

The following myeloma-specific tests should be performed both centrally and locally at sites during screening and as needed (locally) to confirm a response:

- A 24-hour urine protein electrophoresis (UPEP) with urine immunofixation electrophoresis (UIFE) for M-protein quantitation

The following confirmatory assessments are required for all response categories (sCR, CR, VGPR, PR, and minimal response):

- If extramedullary disease was previously present, computed tomography (CT) scan or MRI with bidimensional measurements to confirm reduction in size per IMWG Uniform Response Criteria
- If extramedullary disease was previously present, positron emission tomography (PET)-CT scan, CT scan, or MRI to confirm complete resolution
- 24-hour UPEP/UIFE (performed locally) to confirm VGPR even if a UPEP was not performed during screening

The following additional samples/assessments are required to confirm a sCR or CR:

- SIFE
- SFLC

- 24-hour UPEP/UIFE (performed locally) to confirm CR/sCR even if a UPEP was not performed during screening
- Bone marrow aspiration and biopsy
- If extramedullary disease was previously present, PET-CT scan, CT scan, or MRI to confirm complete resolution

To confirm progressive disease, the following are required:

- If progressive disease is suspected by rising M-protein, SPEP, UPEP, or SFLC analysis should be obtained on two consecutive assessments.
- If progressive disease is suspected on development of new bone lesions or soft tissue plasmacytomas or an increase in size of existing bone lesions or soft tissue plasmacytomas, skeletal survey/CT scan/MRI should be obtained and compared with baseline imaging.
- If progressive disease is suspected on hypercalcemia attributed solely to MM, local laboratory levels of serum calcium should be >11 mg/dL and confirmed on a second assessment.

Extramedullary Disease

All patients with clinically suspected extramedullary disease or known extramedullary disease at the time of screening must undergo imaging during screening to evaluate for the presence/extent of extramedullary disease. This can be performed by CT scan of the chest, abdomen, and pelvis (preferably with IV contrast if renal function is adequate), PET/CT, or whole-body MRI. Patients who are found to have extramedullary disease will undergo repeat imaging (preferably the same modality as performed during screening) every 12 weeks ($\pm$7 days). Imaging should also be performed upon clinical suspicion of progressive disease. Chest X-ray or ultrasound of the abdomen/liver/spleen may be substituted for CT, PET/CT, or MRI if, per the investigator's assessment, patients are not able to safely tolerate these imaging modalities and the anatomic location of the extramedullary disease is compatible with these alternative imaging methods.

Skeletal Survey

A skeletal survey will be completed during screening and as clinically indicated. The skeletal survey may be completed up to 28 days prior to Day 1 of Cycle 1. Plain films and CT scans are both acceptable imaging modalities for assessing skeletal disease. Imaging should include the skull, long bones, chest, and pelvis. If plasmacytomas are seen on skeletal survey, bidimensional tumor measurements should be recorded. The skeletal survey may be omitted if a PET/CT scan or a low-dose, whole-body CT is performed as part of screening.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells [if present])
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, LDH, total and direct bilirubin, ALP, ALT, and AST
- Coagulation: INR, aPTT, and PT (optional)
- HIV serology: HIV-1/2 antibody
- HBV serology: hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test during screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test during screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Quantitative immunoglobulins: IgA, IgG, and IgM
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test within 7 days prior to initiation of study drug. Urine pregnancy tests will be performed on the first day of odd-numbered cycles. If a urine pregnancy test is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Patients who become pregnant while on study must permanently discontinue study treatment as outlined in Section 4.6.1.
- Standard-of-care assessments of bone marrow biopsies and aspirate for local clinical pathology assessment, which will include, but are not limited to, cytogenetic analysis by fluorescence in situ hybridization (FISH; including markers such as 1q gain, del17, t(11:14), t(4;14), t(14; 16))

  The results of these studies should be sent to the Sponsor when available (results should be redacted of patient identifiers other than protocol-assigned patient number).
- Serum β-2 microglobulin

Samples for the following laboratory tests will be sent to one of several central laboratories for analysis:

- Blood samples for leukocyte immunophenotyping/flow cytometry (fluorescence-activated cell sorting [FACS] lymphocyte subsets) including, but not limited to,

enumeration of leukocyte subsets ([redacted]), and assessment NK-cell functional status ([redacted]) by flow cytometry

- Blood sample for WGS, to be collected on Cycle 1, Day 1 (or at any time during the study after Cycle 1, Day 1)
- Plasma for cytokines, including, but not limited to, IL-6 and IFN-γ
- Blood samples for biomarker assays for exploratory assessments that may predict response to RO7297089

  Blood samples will be obtained for biomarker evaluation (including, but not limited to, biomarkers related to MM or tumor immune biology) from all eligible patients according to the schedule in Appendix 3. Blood, plasma, and serum samples will be collected for the determination of changes in blood-based biomarkers. Blood samples may be processed to obtain PBMCs and their derivatives (e.g., RNA and DNA) or cell-free DNA.
- Serum samples for immunogenicity analysis
- Serum samples for PK analysis
- Bone marrow aspirate and biopsy samples

  Prior to Cycle 1, Day 1 dosing; between Cycle 2, Day 8 and Cycle 3, Day 1 dosing; and at the time of confirmation of CR or at disease progression, a bone marrow aspirate and trephine biopsy with an associated pathology report are required. For bone marrow aspirate samples, please refer to the central laboratory manual for the volume of aspirate that should be collected. Trephine/core biopsy tissue samples should preferably be a minimum of 1.5 cm in length (≥ 2 cm is optimal). If paraffin blocks or fresh tissue is unavailable, [redacted] unstained slides should be sent to the Sponsor (see the laboratory manual for further details). For bone marrow aspirates that unexpectedly clot, a paraffin block or [redacted] bone marrow aspirate unstained slides should be sent to the Sponsor or central laboratory per the laboratory manual.
- Analyses of bone marrow aspirate and biopsy samples may include, but are not limited to:
  - Changes in PD biomarkers, RO7297089 pharmacokinetics, and MRD status. Samples may be processed to obtain bone marrow mononuclear cells and their derivatives (e.g., RNA and DNA).
  - Leukocyte immunophenotyping/flow cytometry (FACS lymphocyte subsets) including, but not limited to, enumeration of leukocyte subsets ([redacted]), and assessment BCMA+ target cell depletion, NK-cell functional status (using markers including, but not limited to, [redacted]) by flow cytometry

    Fresh bone marrow aspirate may be used to confirm cytogenetic status at a central testing laboratory by FISH (during screening only).

- In the rare instance that a bone marrow biopsy is not feasible, in patients with extramedullary disease tissue obtained from an extramedullary plasmacytoma is acceptable, but should meet the following criteria:
  - If an excisional biopsy is performed, then a formalin-fixed, paraffin-embedded block (preferred) or a minimum of 15 serially sectioned, unstained slides is required. If ≤10 serially sectioned slides are available, consult with the Medical Monitor. For core-needle biopsy tissue specimens, at least three core tissue samples should be submitted for evaluation.
  - Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate). Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.
  - Acceptable samples include core needle biopsy tissue samples for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps tissue sample biopsies for cutaneous, subcutaneous, or mucosal lesions.
  - Patients who are re-screened after an initial screen failure (see Section 3.1) do not need to undergo a repeat biopsy if this assessment was completed during the initial screening period.

Exploratory biomarker assays may include, but will not be limited to, flow cytometry, genes or gene signatures associated with tumor immunology, and cytokines associated with NK-cell activation. Additional biomarkers may be assessed based on evolving clinical and nonclinical data.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK and ADA analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, bone marrow aspirate, bone marrow biopsy samples and any derivatives thereof will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms

Triplicate ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1). Three interpretable ECG recordings (e.g., without artifacts) must be obtained at each timepoint (±5 minutes). The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Single ECG recordings may be obtained at the end of treatment visit and unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. All ECGs as described above will be submitted to a Sponsor-designated ECG central laboratory for storage and potential analysis. Detailed instructions on ECG acquisitions and transmissions to the ECG central laboratory will be provided in the ECG manual provided for this study. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected through use of Fridericia's formula (QTcF) based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is >500 ms and/or 60 ms longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and triplicate ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 5.1.2.3. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.9 Blood Samples for Whole Genome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.9) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Patient medical information associated with WGS specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the WGS analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Refer to Section 4.5.7 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7297089, diseases, or drug safety:

- Bone marrow aspirate and bone marrow tissue samples performed at the investigator's discretion during the study
- Leftover blood, serum, plasma, PBMC, bone marrow aspirate, and bone marrow tissue samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or

patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be *informed* that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of an anticancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to IMWG Uniform Response Criteria (Appendix 5)
- Patient decision

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced unless enrolled in the dose-escalation cohorts and discontinue prior to completion of the 14-day DLT assessment window.

Patients will return to the clinic for a treatment discontinuation visit 30 (±10) days after the final dose of study drug (see Appendix 1 for additional details). Additionally, patients who discontinue study treatment for reasons other than documented disease progression or relapse should continue to be followed as described in Appendix 2 until disease progression, start of new anti-cancer therapy, or withdrawal from study participation, whichever occurs first.

4.6.1.1 Survival and Subsequent Anti-Cancer Therapy Follow-Up

Following study treatment discontinuation (initial or after re-treatment), patients may be followed for survival and subsequent anti-cancer therapy. Survival and subsequent anti-cancer therapy follow-up information may be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor unless the patient requests to be withdrawn from follow-up. Information on subsequent anti-cancer therapies will include systemic therapies (e.g., chemotherapy, targeted therapy, hormonal therapy), surgery (e.g., resection of metastatic disease), and radiation procedures (radiotherapy to a tumor lesion). If the patient withdraws from the study, the site's staff may use a public information source (e.g., county records) to obtain information about survival status only.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced unless enrolled in the dose-escalation cohorts and discontinue prior to completion of the 14-day DLT assessment window.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

This is the first study in which RO7297089 will be administered to humans. As such, the actual risks are unknown. The following information describing monitoring and management of potential safety risks is based on anticipated pharmacology and mechanism of action, results from nonclinical studies, and published data on similar molecules. Please refer to the RO7297089 Investigator's Brochure for further safety information.

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (Sections 4.1.1 and 4.1.2) and close monitoring, as described below. As described in Section 3.1.1, enrollment of the first patient in each *arm in each* dose-escalation cohort will be staggered such that the respective Cycle 1, Day 1 treatments are administered $\geq$72 hours apart.

After each patient receives the first dose of RO7297089, the investigator should confirm with the Sponsor that the patient has been dosed and should provide a brief summary of the status of the patient in terms of safety and tolerability to RO7297089 (this will be communicated by email and/or telephone; as soon as reasonably possible). In addition, regularly scheduled teleconferences will occur with the investigators and study team (including the Medical Monitor and Safety Scientist) to review the following for each patient: all relevant demographic, adverse event, laboratory, dose administration, available (radiographic) response, and available PK and PD data (e.g., imaging, plasma cytokines and markers of NK-cell activation).

All patients will be monitored closely for toxicity. Patients will be assessed clinically for toxicity prior to each dose using the NCI CTCAE v5.0 grading scale, except for CRS, in which the Modified Cytokine-Release Syndrome Grading System will be used (see Appendix 9). All adverse events and serious adverse events will be recorded during the trial and for up to 90 days after the final dose of study treatment or until the initiation of another systemic anti-cancer therapy, whichever occurs first. To mitigate potential

unknown risks, at least in part, dosing beyond Cycle 1 will be limited to patients who do not demonstrate unacceptable toxicity or compelling evidence of disease progression (see Section 3.1.1.2).

Specific anticipated or potential toxicities associated with administration of RO7297089, as well as the measures taken to avoid or minimize such toxicities in this trial, are described in the following sections.

5.1.1 Potential Risks Associated with RO7297089

5.1.1.1 Infusion-Related Reactions/Cytokine-Release Syndrome

The mechanism of action of RO7297089 is engagement and activation of NK cells against cells expressing BCMA. Therefore, a spectrum of events involving IRRs, CRS, and/or hypersensitivity with or without emergent ADAs, may occur. These reactions may be mild in severity but can also be severe or even fatal. Common signs and symptoms of these reactions could include fever; chills or rigors; alteration in heart rate and blood pressure; dyspnea or chest discomfort; back or abdominal pain; nausea, vomiting, and/or diarrhea; and various types of skin rash. Severe reactions can also include hypotension, hypoxia, other organ dysfunction, and/or neurologic toxicity.

In nonclinical studies, cytokine release with RO7297089 was assessed both in vitro as well as in the toxicity studies in cynomolgus monkeys. Clinical findings consistent with CRS and/or increases in inflammatory cytokines associated with CRS (e.g., IL-6, TNF-α, IFN-γ) due to RO7297089 were not observed in cynomolgus monkeys. IRRs were not observed in cynomolgus monkeys. In vitro studies at clinically relevant concentrations of RO7297089 in the presence of human PBMCs and MMCs expressing BCMA demonstrated minimal increases in inflammatory cytokines consistent with pharmacology. The changes were similar in magnitude to that seen with daratumumab, and were far lower than levels seen with T-cell engaging bispecific antibodies in similar assays.

Other bispecific antibody therapeutics involving NK-cell activation have been associated with IRRs in patients, though CRS was not demonstrated clinically. AFM13 is a tetravalent bispecific antibody with a mechanism of action similar to RO7297089, except that it engages NK cells to target CD30 expressed on B cells in patients with Hodgkin lymphoma and some types of non-Hodgkin lymphoma. In patients with R/R Hodgkin lymphoma treated with single-agent AFM13 in a dose-escalation Phase I study, Grade 1–2 IRRs were seen in 4 patients (14%) and CRS was not reported (Rothe et al. 2015).

Based on these nonclinical data, experience with molecules with a similar mechanism of action, *and clinical experience with to RO7297089 date,* RO7297089 has the potential to cause an IRR and/or CRS, but the likelihood of CRS appears very low (see Section 1.2). *In this current first-in-human, dose-escalation Study GO41582, the observation of IRR events led to the release of an Urgent Safety Measure (USM) on*

4 September 2020 and a subsequent protocol amendment to mandate premedication with corticosteroids. At the time of the USM, 1 of 3 patients in Cohort 1 (60 mg) and 2 of 2 patients in Cohort 2 (180 mg) experienced a Grade 2 IRR in Cycle 1. The IRR events, consisting of shivering/rigors and temperature elevation, occurred either during the infusion or during the post-infusion observation window. To minimize the risk of IRRs, patients will be *premedicated prior to the first administration of RO7297089 for Arms A and B, and prior to the first two doses of RO7297089 for Arm C, unless contraindicated (see Section 4.3.2.1). Administering premedication on the day prior to infusion may also be considered and/or implemented to mitigate IRR. Patients will be* dosed slowly over *a minimum of 2* hours *to mitigate IRR* and monitored closely for 4 hours following their first infusion of RO7297089 *(see* Table 1*)*, with frequent vital sign measurements (see Table 2) to identify potential IRR/CRS. Patients who tolerate RO7297089 infusions well do not require as long an infusion time or observation period with subsequent infusions and will be observed post-infusion as described in Table 1.

Guidelines for management of patients who develop an IRR are summarized in Table 3, with grading according to NCI CTCAE v5.0. Management of Grade ≥ 3 IRR should be immediately discussed between the treating investigator and the Medical Monitor. Refer to Section 5.3.5.1 for adverse event reporting procedures related to IRRs. Guidelines for management of and grading of CRS according to the Modified Cytokine-Release Syndrome Grading System (Appendix 9) are summarized in Appendix 10.

5.1.1.2 Immunogenicity

Administration of therapeutic proteins may lead to the formation of ADAs. The development of ADAs may have an impact on exposure and/or efficacy and can lead to hypersensitivity reactions, including immune complex-mediated responses.

Serum samples will be collected at protocol-defined intervals to monitor for the development of ADAs. Patients who have clinical sequelae that are considered potentially related to an ADA response may also be asked to return for additional follow-up testing.

ADAs to RO7297089 were observed in in cynomolgus monkeys in the toxicity studies, and while an effect on the pharmacokinetics was noted in cynomolgus monkeys, this does not always translate to an effect in humans. There were no adverse findings related to ADA.

As seen with other therapeutic monoclonal antibodies, RO7297089 can form protein aggregates. Non-covalent multimers (predominantly dimers) have been characterized during manufacturing. The impact of non-covalent multimers or aggregates of RO7297089 is not known; however, there could be an increased potential for immunogenicity (Rosenberg 2006).

Patients will be monitored as described above after infusion for any IRR or hypersensitivity reactions, and at regular intervals for the development of ADAs. Any clinical signs and symptoms suggestive of a hypersensitivity reaction, in particular immune complex-mediated reaction possibly due to ADA formation, will be carefully investigated.

Please refer to the RO7297089 Investigator's Brochure for additional details.

5.1.1.3 Infection

Due to its anticipated mode of action resulting in plasma-cell depletion and, potentially, NK-cell depletion, RO7297089 may be associated with hypogammaglobulinemia and an increased risk of infections. Serum Ig levels will be monitored in this study according to the schedule outlined in Appendix 1. Administration of IVIg should be considered for patients with hypogammaglobulinemia who are considered to be at increased risk for infection.

In the repeat-dose toxicity study in cynomolgus monkeys, decrease in plasma cells and hypogammaglobulinemia was not seen; however, decreases in serum IgM and mRNA expression levels of plasma cell markers were noted in all monkeys at all dose levels. This was considered a PD effect of the drug.

RO7297089 should not be administered in the presence of active severe infections. Investigators should exercise caution when considering the use of RO7297089 in patients with history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. Signs and symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment.

Hepatitis B reactivation has been reported with B cell–directed therapies. While B cells are not expected to be effected by RO7297089, patients with a history of chronic hepatitis B infection or positive test results for active or chronic HBV infection (defined by HBsAg and/or positive total HBcAb and positive HBV PCR), or patients with HCV infection as assessed by PCR, will be excluded from this trial as a precaution (see Section 4.1.2). Patients with positive HBV serology but undetectable HBV PCR will be allowed to enroll and may receive HBV prophylaxis at the investigator's discretion.

Patients with known or suspected chronic active Epstein-Barr virus infection will be excluded from this trial due to the risk of secondary macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH) (see Section 4.1.2).

5.1.1.4 Blood Pressure Decrease

In the 4-week IV repeat-dose GLP toxicity study in cynomolgus monkeys, a core battery of safety pharmacology endpoints were assessed, including external multi-lead electrocardiogram (ECG) and non-invasive blood pressure measurements via tail cuff

measurements 24 hours after completion of infusion on Days 9 and 30 of the study. All ECG parameters were normal, as were measurements of pulse rate. The only findings were minimally decreased systolic, diastolic, and mean arterial pressures (19%, 27%, and 20%, respectively) compared to control animals. These changes were noted on Day 30 in the cohort receiving 50 mg/kg of RO7297089 approximately 24 hours post administration of the fifth scheduled dose. These changes were considered non-adverse in the cynomolgus monkey based on the known variance using tail cuff measurements as a measure of blood pressure, lack of correlating cardiovascular parameters, and lack of clinical correlation in the monkeys; however, a relationship to RO7297089 was unable to be ruled out and, as such, a minimal decrease in blood pressure is considered a potential risk when dosing RO7297089 in humans.

Blood pressure will be monitored during this study according to Section 4.5.5 and the schedule of activities (Appendix 1). This will include measurements of blood pressure during infusion of RO7297089 as well as measurements of blood pressure during post-infusion observation periods. In addition, patients will be educated on the potential for blood pressure decreases and will be instructed to inform their study physicians of any changes in blood pressure or clinical signs and symptoms that could indicate blood pressure decrease such as dizziness, lightheadedness, or syncope.

5.1.1.5 Tumor Lysis Syndrome

TLS is a known PD effect of anti-tumor therapy in hematologic malignancies including MM (Fuente et al. 2004; Sezer et al. 2006). TLS has been reported with some therapies for MM (Velcade USPI and SmPC; Kyprolis® [carfilzomib] USPI and SmPC). The inherent risk of TLS is dependent on the malignancy being treated and individual patient characteristics (Coiffier et al. 2008). There is a theoretical risk of TLS if treatment with RO7297089 results in the rapid destruction of a large number of tumor cells.

Due to the potential risk of TLS following RO7297089 administration, patients must have a CrCl $\geq$30 mL/min to participate in this trial (see Section 4.1.1). Prior to dosing during Cycle 1 of RO7297089, the patient's serum chemistry and hematology laboratory samples should be obtained and reviewed and prophylactic measures initiated according to the guidelines described below. Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities prior to the infusion of RO7297089 in Cycle 1 and beyond, otherwise the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing. Laboratory abnormalities suggestive of TLS should prompt immediate action by the treating clinicians, and TLS should be treated aggressively per institutional practice. Access to nephrologist and acute dialysis services must be available in the event of clinically significant TLS.

Patients with elevated uric acid levels prior to RO7297089 treatment or who are considered to be at high risk for TLS as defined in Appendix 14 should receive

prophylaxis for TLS prior to each RO7297089 infusion during Cycle 1 as per institutional guidelines.

5.1.1.6 Lymphopenia

Given the mode of action of RO7297089 mediating destruction of BCMA-expressing plasma cells via engagement of CD16A expressed on NK cells in a manner similar to ADCC, reduction in lymphocyte counts is a potential risk.

In patients with R/R Hodgkin Lymphoma treated with single-agent AFM13, a transient dose-dependent decrease of circulating NK cells was observed. This was felt to be due to margination, but could possibly have been an effect of the drug given the mechanism of action (Rothe et al. 2015).

Patients receiving RO7297089 will be monitored for decreases in lymphocytes as described in Appendix 1. In addition, Grade ≥ 3 lymphopenia that also represents ≥ 50% decrease from baseline (regardless of whether the event otherwise meets criteria for reporting of an abnormal laboratory value as an adverse event) will be considered an adverse event of special interest for this study. Patients with lymphopenia may be considered for antiviral and PCP prophylaxis as per institutional standard.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications and Interruptions

All considerations of dose and schedule modifications should be discussed with the Medical Monitor. The following guidelines regarding dose and schedule modifications should be followed:

- In general, patients receiving RO7297089 who experience a Grade 4 non-hematologic adverse event that is not considered by the investigator to be attributable to another clearly identifiable cause should permanently discontinue all study treatment. However, for patients with Grade 4 adverse events of asymptomatic laboratory changes, study treatment may be resumed upon resolution to Grade ≤ 1 or baseline with approval of the Medical Monitor.
- For patients who experience IRRs with the first dose of RO7297089, or are at increased risk of recurrent IRRs with subsequent doses, the infusion rate may be slowed by 50% (Section 5.1.2.2). Modifications to infusion rate in these circumstances should be discussed with the Medical Monitor.
- In general, patients who experience either an adverse event that meets the definition of a DLT or other Grade 3 adverse event that is not considered by the investigator to be attributable to another clearly identifiable cause (e.g., documented disease progression, concomitant medication, or pre-existing medical condition) will be allowed to delay dosing for up to 2 weeks (or longer if approved by the Medical Monitor) in order to recover from the toxicity. Patients may continue to receive additional infusions of RO7297089, provided that the toxicity has resolved to Grade ≤ 1 (or for laboratory abnormalities, return to ≥ 75% of the baseline value), within 2 weeks.

- A reduced dose for subsequent infusions of RO7297089 should be considered and discussed with the Medical Monitor. Decisions on continued treatment following a DLT or other study treatment–related Grade 3 toxicity should be made following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval of the Medical Monitor, including in the following scenarios:

  Patients with Grade 3 or 4 event of anemia if manageable by red blood cell transfusions as per institutional practice may continue without dose reduction with approval of the Medical Monitor.

  Patients with Grade 3 or 4 events of thrombocytopenia or neutropenia if manageable by transfusions (platelets) or granulocyte colony-stimulating factor (GCSF) as per institutional practice may continue without dose reduction with approval of the Medical Monitor.

- Any patient in whom similar toxicity recurs at a reduced dose should be discontinued from further RO7297089 treatment.

- Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed will be discontinued from study treatment (unless a longer dose delay was approved by the Medical Monitor) and be followed for safety outcomes as described in Section 5.3.1. Exceptions to this on the basis of ongoing clinical benefit may be allowed following investigator assessment of risk versus benefit with approval of the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

The dose of RO7297089 can be reduced up to two times for management of drug-related toxicities. If further dose reduction is indicated after two dose reductions, the patient must discontinue RO7297089. After dose reduction due to drug-related toxicity, the dose of RO7297089 may not be re-escalated.

Patients who discontinue study treatment for reasons other than progressive disease should continue to be followed according to the schedule in Appendix 3.

5.1.2.2 Management Guidelines for Infusion-Related Reactions/Cytokine-Release Syndrome

Guidelines for medical management of IRRs are provided in Table 3. Guidelines for the medical management of CRS are provided in Appendix 10.

Table 3 Management Guidelines for Infusion-Related Reactions

Event [a]	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt study treatment infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Subsequent *infusions* may be administered with premedication in consultation with and with approval of the Medical Monitor. [b] • Patients who experience Grade 3 wheezing, bronchospasm, or generalized urticaria at first occurrence must be discontinued from study treatment. Notes: • If symptoms recur despite premedications with the same or greater severity at subsequent cycles, the infusion must be stopped immediately and patient permanently discontinued from study treatment.
IRR, Grade 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue study treatment and contact Medical Monitor.

IRR = infusion-related reaction.

[a] Refer to NCI CTCAE v5.0 for the grading of symptoms

[b] Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with study treatment only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

5.1.2.3 Management of Increases in QT Interval

RO7297089 should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value

- Sustained absolute QTcF that is > 515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients. The Medical Monitor should be notified as soon as possible.

In rare circumstances, it may be acceptable to resume study drug, at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- DLTs
- Grade ≥ 2 IRR
- Any grade CRS
- TLS (Grade ≥ 3 by definition)
- Grade ≥ 3 infection
- Grade ≥ 3 lymphopenia that also represents ≥ 50% decrease from baseline (regardless of whether the event otherwise meets criteria for reporting of an abnormal laboratory value as an adverse event, as described in Section 5.3.5.5)

5.2.4 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

During the DLT assessment window, adverse events identified as DLTs, as defined in Section 3.1.1.1, are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 90 days after the final dose of study drug or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 5.0) will be used for assessing adverse event severity, with the exception of CRS, which is graded according to the Modified Cytokine-Release Syndrome Grading System established by Lee et al. (2019) and is described in Appendix 9. Patients who are hospitalized to extend the observation period following study drug administration, either at the discretion of the investigator or because the patient experienced an IRR during or following the first dose (see Section 4.3.2.1), should not automatically be considered to have had a Grade 3 adverse event. In such cases, the investigator should consider whether the adverse event required hospitalization due to the nature and severity of the symptoms when determining the severity of the adverse event.

Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon rechallenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., “infusion-related reaction” or “anaphylactic reaction”) on the Adverse Event eCRF. Events that occur after the start of study drug administration and at any time during a given cycle, that are judged by the investigator to be consistent with CRS, should be recorded as “cytokine-release syndrome” on the Adverse Event eCRF. If possible, for these events, avoid ambiguous terms such as "systemic reaction." Associated signs, symptoms, and laboratory abnormalities should be recorded on the dedicated Infusion-Related Reaction eCRF, or if CRS is suspected, on the dedicated Cytokine Release Syndrome eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction or Cytokine Release Syndrome eCRF as applicable.

In addition to documenting IRR and/or CRS on the Adverse Event eCRF, non-serious events of any grade CRS and Grade ≥2 IRR should be reported as a non-serious adverse event of special interest (see Section 5.2.3).

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious"

to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of Multiple Myeloma.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of

reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of multiple myeloma, “multiple myeloma progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Multiple Myeloma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization solely for coordination of care, including hospice arrangements
- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

  Patients who are hospitalized to extend the observation period following study drug administration, either at the discretion of the investigator or because the patient experienced an IRR during or following the first dose (see Section 4.3.2.1), should not automatically be considered to have had a serious adverse event. In such cases, the investigator should consider whether the adverse event required hospitalization (regardless of the need for observation) or met seriousness criteria unrelated to hospitalization when determining whether an adverse event is serious.

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

5.3.5.12 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For RO7297089, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with RO7297089, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- DLTs during the DLT assessment window (defined in Section 5.2.4; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted] (South San Francisco, CA, USA)

Email: [redacted]

Alternate Medical Monitor Contact Information

CRO Medical Monitor contact information:

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted] (Belgium)

5.4.2 Reporting Requirements for Serious Adverse Events, Adverse Events of Special Interest, and Dose-Limiting Toxicities

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study drug. DLTs will be reported during the DLT assessment window. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC)

system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 90 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial

Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 90 days after the final dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
RO7297089	RO7297089 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

No formal hypothesis testing is planned. Descriptive statistics will be used to summarize the safety, tolerability, pharmacokinetics, and clinical activity of RO7297089. Data will be described and summarized as warranted by number of patients in question. Listings will be used in place of tables for small numbers of patients. All analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of study drug.

Continuous variables will be summarized using means, standard deviations, median and ranges; categorical variables will be presented using counts and percentages. All summaries will be presented by dose cohort to which a patient was originally assigned.

6.1 DETERMINATION OF SAMPLE SIZE

Sample size of the dose escalation study is based on the mCRM-EWOC design and not based on statistical power calculations. A minimum of 9 evaluable patients and approximately 30–50 evaluable patients will be enrolled for dose-escalation.
A simulation study has been conducted to evaluate the sample size (see Table 3 in Appendix 11). Approximately 30 patients may be enrolled in the expansion cohort to better characterize PK, PD, and preliminary activity signals at the presumed RP2D.

A sample size of thirty patients is a reasonable size for the expansion cohort in order to obtain an estimate of the response rate; with a sample size of 30 and an observed response rate of 20%, the 90% confidence interval for the true response rate is (8%, 32%), corresponding with 2 and 10 responses, and the expected number of responses is 6.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. The study is open-label; therefore, no blinded treatment will be administered. Patients will be assigned to a dose/regimen rather than randomized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race and ethnicity, weight, and disease characteristics such as duration of malignancy) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by originally assigned dose level.

6.4 SAFETY ANALYSES

The primary objective for this study is to evaluate the safety of RO7297089, including estimation of the MTD and characterization of DLTs, on the basis of the following endpoints:

- Nature, frequency, severity, and timing of adverse events, including DLTs
- Changes in vital signs, physical findings, and clinical laboratory results during and following RO7297089 administration

The safety analysis population will consist of all patients who received at least one dose of study drug. Statistical summaries will be descriptive in nature (e.g., incidence rates, means, and percentiles).

Primary Safety Model (mCRM-EWOC)

An mCRM-EWOC model will be utilized to inform decision-making about the dose of RO7297089. All patients will be followed through the DLT window (*14 days; see Figure 2*) and be enrolled in a sequential manner. Patients within a cohort will be sequentially enrolled in cohorts of three patients each, which, if required, can be expanded with additional patients.

The dose-toxicity relationship will be described by a two-parameter logistic regression model, which can be updated anytime by incorporating available information from all patients. A minimal informative prior will be used.

The Sponsor and Investigators will evaluate the next dose recommended by the mCRM-EWOC design and agree on the dose for the subsequent cohort. At each dose-escalation step, the dose can be escalated, de-escalated, or an additional cohort at that same dose level could be enrolled.

The mCRM will continue until a maximum of approximately 40 patients, or all rules in a pre-defined set of MTD precision criteria, have been reached; or if it is concluded that the RP2D has been defined, using multiple parameters of safety, PD, and efficacy data.

The set of MTD precision criteria is:

- At least 9 patients have accrued overall;
- At least 6 patients have been accrued near the MTD dose where “near” is defined as being within 20% of the MTD;
- The probability that the MTD lies within the target toxicity interval is above 40%.

After the dose-escalation phase, a tentative RP2D, which will guide the recommended dose in expansion, will be defined. The final RP2D will be estimated based on the DLT occurrence rate in all patients evaluable for DLTs in the dose-escalation and dose-expansion parts of the study. The model will be implemented by R and Jags software.

All patients from the safety analysis population who follow the protocol-specified dose regimen within the DLT observation period and have undergone the scheduled safety evaluations, or who discontinued earlier due to a DLT, will be included in the MTD-determined analysis.

Clinical judgment can always override the Bayesian adaptive design recommendations in the dose-selection process.

6.4.1 Analyses of Exposure, Adverse Event, Laboratory, and Vital Sign Data

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

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

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

6.5 PHARMACOKINETIC ANALYSES

Individual and mean serum RO7297089 concentration versus time data will be tabulated and plotted. The serum pharmacokinetics of RO7297089 will be summarized by estimating the following:

- AUC
- C_{max}
- t_{max}
- C_{min}
- Total clearance
- Volume of distribution at steady state

- Half-life (as appropriate for data collected)

Compartmental, non-compartmental, and/or population methods may be considered. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum), as appropriate. Additional PK analyses may be conducted as appropriate.

6.6 ACTIVITY ANALYSES

Response assessment data and duration of response will be summarized for all patients by cohort.

Objective response is defined as a sCR, CR, VGPR, or PR as determined by investigator assessment using IMWG response criteria. Patients with missing or no response assessments will be classified as non-responders. The objective response rate will be summarized for patients receiving the recommended Phase II dose.

Among patients with an objective response, duration of response will be defined as the time from the initial objective response to the time of disease progression or death. If a patient does not experience disease progression or death before the end of the study, duration of response will be censored at the day of the last tumor assessment. If no tumor assessments were performed after the time of first objective response, duration of response will be censored at the time of first objective response.

OS is defined as the time from the first day of study treatment (Day 1 of Cycle 1) to death. If a patient has not experienced death, OS will be censored at the day of last contact. Preliminary OS data may be tabulated and summarized using time-to-event analyses for patients receiving the RP2D.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of treatment emergent ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at

baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, activity, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 INTERIM ANALYSES

Continuous safety monitoring and interim analyses will be performed for the expansion portion of the study to guide potential early stopping of enrollment in the event of unacceptable toxicity or a lower than expected response rate.

A Bayesian posterior probability approach (Thall and Simon 1994) with a uniform prior will be used to evaluate toxicity, including the rate of DLTs. If at any time in the expansion cohort, the number of observed DLTs indicates that there is an approximately 80% chance that the true DLT rate is $\geq$ 20% (e.g., DLTs observed in 2/5, 3/10, 4/15, 5/20 patients), accrual to the cohort may be paused and the ISC will meet to determine whether further enrollment in the cohort should be halted taking into account feedback from study investigators.

A similar approach will be used to assess the response rate. Specifically, after approximately 15 patients in the expansion cohort have completed their first tumor assessment, an interim analysis will be conducted to inform potential early stopping of enrollment if observed response rates are lower than expected. Using the Bayesian posterior probability approach with a uniform prior, the cohort may be stopped if the objective response rate is less or equal to 25% with a probability greater or equal to 60%. This would be the case for example if 2 or fewer out of the first 15 patients have an objective response. At each interim analysis, the ISC will review the response data and decide whether to recommend an early decision to stop enrollment in the subgroup due to futility. Additional futility analyses may be conducted in periodic review of efficacy data. In all cases, decisions to stop enrollment into the expansion cohort will be made in consultation with study investigators.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and all non-CRF data types (i.e., ECG, IxRS, and sample results data) will be sent directly to the Sponsor,

using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a

separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will

permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc.

A CRO may provide clinical monitoring, data management, and medical monitoring support. Genentech will conduct CRO oversight, approve patient eligibility, make decisions regarding dosing levels and schedules, provide primary medical monitoring, and conduct statistical programming and analysis.

EDC will be utilized for this study. An IxRS will be used to assign patient numbers. A central laboratory will be used for a subset of laboratory assessments as specified in Section 4.5; otherwise, local laboratories will be used. Central review facilities will be used to collect and analyze ECGs.

An ISC will be employed to monitor and evaluate patient safety throughout the study.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Timepoint	Screen [a]	Cycle 1							Cycle 2		Cycle ≥3		Cycle for First Dose of an Intrapatient Dose Escalation		End of Treatment Visit [v]
		D1 [b]	D2		D3	D8 [b]	D9		D1 [b]	D8 [b]	D1 [b]	D8 [b]	D1 [b]	D8 [b]	
			Arm A (flat) *Arm C (step)* 20–24 hr After EOI	*Arm B (split)*	*Arms A and C:* 40–48 hr After EOI *Arm B:* *20–24 hr After EOI*		20–24 hr After EOI								
Written informed consent	x [c]														
Review inclusion/exclusion criteria	x														
Medical history and demographic data	x														
Height (screening only) and weight	x	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	x
ECOG performance status	x	x							x		x		x		x
Complete physical exam [e]	x														
Targeted physical exam [f]		x				x			x		x		x		x
Concomitant medications [g]	x	x	x	*x*	x	x	x		x	x	x	x	x	x	x
Adverse events [h]	x	x	x	*x*	x	x	x		x	x	x	x	x	x	x
12-lead ECGs [i]	x	x		*x*		x					x		x		x
HBV, HCV, and HIV screening [j]	x														

Appendix 1: Schedule of Activities

		Cycle 1						Cycle 2		Cycle ≥3		Cycle for First Dose of an Intrapatient Dose Escalation		End of Treatment Visit [v]
		D1 [b]	D2		D3	D8 [b]	D9	D1 [b]	D8 [b]	D1 [b]	D8 [b]	D1 [b]	D8 [b]	
Timepoint	Screen [a]		*Arm A (flat) Arm C (step)* 20–24 hr After EOI	*Arm B (split)*	*Arms A and C:* 40–48 hr After EOI *Arm B:* 20–24 hr After EOI		20–24 hr After EOI							
Hematology [k]	x	x	x	x	x	x	x	x	x	x		x		x
Liver function test [l]	x	x	x	x	x	x	x	x	x	x		x		x
Chemistry panel [m]	x	x	x	x	x	x	x	x	x	x		x		x
Coagulation (aPTT, PT [optional], INR)	x													
Pregnancy test [n]	x									x (odd cycles)		x (if odd cycle)		x
Serum β-2 microglobulin	x									x (odd cycles)		x (if odd cycle)		
Immunoglobulins (IgG, IgM, IgA)	x	x								x (odd cycles)		x (if odd cycle)		
SPEP with SIFE [o]	x	x								x (odd cycles)		x (if odd cycle)		
Serum free light chains [o]	x	x								x (odd cycles)		x (if odd cycle)		

Appendix 1: Schedule of Activities

Timepoint	Screen [a]	Cycle 1						Cycle 2		Cycle ≥3		Cycle for First Dose of an Intrapatient Dose Escalation		End of Treatment Visit [v]
		D1 [b]	D2		D3	D8 [b]	D9	D1 [b]	D8 [b]	D1 [b]	D8 [b]	D1 [b]	D8 [b]	
			Arm A (flat) Arm C (step) 20–24 hr After EOI	*Arm B (split)*	*Arms A and C:* 40–48 hr After EOI *Arm B:* 20–24 hr After EOI		20–24 hr After EOI							
Historical values for multiple myeloma labs [w]	*x*													
Bone marrow biopsy and aspirate [o, p]	x [q]								x (between C2D8 and C3D1)	Repeat as clinically indicated to confirm complete response and/or progression.				
RO7297089 administration [r]		x [s]		*x* [s]		x [s]		x	x	x	x	x [s]	x	
Skeletal survey (–28 to –1 days relative to C1D1) [t]	x		Repeat as clinically indicated											
Imaging (as needed) to assess extramedullary disease	x		If extramedullary disease is present at screening, repeat every 12 weeks and as needed to confirm response or progression.											
24-hour UPEP with UIFE	x [o, u]		Repeat as clinically indicated to confirm response or progression.											
Serum PK		See Appendix 3 for PK collection schedule.												
Serum ADA		See Appendix 3 for ADA collection schedule.												
Biomarkers		See Appendix 3 for biomarker collection schedule.												
Whole blood for flow cytometry and PBMC isolation, cell-free DNA, WGS		See Appendix 3 for whole blood collection schedule.												

C = Cycle; CMV = cytomegalovirus; CT = computed tomography; D = Day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; *EOI = end of infusion;* GGT = gamma-glutamyl transpeptidase; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; hr = hour; IRR = infusion-related reaction; min = minute; *M-protein = monoclonal protein (M-protein);* MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; PET = positron emission tomography; PK = pharmacokinetic; Screen = screening; *SFLC = serum free light chains;* SIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis; UIFE = urine immunofixation electrophoresis; UPEP = urine protein electrophoresis; WGS = whole genome sequencing.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used; these tests do not need to be repeated for screening. Hematology panel, chemistry panel should be performed within 14 days of Cycle 1, Day 1. SPEP and serum free light chains should be repeated on Day 1 of Cycle 1.

[b] On dosing days, all pre-infusion assessments are to be performed before RO7297089 infusion, unless otherwise specified; pre-infusion local laboratory samples should be drawn 0–24 hours prior to infusion for Cycles 1 and 2, and 0–72 hours for Cycles ≥ 3. Prior to the initiation of RO7297089 dosing on C1D1, *C1D2 (Arm B only),* C1D8, C2D1, and C2D8, the results of local laboratory assessments should be reviewed by the investigator or a delegate.

[c] Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

[d] Includes systolic and diastolic blood pressure, respiratory rate, pulse rate, and body temperature while the patient is in a sitting or semi-supine position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Please refer to Table 2 in Section 4.5.5 for frequency of vital sign monitoring.

[e] A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[f] Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, neurologic, and any system that might be associated with tumor assessment [e.g., those systems associated with symptoms] or potential drug-related toxicity; see Section 5.1.1). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[g] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until the end of treatment visit.

[h] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study drug or until initiation of another anti-cancer therapy, whichever occurs first. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.3.4). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[i] See Section 4.5.8 for details. Obtain 12-lead digital ECG measurements in triplicate (immediately consecutive ECGs until three evaluable ECGs are recorded) at the following timepoints: Screening; 30–60 minutes pre-infusion on C1D1, C1D8, C3D1, and Day 1 of any first cycle with a higher dose for patients who undergo intrapatient escalation; and 0–30 minutes after end of infusion on C1D1 *(Arms A and C), C1D2 (Arm B)*, C1D8, C3D1, and Day 1 of any first cycle with a higher dose for patients who undergo intrapatient dose escalation. Obtain post-screening ECGs as close as possible to scheduled serum PK samples (see Appendix 3). Perform non-triplicate ECGs at end of treatment and when clinically indicated in any patient with evidence of, or suspicion for, clinically significant signs or symptoms of cardiac dysfunction.

[j] HBsAg, HBcAb, HCV antibody, and HIV serology are required. Patients whose hepatitis B serology results cannot rule out acute or chronic HBV infection must be negative for HBV by PCR to be eligible for study participation. Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.

[k] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells [if present]).

[l] Liver function tests include total and direct bilirubin, total protein, albumin, ALT, AST, ALP.

[m] Chemistry panel includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, calcium, phosphorous, LDH.

[n] All women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug. Thereafter, perform a urine pregnancy test on the first day of odd-numbered cycles. If a urine pregnancy test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Patients who become pregnant while on study must permanently discontinue study treatment as outlined in Section 4.6.1.

[o] Central testing is required for these assessments.

[p] See Section 4.5.7 and specific instructions and description of supplies in the laboratory manual regarding bone marrow sample harvesting. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.

[q] The screening bone marrow biopsy and aspirate may be performed after all other screening tests have been completed and after the Medical Monitor has confirmed that the patient is eligible for the trial. Patients who are re-screened after an initial screen failure (see Section 3.1) do not need to undergo a repeat bone marrow biopsy and aspirate if these assessments were completed during the initial screening period.

[r] For Cycles $\geq$2, study drug infusions should occur on Day 1 and Day 8 of each 14-day cycle but may be given up to $\pm$2 days from the scheduled date (with a minimum of 5 days between doses) for logistic/scheduling reasons. All timepoints listed are relative to end of infusion unless otherwise noted.

[s] Patients should be monitored *after each infusion as described in* Table 1. Patients undergoing intrapatient dose escalation should also be monitored following their first dose-escalated infusion*(s) as described in Section 4.3.2.1*.

[t] Skeletal survey may be omitted if a PET/CT scan or a low-dose, whole-body CT is performed as part of screening.

[u] The baseline 24-hr UPEP with UIFE will be analyzed both centrally and locally. Any other 24-hr UPEP that is required to assess patient status will be done locally. A 40-mL aliquot from a single 24-hr UPEP collection for both the local and central analyses is acceptable. See specific instructions and description of supplies in the laboratory manual.

[v] Patients who complete the treatment period will return to the clinic for an end of treatment visit 30 (± 10) days after the last infusion of study drug. Patients who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit 30 (± 10) days after the last infusion of study drug.

[w] *Regardless of M-protein or SFLC laboratory values used for screening, at least three historical values of M-protein (or SFLC if light chain–only disease) from the end of prior therapy to the initiation of study treatment with RO7297089 will be collected if available.*

Appendix 2
Schedule of Activities: Post-Treatment Follow-Up

Assessments/Procedures	Post-Treatment Follow-Up [a]
Targeted physical examination [b]	Every 3 months
Vital signs (blood pressure, pulse rate, and body temperature)	Every 3 months
ECOG Performance Status	Every 3 months
Tumor assessments including SPEP with SIFE and SFLCs performed centrally; UPEP with UIFE and imaging performed locally as clinically indicated	Every 3 months
Total IgA, IgG, IgM	Every 3 months
Hematology [c]	Every 3 months × 2, then every 6 months
Serum chemistry [d]	Every 3 months × 2, then every 6 months
Bone marrow biopsy and aspirate [e]	As needed to confirm relapse

ADA = anti-drug antibody; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; PK = pharmacokinetic; SFLC = serum free light chain; SIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis; UIFE = urine immunofixation electrophoresis; UPEP = urine protein electrophoresis.

[a] Schedule corresponds to visit timepoints only for patients who do not discontinue the study due to progressive disease. Perform assessments until disease progression, start of new anti-cancer therapy, or withdrawal from study participation, whichever occurs first. Continue to follow patients on this schedule timed from the treatment termination visit 30 days (± 10 days) after the last dose of RO7297089 administered. The first 2 visits should occur within ± 7 days from the scheduled date, while subsequent visits should occur within ± 14 days from the scheduled date.

[b] Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, neurologic, and any system that might be associated with tumor assessment [e.g., those systems associated with symptoms], or potential drug-related toxicity; see Section 5.1.1). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[c] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells [if present]).

[d] Chemistry panel includes sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, calcium, phosphorous, LDH.

[e] Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.

Appendix 3
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Pre-infusion [a]	Peripheral biomarkers (plasma and serum)
		Flow cytometry and PBMC isolation (whole blood)
		Cell-free DNA (whole blood)
		WGS (whole blood) [b]
		PK (serum)
		Exploratory PK (serum)
		ADA (serum)
	End of infusion (+30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)
	2 hr after end of infusion (±30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)
Cycle 1, Day 2 *(Arms A and C)*	*20*–24 hr after end of C1D1 infusion	Peripheral biomarkers (plasma and serum)
		Flow cytometry and PBMC isolation (whole blood)
		PK (serum)
Cycle 1, Day 2 (Arm B)	*Pre-infusion* [a]	*Peripheral biomarkers (plasma and serum)*
		Flow cytometry and PBMC isolation (whole blood)
		PK (serum)
		Exploratory PK (serum)
		ADA (serum)
	End of infusion (+30 min)	*Peripheral biomarkers (plasma and serum)*
		PK (serum)
	2 hr after end of infusion (±30 min)	*Peripheral biomarkers (plasma and serum)*
		PK (serum)

Appendix 3: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type
Cycle 1, Day 3	*Arms A and C: 40–*48 hr after end of C1D1 infusion *Arm B: 20–24 hr after end of C1D2 infusion*	Peripheral biomarkers (plasma and serum)
		Flow cytometry and PBMC isolation (whole blood)
		PK (serum)
Cycle 1, Day 8	Pre-infusion [a]	Peripheral biomarkers (plasma and serum)
		Flow cytometry and PBMC isolation (whole blood)
		PK (serum)
		Exploratory PK (serum)
	End of infusion (+30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)
	2 hr after end of C1D8 infusion (±30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)
Cycle 1, Day 9	*20–*24 hr after end of C1D8 infusion	Peripheral biomarkers (plasma and serum)
		Flow cytometry and PBMC isolation (whole blood)
		PK (serum)
Cycle 2, Day 1	Pre-infusion [a]	Peripheral biomarkers (plasma and serum)
		Flow cytometry and PBMC isolation (whole blood)
		PK (serum)
		Exploratory PK (serum)
		ADA (serum)
	End of infusion (+30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)
Cycle 2, Day 8	Pre-infusion [a]	Peripheral biomarkers (plasma and serum)
		PK (serum)
	End of infusion (+30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)

Appendix 3: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type
Cycle 3, Day 1	Pre-infusion [a]	Peripheral biomarkers (plasma and serum)
		Flow cytometry and PBMC isolation (whole blood)
		PK (serum)
		Exploratory PK (serum)
		ADA (serum)
	End of infusion (+30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)
Cycle 3, Day 8	Pre-infusion [a]	Peripheral biomarkers (plasma and serum)
		PK (serum)
	End of infusion (+30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)
Cycles 4, 6, and 8, Day 1	Pre-infusion	Peripheral biomarkers (plasma and serum)
		Cell-free DNA (whole blood) [c]
		ADA (serum)
		PK (serum)
Cycle 14, Day 1, and Day 1 every six cycles thereafter (i.e., Cycles 20, 26, 32, etc.)	Pre-infusion	Peripheral biomarkers (plasma and serum)
		PK (serum)
		ADA (serum)
Day 1 of any intrapatient dose escalation	Pre-infusion [a]	Peripheral biomarkers (plasma and serum)
		PK (serum)
		Exploratory PK (serum)
		ADA (serum)
	End of infusion (+30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)
	2 hr after end of infusion (±30 min)	Peripheral biomarkers (plasma and serum)
		PK (serum)

Visit	Timepoint	Sample Type
End of treatment visit	Any time	Flow cytometry and PBMC isolation (whole blood)
		Cell-free DNA (whole blood)
		Peripheral biomarkers (plasma and serum)
		PK (serum)
		ADA (serum)

ADA = anti-drug antibody; C = cycle; D = day; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; WGS = whole genome sequencing.

Note: Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] Pre-infusion collection should be taken within 2 hours prior to infusion.

[b] Whole blood sample for WGS should be collected on Cycle 1, Day 1; however, it may be collected at any time during the study after Cycle 1, Day 1.

[c] Cell-free DNA will only be collected on Cycle 4, Day 1.

Appendix 4
Guidelines for the Determination of Prior Lines of Therapy

Source: Rajkumar et al. 2014.

LINE OF THERAPY

A line of therapy is defined as ≥ 1 complete cycle of a single agent, combination regimen of several drugs, or a planned sequential therapy of various regimens (e.g., induction with a multi-agent regimen followed by autologous stem cell transplantation, consolidation and lenalidomide maintenance is considered one line).

NEW LINE OF THERAPY

A treatment is considered a new line of therapy if any one of the following three conditions is met:

Definition of a New Line of Therapy	Comments
Discontinuation of one treatment regimen and start of another	A regimen is considered to have been discontinued if all drugs in that given regimen have been stopped. The reasons for discontinuation, addition, substitution, or SCT do not influence how lines are counted.
Unplanned addition or substitution of one or more drugs in a regimen	Unplanned addition of a new drug or switching to a different drug (or combination of drugs) due to any reason is considered a new line of therapy.
In patients undergoing >1 SCT, each SCT is considered a new line of therapy	Except in the cases of a planned tandem SCT performed <6 months from the first SCT, each additional SCT is considered a new line of therapy.

SCT = stem cell transplant.

INTERRUPTIONS AND DOSE MODIFICATIONS

If a regimen is interrupted or discontinued for any reason and the same drug or combination is restarted without any intervening regimen, then it should be counted as a single line.

If a regimen is interrupted or discontinued for any reason and then restarted at a later timepoint, but one or more other regimens were administered in between, or the regimen is modified through the addition of one or more agents, then it should be counted as two lines.

Appendix 5
International Myeloma Working Group Uniform Response Criteria (2016)

Adapted from Durie et al. 2015 and Kumar et al. 2016.

COMPLETE RESPONSE AND OTHER RESPONSE CATEGORIES

Response Subcategory	Response Criteria
All response categories require two consecutive assessments made any time before starting any new therapy.	
sCR	CR as defined below, plus: Normal FLC ratio and absence of clonal cells in BM by immunohistochemistry (kappa/lamda ratio ≤ 4:1 or ≥ 1:2 for kappa and lambda patients, respectively after counting ≥ 100 plasma cells) [a]
CR	No evidence of initial monoclonal protein isotype(s) on immunofixation of the serum and urine, [b] disappearance of any soft tissue plasmacytomas, and ≤5% plasma cells in BM
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis; or ≥90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 hr
PR	≥50% reduction of serum M-protein and reduction in 24-hour urine M-protein by ≥90% or to <200 mg/24 hr • If the serum and urine M-protein are unmeasurable, 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 unmeasurable and serum FLC assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline BM plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) [c] of soft tissue plasmacytomas is also required.
MR	≥25% but ≤49% reductions of serum M-protein and reduction in 24-hour urine M-protein by 50%–89% • In addition to the above criteria, if present at baseline, 25%–49% reduction in the size (SPD) [c] of soft tissue plasmacytomas is also required.
SD	Not meeting criteria for MR, CR, VGPR, PR, or PD

DISEASE PROGRESSION AND RELAPSE

Relapse Subcategory	Relapse Criteria
PD [d, e]	Any one or more of the following criteria: • Increase of ≥25% from lowest response value in one or more of the following: • Serum M-protein (absolute increase must be ≥0.5 g/dL) • Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL • Urine M-protein (absolute increase must be ≥200 mg/24 hr) • 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) • In patients without measurable serum and urine M-protein levels and without measurable disease by FLC: BM plasma cell percentage irrespective of baseline status (absolute % must be ≥10%) [b] • Appearance of new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis • ≥ 50% increase in circulating plasma cells (minimum 200 cells per microliter) if this is the only measure of disease
Clinical relapse	Requires one or more of the following: • Direct indications of increasing disease and/or end organ dysfunction (CRAB features) [f] related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or PFS but is listed here as something that can be reported optionally or for use in clinical practice. • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. • Hypercalcemia >11 mg/dL (2.65 mmol/L) • Decrease in hemoglobin of ≥2 g/dL (1.25 mmol/L) not related to therapy or other non-myeloma related conditions • Rise in serum creatinine by 2 mg/dL or more (177 μmol/L or more) from the start of therapy and attributable to myeloma • Hyperviscosity related to serum paraprotein

Relapse Subcategory	Relapse Criteria
Relapse from CR (to be used only if the endpoint studied is PFS) [c]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the BM • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

BM = bone marrow; CR = complete response; CT = computed tomography; FLC = free light chain; M-protein = monoclonal protein; MR = minimal response; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; SD = stable disease; SPD = sum of the products of diameters; VGPR = very good partial response.

[a] Special attention should be given to the emergence of a different M-protein following treatment, especially in the setting of patients having achieved a conventional CR, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time, and in some studies, have been associated with a better outcome. Also, appearance of IgGk in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

[b] In some cases it is possible that the original M-protein light-chain isotype is still detected on immunofixation, but the accompanying heavy-chain component has disappeared; this would not be considered a CR even though the heavy-chain component is not detectable, since it is possible that the clone evolved to one that secreted only light chains. Thus, if a patient has IgA lambda myeloma, then to qualify as a CR there should be no IgA detectable on serum or urine immunofixation; if free lambda is detected without IgA, then it must be accompanied by a different heavy-chain isotype (IgG, IgM, etc.). Modified from Durie et al. 2006. Requires two consecutive assessments to be carried out at any time before the institution of any new therapy (Durie et al. 2015).

[c] Plasmacytoma measurements should be taken from the CT portion of the PET/CT or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, the skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

[d] Positive immunofixation alone in a patient previously classified as achieving a CR will not be considered progression. Criteria for relapse from a CR should be used only when calculating disease-free survival.

[e] In the case where a value is felt to be a spurious result per investigator discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.

[f] CRAB features = calcium elevation, renal failure, anemia, lytic bone lesions.

Appendix 6
Modified Cockcroft–Gault Equation (Using Ideal Body Mass Instead of Mass)

$$eCCr = \frac{(140 - Age) \cdot IBM\ (kg) \cdot [0.85\ \text{if female}]}{72 \cdot \text{serum creatinine (mg/dL)}}$$

Or, if serum creatinine is in μmol/L:

$$eCCr = \frac{(140 - Age) \cdot IBM\ (kg) \cdot [1.23\ \text{if male, } 1.04\ \text{if female}]}{\text{serum creatinine (μmol/L)}}$$

(IBM) should be used:

$$IBM\ (kg) = [(\text{height in cm} - 154) \times 0.9] + (50\ \text{if male, } 45.5\ \text{if female})$$

eCCR = estimated creatinine clearance; IBM = ideal body mass.

Appendix 7
Recommended Anaphylaxis Management

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Appropriate monitors (ECG, blood pressure, pulse oximetry)
- Oxygen and masks for oxygen delivery
- Airway management devices per standard of care
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Salbutamol (or albuterol or equivalent)
- Antihistamines (H1 and H2 blockers)
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional assistance.
- Maintain an adequate airway.
- Provide oxygen.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
- Administer epinephrine first, followed by antihistamines, albuterol, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 8
Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes [a]	Sensitive Substrates [b]	Substrates With Narrow Therapeutic Range [c]
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP2B6 [d]	Bupropion, efavirenz	
CYP2C8	Repaglinide [e]	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A [f]	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, [g] cisapride, [g] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine [g]
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine

AUC = area under the concentration–time curve.

[a] Note that this is not an exhaustive list. For an updated list, see the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

[b] Sensitive CYP substrates refer to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[c] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

[d] The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

[e] Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.

[f] Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

[g] Withdrawn from the United States market because of safety reason.

Appendix 9
Modified Cytokine-Release Syndrome Grading System

Source: Lee et al. 2019.

Grade [a]	Toxicity
Grade 1	Fever ≥ 38°C with or without constitutional symptoms
Grade 2	Fever ≥ 38ºC with either: Hypotension – responding to fluids but not requiring vasopressors Hypoxia – requiring low-flow nasal cannula (≤ 6 L/min) or blow-by oxygen to maintain oxygen saturation Organ toxicity: [b] Grade 2
Grade 3	Fever ≥ 38ºC with either: Hypotension – requiring single vasopressor (with or without vasopressin) Hypoxia – requiring high flow nasal cannula (> 6 L/min), facemask, non-rebreather mask, or Venturi mask to maintain oxygen saturation Organ toxicity: [b] Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Fever ≥ 38ºC with either: Hypotension – requiring multiple vasopressors (excluding vasopressin) Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation) Organ toxicity: [b] Grade 4 (excluding transaminitis)
Grade 5	Death

CRS = cytokine-release syndrome.

[a] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause (e.g., if a patient has a temperature of 39°C, is on 4 L/min of oxygen by nasal cannula, and has hypotension requiring the use one vasopressor, this would be considered Grade 3 CRS).

[b] Organ toxicities associated with CRS may be graded according to NCI CTCAE v5.0.

Appendix 10
Management Guidelines for Cytokine-Release Syndrome

Guidelines for management of CRS are summarized in Table 1 below based on the modified grading scale as described in Appendix 9. Management of Grade ≥3 IRR and/or CRS should be immediately discussed with the Medical Monitor. As noted below, even moderate presentations of CRS in patients with extensive comorbidities should be monitored closely with consideration given to intensive care unit admission and therapeutic intervention.

Refer to Section 5.3.5.1 for adverse event reporting procedures related to IRR and CRS.

Table 1 Management Guidelines for Cytokine-Release Syndrome

Toxicity [a]	Action to Be Taken
Grade 1 Fever [b] ≥ 38ºC with or without constitutional symptoms (such as: nausea, fatigue, headache, myalgia, malaise)	**Immediate actions:** • If infusion still ongoing, slow the infusion rate up to 50% or interrupt infusion. • Treat symptomatically as indicated, including antihistamines, antipyretics, and/or analgesics as needed. • Treat fever and neutropenia if present. • Monitor fluid balance; administer IV fluids as clinically indicated. **Restarting infusion:** • If study medication infusion was interrupted, wait until 30 minutes after the event has resolved before restarting the infusion at 50% of the original infusion rate. **Next cycle:** • Pretreat with antihistamines and antipyretics/NSAIDS.
Grade 2 Fever [b] ≥ 38ºC with either: Hypotension - responding to fluids but no required vasopressor and/or Hypoxia – requiring ≤ 6 L/min by nasal cannula or blow-by to maintain oxygen saturation Organ toxicity: Grade 2	**Immediate actions:** • Follow all Grade 1 recommendations. • Hold further study medication treatment until symptoms completely resolved. • Consider treatment with IV corticosteroids (methylprednisolone 2 mg/kg/day or, if neurologic symptoms are present, dexamethasone 10 mg). • Consider administering cytokine therapy. • Monitor cardiac and other organ function closely. • Provide hemodynamic support as indicated. • Provide oxygen for hypoxia. • Admit to ICU as appropriate. • If no improvement within 24 hours, manage as a Grade 3 event: – Notify Medial Monitor. – Initiate work-up and assess for signs and symptoms of MAS/HLH. [c] – May receive the next dose of study medication if symptoms resolve to Grade ≤ 1 for 3 consecutive days with approval of Medical Monitor.

Table 1 Management Guidelines for Cytokine-Release Syndrome (cont.)

Event [a]	Action to Be Taken
Grade 2 (cont.)	**Restarting infusion:** • Wait until 30 minutes after the event has resolved before restarting the infusion at up to 25% of the original infusion rate. • If hypotension or hypoxia recurs, stop infusion immediately. Study medication should not be re-administered (re-started) again during this cycle. – If hypotension or hypoxia recurs, manage as a Grade 3 event. **Next cycles:** • May receive the next dose of study medication if symptoms resolve to Grade ≤ 1 for 3 consecutive days with approval of Medical Monitor, as follows: – Pretreat with antihistamines, antipyretics and/or analgesics as clinically indicated. – Pretreat with IV corticosteroids (methylprednisolone 80 mg or dexamethasone 16 mg) at least 60 minutes prior to the administration of study medication – Administer study medication at 50% of the initial infusion rate of the previous cycle. **Subsequent cycles:** • If there is an occurrence of IRR or CRS Grade ≥ 3 in any of the subsequent cycles, permanently discontinue study medication regardless of recovery (see Grade 3 management guidelines). • If there is an occurrence of a Grade ≤ 2 CRS in subsequent cycles, manage as indicated by severity (see Grade 1 or Grade 2 management guidelines).

Table 1 Management Guidelines for Cytokine-Release Syndrome (cont.)

Grade [a]	Action to Be Taken
Grade 3 Fever [b] ≥ 38ºC with either: Hypotension – requiring a single vasopressor (with or without vasopressin) and/or Hypoxia – requiring > 6 L/min oxygen by nasal cannula, facemask, non-rebreather mask, or Venturi mask to maintain oxygen saturation Organ toxicity: Grade 3 organ toxicity or Grade 4 transaminitis	**Immediate actions:** • Stop further infusion of study medication • Admission to ICU is recommended • Treat symptomatically as indicated, including antihistamines, antipyretics, and/or analgesics as needed. • Provide other supportive care as clinically indicated (e.g., fever and neutropenia, infection). • Monitor fluid balance; administer IV fluids as clinically indicated. • Treat with IV corticosteroids (methylprednisolone 2 mg/kg/day or, if neurologic symptoms are present, dexamethasone 10 mg). • Consider anti-cytokine therapy. • Monitor cardiac and other organ function closely. • Provide oxygen for hypoxia. • Notify Medial Monitor. • Initiate work-up and assess for signs and symptoms of MAS/HLH. [c] **Restarting infusion:** • Study medication should not be administered again during this cycle.

Table 1 Management Guidelines for Cytokine-Release Syndrome (cont.)

Grade [a]	Action to Be Taken
Grade 3 (cont.)	**Next cycle:** • If the patient had a Grade ≥ 2 IRR or CRS in any previous cycle, permanently discontinue study medication. • If patient does not recover (is febrile or still on vasopressors) within 8 hours after corticosteroid and anti-cytokine treatment, permanently discontinue study medication. • If patient recovers (is afebrile and off vasopressors) within 8 hours following corticosteroid and anti-cytokine treatment, study medication can be administered in next cycle, as follows: – Pretreat with antihistamines, antipyretics and/or analgesics as clinically indicated. – Pretreat with IV corticosteroids (methylprednisolone 80 mg or dexamethasone 16 mg) at least 60 minutes prior to the administration of study medication. – Hospitalize patient for 24 hours. – Administer study medication at 50% of the initial infusion rate of the previous cycle. [d] **Subsequent cycles:** • If a Grade ≥3 CRS recurs, permanently discontinue study medication. • If there is an occurrence of a Grade ≤ 2 CRS in subsequent cycles, manage as indicated by severity (i.e., Grade 1 or Grade 2 management guidelines).

Table 1 Management Guidelines for Cytokine-Release Syndrome (cont.)

Grade [a]	Action to Be Taken
Grade 4 Fever [b] ≥ 38ºC with either: Hypotension – requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia – requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation) Organ toxicity: Grade 4 (excluding transaminitis)	**Immediate actions:** • Follow all Grade 3 management guidelines. • Permanently discontinue study treatment.

CRS = cytokine-release syndrome; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; MAS = macrophage activation syndrome.

a Modified CRS grading per ASTCT (Lee et al. 2019). Refer to Appendix 9 for the complete description of grading of symptoms.

b Fever is defined as temperature ≥ 38ºC not attributable to any other cause. In patients who have CRS and then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

c Refer to Appendix 12 for HLH/MAS diagnostic criteria.

d If the patient does not experience CRS during the next infusion at the 50% reduced rate, the infusion rate can be increased to the initial rate in subsequent cycles upon discussion with Medical Monitor. However, if this patient experiences another CRS event, the infusion rate should be reduced by 25%–50% depending on the severity of the event.

Appendix 11
Modified Continuous Reassessment Method with Escalation with Overdose Control Design

Details of the mCRM-EWOC design used in the study are descripted in this appendix. In addition, the design operating characteristics are evaluated through comprehensive simulations in this section. In this study, the MTD is defined as the dose maximizing the posterior probability that the DLT rate belongs to [0.20,0.35], while keeping the probability of overdose below 0.25. The details of the mCRM-EWOC design will be described below. Calculations are done using R package crmPack 0.1.9 (https://cran.rproject.org/web/packages/crmPack/index.html).

Dose-Response Model

The probability of DLTs over doses (dose-DLT response curve) will be described by a two-parameter logistic regression model:

$$logit(p(d)) = \alpha + \beta\left(\frac{d}{d^*}\right)$$

where p(d) stands for the DLT rates under a dose level d, and d* is set to 1200 mg in the study as the reference dose. Thus, the dose-DLT response curve follows a sigmoidal shape and can be flexibly adjusted by a parameter

$$\theta = \begin{pmatrix} \alpha \\ log\beta \end{pmatrix} \sim N(\mu, \Sigma)$$

It is common to assume such a sigmoidal curve since usually the DLT rate increases monotonically while dose levels go up, but not in a linear way because it has a minimal level 0 and will reach a plateau when dose is very high. It is anticipated that RO7297089 would have a similar dose-DLT relationship.

Prior Setting

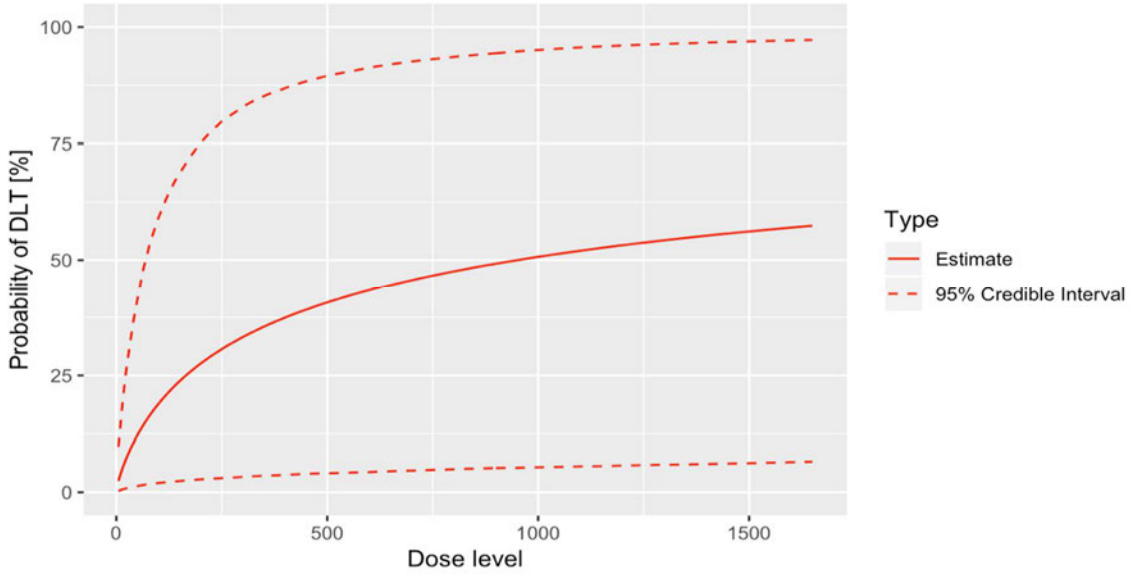
In particular, a minimal informative multiple normal prior (Neuenschwander et al. 2008) is utilized for θ in the dose-escalation. It is conservatively assumed that it would be very unlikely (with a 95% confidence) that a 30% or higher and a 30% or lower DLT rates are associated with the starting dose, i.e., 60 mg, and the 1650 mg dose, respectively. The parameters of the minimal informative prior are listed below:

$$\mu = (0.2098152, 0.7905444)$$

$$\Sigma = \begin{pmatrix} 2.3807734 & 0.32675892 \\ 0.3267589 & 0.07025577 \end{pmatrix}$$

The prior distribution is displayed in Figure 1, which is consistent with what is assumed: it would be unlikely that a 60 mg dose corresponds to a 30% or higher DLT rate, and a 1650 mg dose corresponds to a 30% or lower DLT rate.

Figure 1 Prior Distribution of the mCRM-EWOC Design



Cohort Size

All cohorts will enroll at least 3 patients and may be expanded with additional patients in order to collect additional data on PK, PD or safety. For details see Section 3.1.1 of the protocol.

Maximum Allowable Dose Increments

The maximum allowable dose increment throughout the study is 200% or a 3-fold increase from the current dose.

Next Dose Selection

The selection dose for the next cohort will be guided by the mCRM-EWOC model, subject to clinical judgment and mandated safety constraints that limit the size of maximum allowable dose increments. Clinical judgment always overrides model estimates in the selection of the next dose. The Sponsor, in consultation with the Investigators, can modify the dose to be used in the next cohort of patients as deemed appropriate at any time during the trial.

Stopping Rules

The dose-escalation trial will continue until the recommended Phase II dose (RP2D) has been determined or the maximum sample size of ~40 is reached or pre-specified precision rules have been fulfilled:

- At least 9 patients have accrued overall;
- At least 6 patients have been accrued near the MTD dose where “near” is defined as being within 20% of the MTD;
- The probability that the MTD lies within the target toxicity interval is above 40%.

The Sponsor in consultation with the Investigators may decide to stop the escalation prior to above stopping criteria are met if the RP2D has been determined.

The mCRM-EWOC Algorithm

Patients in the first cohort will be treated with the starting dose. Prior to open a new cohort, the available DLT data will be used to update the mCRM-EWOC model through a Bayesian approach. That is, the posterior probability of parameter θ from the logistic model will be estimated by using the DLT data from all eligible patients who complete the DLT observation period. A recommended dose, d_r, for the next cohort will be calculated using the updated mCRM-EWOC model, i.e., $P(d_r)\text{overdose} < 25\%$ and

$d_r=\min(d_{rmax},\max\{d_i:P(p(d_i)\in[0.2,0.35])\})$ where d_{rmax} is the highest next dose subject to the maximal increment rule.

Patients in the next cohort will be treated at the dose recommended by such an algorithm (possibly reduced based on clinical judgment). This process is repeated until the stopping criterion is met.

Hypothetical Trials

Several hypothetical trials are reported here to illustrate the behavior of the design in specific situations.

The first scenario illustrates how dose will be escalated assuming no DLTs are observed. The mCRM-EWOC model considered doses under a dose grid of every 5 mg from 60 mg to 100 mg and then every 10 mg up to 1650 mg.

Table 1 shows the different levels suggested by the mCRM-EWOC design. The results show that, in the absence of observed DLTs, the design will reach high doses based in 4 cohorts.

Table 1 Dose Escalation Path in Absence of Observed DLTs

Current Cohort Dose (mg)	Recommended Next Dose Increment % If No DLTs In Current Cohort
60	200
180	178
500	136
1180	36
1600	3
1650	

Additionally, the impact on dose-escalation of the occurrence of a first DLT is examined for all possible DLT frequencies (1 to 3, when the cohort size is 3) assuming that no DLTs occur until the given dose. The recommended next doses suggested by the design after the DLTs are reported in Table 2.

The results show that the design will adequately adapt the dose in the presence of observed DLTs.

Table 2 Impacts on Dose-Escalation of the Occurrence of First DLTs

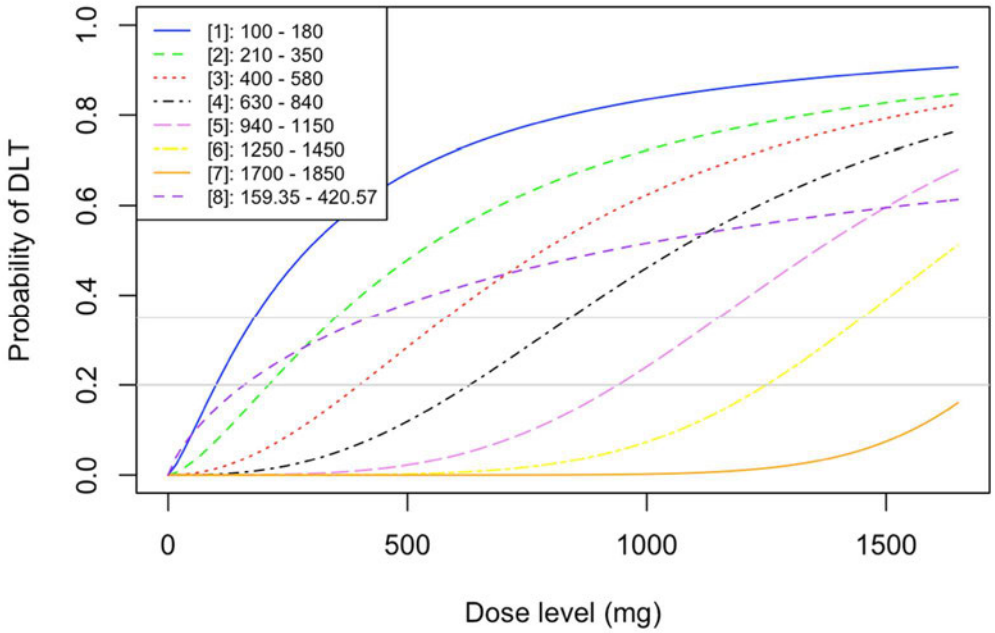
First DLT at Dose	DLTs/cohort size	Next Dose	Increment (%)
60	1/3	100	67
	2/3	40	-33
	3/3	25	-58
180	1/3	180	0
	2/3	95	-47
	3/3	60	-67
500	1/3	450	-10
	2/3	220	-56
	3/3	130	-74
1180	1/3	880	-25
	2/3	500	-58
	3/3	290	-75
1600	1/3	1650	3
	2/3	1110	-31
	3/3	530	-67

Simulations

A simulation study is conducted to evaluate the operating characteristics (sample size, estimated MTD, number of patients treated, overdose, etc.) for the chosen design parameters (priors, reference dose, stopping rules).

Scenarios with different toxicity profiles are simulated with hypothetical MTDs from 60 mg (low MTD) to >1650 mg (illustrating a scenario for which no toxicities are expected). The dose grid in simulations is set as 60 mg to 100 mg by 5 mg as a unit followed by increments of 10 mg all the way up to 1650 mg. The starting dose is 60 mg. Simulations are conducted based on 3-patient cohorts throughout the entirety of the study.

Figure 2 "True" Scenarios Used for Simulations



Each scenario uses 1000 simulated trials, analyzed by generating a MCMC chain run for 15000 iterations following a 5000-iteration burn-in period. Every one out of 2 iterations are saved after the burn-in i.e., step=2. Random manual checks revealed no significant MCMC convergence issues using standard convergence diagnostics.

The design is evaluated using the following criteria: the MTD chosen, the number of subjects treated at doses higher than the MTD and the sample size of the trials. The following table demonstrates the simulation study result.

According to the simulation study, the mCRM-EWOC has a relatively good performance in terms of controlling the safety and identifying MTD efficiently (Table 3).

Table 3 Operating Characteristics of the mCRM-EWOC Design with Respect to the Chosen Scenarios

		mCRM-EWOC			
Scenario	Target Dose Interval in True Scenario (mg)	Overall N of Patients	N Patients Treated above Target Toxicity Interval	Proportions of DLTs in the trials	Doses selected as MTD (mg)
1	100 - 180	15 (9, 21)	5 (0, 12)	27.8% (22.1%, 33.3%)	146.2 (80, 210)
2	210 - 350	17 (12, 24)	4 (0, 9)	23.4% (16.7%, 28.6%)	258 (160, 410)
3	400 - 580	19 (15, 24)	3 (0, 9)	20.1% (16.7%, 25%)	440.9 (270, 601)
4	630 - 840	21 (15, 27)	5 (0, 9)	18.8% (14.2%, 23.8%)	647 (420, 960)
5	940 - 1150	22 (18, 27)	4 (0, 6)	16.8% (12.5%, 20.8%)	949.4 (620, 1370)
6	1250 - 1450	22 (18, 27)	5 (3, 9)	14.6% (11.1%, 18.5%)	1299.8 (900, 1640)
7	1700 - 1850	34 (18, 42)	0 (0, 0)	10.3% (4.8%, 14.3%)	1622.7 (1550, 1650)
8	159 - 421	17 (9, 24)	3 (0, 9)	23.8% (16.7%, 33.3%)	263.7 (110, 470)

Appendix 12
Diagnosis and Management of Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS)

CRS may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 1.

Table 1 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue study drug and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

REFERENCES

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

Appendix 13
AIDS-Defining Illnesses

Patients with a history of HIV should be carefully questioned regarding their history of opportunistic infections and other AIDS-defining illnesses in the past 12 months prior to study enrollment. Patients with any history of HIV and an AIDS-defining illness listed in the table below are excluded from participating in the study. Contact the Medical Monitor regarding any uncertainty over illnesses listed below.

AIDS-Defining Illnesses

• Candidiasis of the esophagus, bronchi, trachea, or lungs (excluding the mouth [thrush]) • Cervical Cancer, invasive • Coccidioidomycosis, disseminated or extrapulmonary • Cryptococcus, extrapulmonary • Cytomegalovirus infection (other than liver, spleen, or lymph nodes) • HIV-related encephalopathy • Herpes Simplex: chronic ulcers $>$ 1 month duration, bronchitis, pneumonitis, or esophagitis	• Histoplasmosis, disseminated or extrapulmonary • Isosporiasis, chronic intestinal ($>$ 1 month duration) • Kaposi sarcoma • Lymphoma, Burkitt (or equivalent term) • Lymphoma, immunoblastic (or equivalent term) • Lymphoma, brain, primary • Mycobacterium avium complex of *M. kansasii*, disseminated or extrapulmonary	• Mycobacterium tuberculosis, any site • Mycobacterium, other species, disseminated or extrapulmonary • Pneumocystis pneumonia • Pneumonia, recurrent • Progressive multifocal leukoencephalopathy • Salmonella septicemia, recurrent • Toxoplasmosis of the brain • Wasting Syndrome due to HIV

Reference: Centers for Disease Control and Prevention. Appendix A: AIDS-Defining Conditions. MMWR. 2008;57(RR10):9.

Appendix 14
Criteria for Identifying Multiple Myeloma Patients at High Risk for Tumor Lysis Syndrome

Reference: Minasyan and Henrici 2015.

Patients meeting any of the following criteria will be considered at high risk for tumor lysis syndrome (TLS):

- Prior history of TLS caused by previous multiple myeloma therapy
- Pre-existing renal insufficiency (serum creatinine >1.5 mg/dL, or CrCl <60 mL/min)
- High tumor burden, defined as increased serum LDH ($>2\times$ ULN), increased beta-2 microglobulin (≥ 5.5 mg/dL), hypercalcemia (serum Ca >12 mg/dL), or per investigator's clinical judgment (e.g., based on the magnitude of diffuse bone marrow disease and multiple lytic lesions)

Appendix 15
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead