Poseida Therapeutics, Inc.

Open-Label, Multicenter, Phase 1 Study to Assess the Safety of P-BCMA-101 in Subjects with Relapsed / Refractory Multiple Myeloma (MM) Followed by a Phase 2 Assessment of Response and Safety (PRIME)

PROTOCOL NUMBER P-BCMA-101-001 A5

AMENDMENT 5

PROTOCOL DATE

ORIGINAL: 14 MARCH 2017

AMENDMENT 1: 26 JULY 2017

AMENDMENT 2: 03 APRIL 2018

AMENDMENT 3: 24 JANUARY 2019

AMENDMENT 4: 06 MARCH 2019

AMENDMENT 5: 20 SEPTEMBER 2019

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: Open-Label, Multicenter, Phase 1 Study to Assess the Safety of P-BCMA-101 in Subjects with Relapsed / Refractory Multiple Myeloma (MM) Followed by a Phase 2 Assessment of Response and Safety (PRIME)

I, the undersigned, have reviewed the protocol, including the appendices, and I will conduct the clinical study as described and will adhere to the current International Conference on Harmonisation (ICH) "Guideline for Clinical Practice" (GCP) and all the ethical and regulatory considerations stated or any applicable local laws.

Investigator Name	
Investigator Title	
Investigator Site and Address	
Investigator Signature	
Date	

CLINICAL STUDY PROTOCOL

Title: Open-Label, Multicenter, Phase 1 Study to Assess the Safety of P-BCMA-101 in Subjects with Relapsed / Refractory Multiple Myeloma (MM) Followed by a Phase 2 Assessment of Response and Safety (PRIME)

Product Name: P-BCMA-101

Protocol Number: P-BCMA-101-001 A5

Regulatory Agency Identifying Number: [redacted]

DATE OF ORIGINAL PROTOCOL: 14-MAR-2017

Amendment Number	Date
1	26 July 2017
2	03 April 2018
3	24 January 2019
4	06 March 2019
5	20 September 2019

SYNOPSIS

Title:	Open-Label, Multicenter, Phase 1 Study to Assess the Safety of P-BCMA-101 in Subjects with Relapsed / Refractory Multiple Myeloma (MM) Followed by a Phase 2 Assessment of Response and Safety (PRIME)
Study Number:	P-BCMA-101-001
Phase:	Phase 1 / 2
Name of Investigational Product:	P-BCMA-101 and Rimiducid Autologous CAR-T Cells Engineered to Contain an Anti-B-Cell Maturation Antigen (BCMA) Centyrin Coupled to TCR ζ and 4-1BB Signaling Domains (CARTyrin)
Brief Description of Investigational Product:	P-BCMA-101 is comprised of T cells genetically modified using an electroporation-based, non-viral (DNA transposon) gene delivery system called the piggyBac™ (PB) DNA modification system, which efficiently moves DNA from a plasmid to a chromosome via a "cut and paste" mechanism. Compared to lentivirus or γ–retrovirus transduction, PB offers advantages, including a safer insertion profile, higher levels of transgene expression, stable and longer duration transgene expression, and a highly enriched, favorable T stem cell memory (Tscm) phenotype. P-BCMA-101 cells are autologous T cells harvested from the subject [redacted]
Test Product, Dose, Route of Administration:	Phase 1: Single Administration- dose levels of P-BCMA-101 administered intravenously as a single dose. Dose levels will be tested by cohort in the 3+3 escalation design described in the Study Design. Phase 1: Cycle Administration- multiple doses of P-BCMA-101 administered intravenously in 2 cycles (Cohort A and Cohort C) or 3 cycles (Cohort B) of 2 weeks each. The total dose administered will follow the 3+3 design starting at ≤ the maximum tolerated dose (MTD) as determined during single dose escalation. In the first cycle for both Cohorts A and B, 1/3 the total dose will be administered. In

	Cohort A up to 2/3 the total dose will be administered in the 2nd cycle. In Cohort B up to 1/3 the total dose will be administered in each of the 2nd and 3rd cycles. In Cohort C up to 2/3 the total dose will be administered in the 1st cycle and up to 1/3 the total dose will be administered in the 2nd cycle. Phase 1: Combination Administration- P-BCMA-101 will be administered in combination with approved therapies: lenalidomide (Cohort R: [redacted] before P-BCMA-101 infusion; and Cohort RP: [redacted] before apheresis [redacted] before P-BCMA-101 infusion) and rituximab (Cohort RIT: [redacted] The dose of P-BCMA-101 administered will follow the 3+3 design starting at ≤ the MTD as determined during dose escalation. Phase 2: P-BCMA-101 administered intravenously as a total dose of 6-15 × 10^6 cells/kg. Rimiducid may be administered intravenously at 0.4 mg/kg if clinically indicated. Subjects who meet the criteria in Section 15.4 may be eligible to receive another infusion of P-BCMA-101.
Reference Therapy:	None

Objectives	**Endpoints**
Primary: The primary objective of this study is: **Phase 1:** To determine the safety and maximum tolerated dose (MTD) of P-BCMA-101 based on dose limiting toxicities (DLT) **Phase 2:** To assess the safety and efficacy of P-BCMA-101	**Primary:** **Phase 1:** Number of subjects with DLT at each dose level to define an MTD **Phase 2:** • Safety and tolerability based on adverse events (AEs), examinations, and standard laboratory studies • Overall response rate (ORR) and duration of response (DOR) by International Myeloma Working Group Criteria (Kumar, 2016) as assessed by an independent review committee (IRC)

Secondary:
Secondary objectives of this study are to evaluate:
Phase 1:
• The safety and feasibility of P-BCMA-101
• The anti-myeloma effect of P-BCMA-101
• The effect of cell dose to guide selection of doses for further assessment in Phase 2/3 studies
Phase 2:
• Incidence and severity of cytokine release syndrome (CRS)
	Secondary:
	The following secondary endpoints will be evaluated:
	Phase 1:
	• Ability to generate protocol-proscribed doses of P-BCMA-101
	• Safety and tolerability based on AEs, examinations, and standard laboratory studies
	• CRS graded using Lee criteria (Lee, 2014)
	• Efficacy based on International Myeloma Working Group (IMWG) Uniform Response Criteria (Rajkumar, 2011; Kumar 2016; Cavo, 2017)
	  ○ Overall response rate (ORR)
	  ○ Time to response (TTR)
	  ○ Duration of response (DOR)
	  ○ Progression free survival (PFS)

• Additional efficacy endpoints	○ Overall survival (OS) **Phase 2:** • CRS graded using Lee criteria (Lee, 2014) • Rate of IL-6 antagonist, corticosteroid, and rimiducid use • OS, PFS, TTR, minimal residual disease (MRD) negative rate

[redacted]

Subject Population and Number	Adults with confirmed relapsed / refractory MM. Up to approximately 120 subjects are planned for Phase 1. Approximately 100 evaluable subjects will be treated in Phase 2.
Study Centers	Up to 20 sites are planned for the study.
Study Design	The study will be conducted in multiple parts, a Phase 1, open-label, single ascending dose (SAD) phase; a Phase 1, multiple dose, cycle administration phase; a Phase 1, combination administration with lenalidomide or rituximab phase; and a Phase 2, open-label, efficacy and safety phase, in adult subjects with relapsed / refractory MM. Only sites that are experienced in managing oncology subjects and stem-cell/bone marrow transplant with the resources to manage the types of acute emergent events expected with chimeric antigen receptor (CAR)-T cell administration will be selected to participate in this study. A Safety Committee will meet regularly to review data throughout the study. Subjects meeting the protocol entry criteria will be eligible to enroll in the study. After a subject enrolls, leukapheresis will be performed to obtain peripheral blood mononuclear cells (PBMCs) which will be sent to a manufacturing site to produce P-BCMA-101 CARTyrin-T cells. The cells will then be returned to the

	investigational site and, after a standard chemotherapy-based conditioning regimen, will be administered to the subject as described below. **Phase 1:** Phase 1 of the study is comprised of an open-label, multi-center, single ascending dose (SAD), multiple cohort study; a multiple dose cycle administration cohort study; and a combination administration study, in up to approximately 120 adult subjects. Phase 1 of the study will follow a 3 + 3 design of dose-escalating cohorts, wherein 3 subjects are initially planned to be dosed with P-BCMA-101 T cells for each cohort (Table 1). The Safety Committee may recommend enrollment of additional subjects in a cohort to further evaluate the outcomes observed at that dose level. For each of the first 2 cohorts, dosing of the first 3 subjects will be staggered. If Grade 3-related toxicity, CRS, or DLT is reported, the Safety Committee will review the data and determine whether to proceed to the next subject. The Safety Committee will review the data at the end of each cohort to determine progression to the next cohort. At the discretion of the Safety Committee, beginning with the 3rd cohort, dosing of the first and second subject in each cohort will be staggered. DLT is defined as any National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥3 event at least possibly related to P-BCMA-101, including uncontrollable expansion of P-BCMA-101 cells, and not attributable to the underlying disease or lymphodepleting chemotherapy regimen with onset within the first 28 days following the last P-BCMA-101 infusion with the following exceptions: • Grade 3 or 4 neutropenia with or without neutropenic fever resolving within 28 days following the last P-BCMA-101 cell infusion • Grade 3 fever • Grade 3 or 4 thrombocytopenia, with or without bleeding due to thrombocytopenia, resolving within 28 days following the last P-BCMA-101 cell infusion • Grade 3 or 4 anemia and lymphopenia • Grade 3 or 4 hypogammaglobulinemia • Alopecia • Grade 3 or 4 nausea, vomiting or diarrhea which responds to medical treatment within 24 hours • Immediate hypersensitivity reactions (fever, rash, bronchospasm) occurring within 2 hours of cell infusion (related to cell infusion) that are reversible to a Grade 2 or less within 6 hours of cell administration with standard antihistamine-based therapy • Grade 3 encephalopathy that recovers to less than Grade 2 within 28 days • Grade 3 CRS per Lee criteria (Lee, 2014) that resolves within 14 days • Grade 3 non-hematological laboratory abnormalities that recover to ≤Grade 2 in 14 days • Grade 4 non-hematological laboratory abnormalities that recover to ≤Grade 2 in 7 days

Table 1: Dose Escalation Guidelines

Outcome: **(# subjects with DLT)**	***Action:***
0 out of 3 subjects	Escalate dose for next cohort of 3 subjects
1 out of 3 subjects	Treat next 3 subjects at the same dose
≥2 out of 3 subjects	Halt dose escalation; treat at least 6 subjects at a lower dose to determine the MTD[1]
1 out of 6 subjects	Escalate dose for next cohort of 3 subjects
≥2 out of 6 subjects	Halt dose escalation; treat at least 6 subjects at a lower dose to determine the MTD[1]

1. MTD – the highest dose for which no more than 1 of 6 treated subjects exhibits DLT

The 3 + 3 dose escalation will be conducted as follows, with the Safety Committee reviewing the data at the end of each cohort to determine the outcome. Beginning with Cohort 1, at least 3 subjects will be dosed in the cohort. If no DLT through Day 28 after last dose is observed in the first 3 subjects, then escalation may proceed to the next cohort. If DLT is observed in 1 of the first 3 subjects, then at least 3 additional subjects will be treated at this dose level. If no further DLT is observed, escalation may proceed. If DLTs are observed in 2 or more of 3 or 6 subjects, the MTD will be considered to be at the next lower dose level and further enrollment may take place at a lower dose level, or an intermediate dose level may be tested at the discretion of the Safety Committee. In the event that 2 or more subjects experience DLTs in Cohort 1, the Safety Committee, after reviewing available data, may elect to dose 3 subjects in Cohort -1 with the same 3 + 3 expansion rules. In the event that 2 or more subjects experience DLTs in Cohort -1, the Safety Committee, based on consideration of safety and efficacy data to assess risk vs. benefit, may elect to dose 3 subjects at a lower dose with the same 3 + 3 expansion rules or discontinue the study.

Proposed Doses (P-BCMA-101 cells/kg/dose) include:

Cohort minus 1: 0.25×10^6
Cohort 1: 0.75×10^6
Cohort 2: 2×10^6
Cohort 3: 6×10^6
Cohort 4: 10×10^6
Cohort 5: 15×10^6

Additional subjects may be dosed in a cohort at the direction of the Safety Committee based on the safety and efficacy data from that cohort to further evaluate the effects of P-BCMA-101, provided the dose does not exceed the MTD. If Cohort 5 is completed without concluding an overall MTD, the Safety Committee may elect to assess further escalation cohorts in 5-10 $\times 10^6$ P-BCMA-101 cells/kg increments.

Phase 1 – Single Dose Administration:

In the Phase 1 single dose administration portion of the study, a single dose P-BCMA-101 will be administered once intravenously.

	Phase 1 – Cycle Administration: In the Phase 1 cycle dose administration portion of the study, multiple doses of P-BCMA-101 will be administered intravenously in 2 cycles (Cohort A and Cohort C) or 3 cycles (Cohort B) of 2 weeks each. The total dose administered will follow the 3+3 design starting at ≤ the MTD as determined during single dose escalation. In the first cycle for both Cohorts A and B, 1/3 the total dose will be administered. In Cohort A up to 2/3 the total dose will be administered in the 2nd cycle. In Cohort B up to 1/3 the total dose will be administered in each of the 2nd and 3rd cycles. In Cohort C up to 2/3 the total dose will be administered in the 1st cycle and up to 1/3 the total dose will be administered in the 2nd cycle. The same 3+3 dose escalation and/or de-escalation rules described for single administration will be utilized These procedures are detailed in Section 15.5. **Phase 1 – Combination Administration:** P-BCMA-101 will be administered in combination with approved therapies: lenalidomide (Cohort R and Cohort RP) and rituximab (Cohort RIT). The dose of P-BCMA-101 administered will follow the 3+3 design starting at ≤ the MTD as determined during dose escalation. The same 3+3 dose escalation and/or de-escalation rules described for single administration will be utilized. These procedures are detailed in Section 15.6. **Phase 2:** Phase 2 of the study is an open-label, multi-center study in approximately 100 adult subjects with relapsed and/or refractory MM. Subjects will receive a total dose of 6-15 × 10^6 cells/kg (per the schedule determined in Phase 1). **Study visits** Treated subjects in Phase 1 and Phase 2 will undergo serial measurements of safety, tolerability and response (myeloma staging). These measures will be obtained at Screening, Enrollment or Baseline Visit and the Conditioning Chemotherapy Period. The P-BCMA-101 Administration Period and follow-up visits in both Phase 1 and Phase 2 will be at Day 10, Week 2, 3, 4, 6, 8, Month 3, 4, 5, 6, 7, 8, 9, and then every 3 months thereafter for up to 24 months after P-BCMA-101 administration. After completing or withdrawing from this protocol, consenting subjects who have received P-BCMA-101 should enroll in a separate protocol that allows for continued follow-up for a total of 15 years after last dosing to evaluate long-term safety. **Screening Visit** Consented subjects will undergo a Screening Visit to determine eligibility. Subjects who meet all the inclusion criteria and none of the exclusion criteria will return for the Enrollment and Leukapheresis Visits. **Enrollment Visit** Eligible subjects will return for an Enrollment visit to provide samples and measurements that must be collected in advance of Leukapheresis. Enrollment assessments are to be conducted 14 days (± 3 days) prior to Leukapheresis or have medical monitor approval. **Leukapheresis Visit** Eligible subjects who enroll will return and undergo leukapheresis to obtain PBMCs for P-BCMA-101 manufacturing. This visit should occur within ~28 days

	of the Screening Visit. Once the product is manufactured, subjects will return for the combination therapy (if applicable), Conditioning Chemotherapy and P-BCMA-101 cell Administration Periods approximately 4 weeks after the Leukapheresis Visit. If P-BCMA-101 cells that meet release criteria cannot be manufactured from the leukapheresis sample, a second leukapheresis and manufacturing may be attempted. If the second attempt also fails, the subject will be withdrawn from the study and considered not to have undergone study treatment. Subjects who experience rapid disease progression following the Leukapheresis Visit and prior to the Conditioning Chemotherapy and P-BCMA-101 cell Administration Period may be administered salvage therapy at the discretion of the Investigator. Salvage therapy should not be used unless necessary and will be determined by the subject's clinical history (previously used agents are preferred, and medical monitor approval needed) at the discretion of the Investigator. If a subject receives salvage therapy, the Conditioning Chemotherapy and P-BCMA-101 cell Administration Period should be scheduled at least 2 weeks or 5 half-lives after the date of the last treatment of salvage therapy and the subject should meet the criteria described in Sections 4 and 6 regarding entry criteria (including those for measurable MM) and concomitant medications. The subject's response to the salvage therapy will be evaluated by the Investigator and medical monitor to determine whether the subject will remain eligible to receive the Investigational Product. Subjects will be permitted to receive radiation therapy or plasmapheresis and exchange for palliative purposes throughout the study period. **Baseline Visit (Day -12 to Day -6)** Once the product is manufactured, during the week prior to starting Conditioning Chemotherapy, subjects will return for Baseline assessments and to confirm continued eligibility. The following assessments should be repeated within 72 hours prior to Day -5: Mini Mental Status Exam (MMSE), physical exam, vital signs, chemistry panel including electrolytes and magnesium, hematology including B and T cell counts, coagulation, assessment of circulating myeloma/plasma cells, and pregnancy test (if applicable). A baseline myeloma response assessment must be conducted within 7 days of initiating conditioning chemotherapy and combination therapy. The baseline Fresh Sample of Bone Marrow and Tumor is not used to confirm eligibility and the 7-day window is intended to provide flexibility for subjects and investigators; if a new bone marrow biopsy/aspirate was performed and provided during Screening, this does not need to be repeated during the Baseline visit. **Conditioning Chemotherapy and P-BCMA-101 Cell Administration Period** Before dosing with the P-BCMA-101 cell infusion, subjects will receive a conditioning lymphodepletion chemotherapy regimen of 300 mg/m^2 of cyclophosphamide and 30 mg/m^2 of fludarabine, with each chemotherapy agent given intravenously daily for 3 consecutive days (Day -5 through Day -3). Subjects should continue to meet entry criteria at the time of initiation of conditioning chemotherapy or have medical monitor approval. For subjects in Cohort R, Cohort RP and Cohort RIT, the combination therapy should be administered prior to conditioning chemotherapy on applicable days. After 2 rest days following the lymphodepletion chemotherapy regimen, subjects will be dosed with P-BCMA-101 administered intravenously over approximately 5 to 20 mins (Day 0) (subjects should be pre-medicated with acetaminophen and

	diphenhydramine). Prior studies conducted with CAR-T therapies have observed peak toxicity to occur within 3-7 days of investigational product administration. Study subjects will be closely monitored during and after the infusion and for approximately 7 days afterwards. This observation period will include serial assessments of AEs, including the emergence of P-BCMA-101 cell-related toxicities, such as CRS, for all subjects. CRS will be graded using the Lee criteria (Lee, 2014). Guidance regarding grading and management of AEs can be found in Section 8 of this protocol and in the Study Reference Manual. Guidance for the use of rimiducid for significant P-BCMA-101-related toxicity can be found in Section 15.3 and the Study Reference Manual. Subjects may be admitted to the hospital for the P-BCMA-101 administration if the Investigator deems appropriate based on an individual patient's risks. Admission is not required, but subjects should remain within 50 miles of the hospital through approximately 14 days after last dose of P-BCMA-101 and assessed for admission in case of symptoms of CRS or neurotoxicity such as fever. If admitted, subjects will not be discharged until they are assessed as stable by the Investigator. Subjects may be maintained as an inpatient before P-BCMA-101 administration during lymphodepleting chemotherapy or after the above criteria are met as the Investigator deems appropriate. **Follow up visits:** Day 10, Week 2, 3, 4, 6, 8, Month 3, 4, 5, 6, 7, 8, 9, 12, 15, 18, 21 and 24. Subjects will return for regular follow up after last dose of P-BCMA-101 and will undergo serial assessment of safety, tolerability and anti-myeloma response as specified in the Schedule of Events. **Repeat Administration:** If sufficient P-BCMA-101 cells remain from manufacturing when a subject's disease progresses, with Safety Committee approval additional cells may be administered up to the highest dose level that has successfully completed dose-limiting toxicity assessment. In order to receive an additional P-BCMA-101 T-cell infusion, subjects will be assigned a new subject identification number, they will have to meet all eligibility criteria as described for the initial dosing, and will undergo the same screening, enrollment, conditioning chemotherapy, and follow-up procedures except for leukapheresis. Retreatment procedures are outlined in Section 15.4.
Safety Monitoring	A Safety Committee comprised of the Investigators and a clinical representative of the sponsor will be established and will review data regularly for all subjects and for each cohort to determine dose escalation and enrollment.
Inclusion Criteria	1. Must have signed written, informed consent. 2. Males or females, ≥18 years of age. 3. Must have a confirmed diagnosis of active MM as defined by the IMWG criteria at initial diagnosis (Rajkumar, 2014). 4. Must have measurable MM as defined by at least 1 of the following criteria: Phase 1: • Serum M-protein greater or equal to 0.5 g/dL (5 g/L) • Urine M-protein greater or equal to 200 mg/24 h

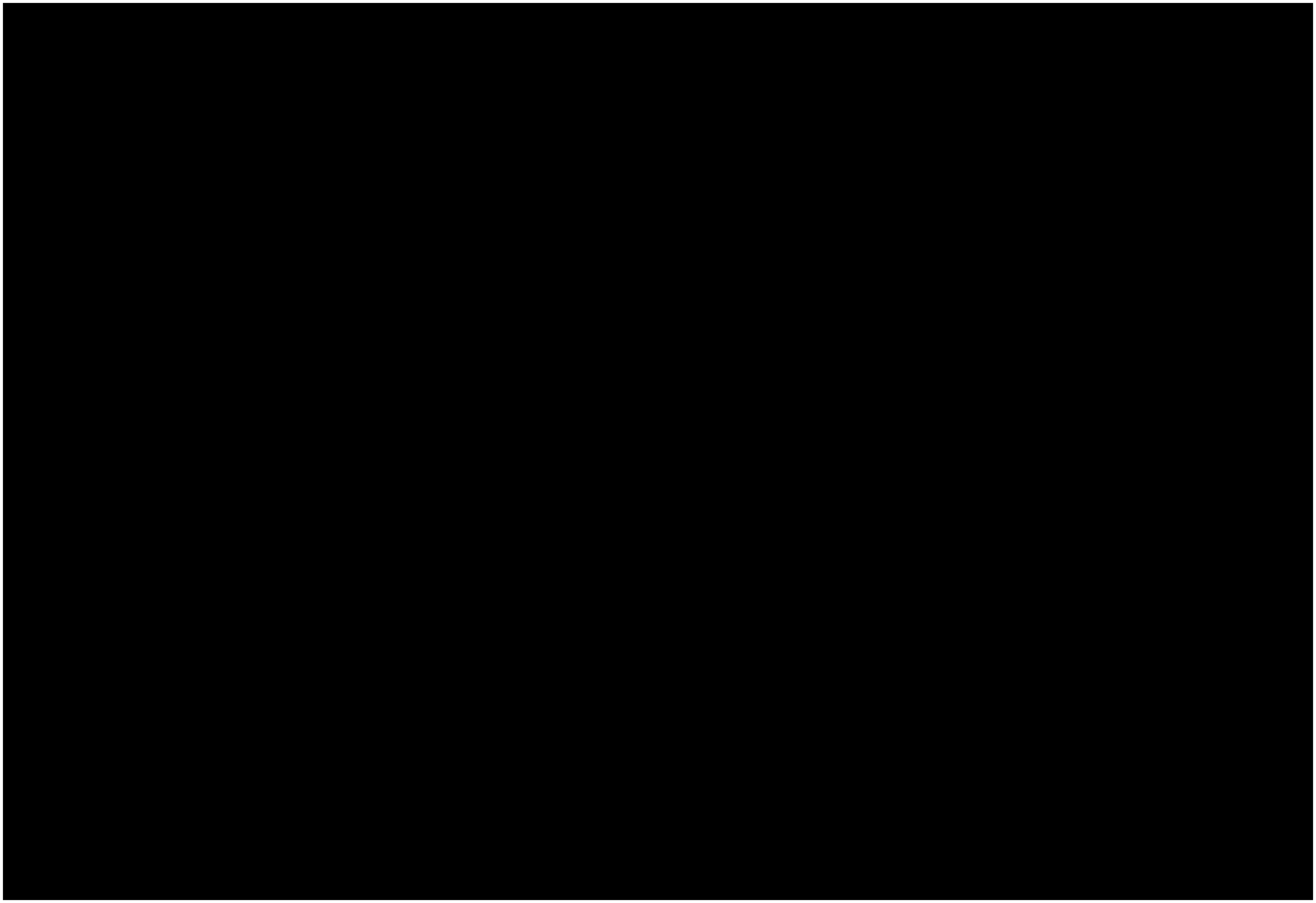
	• Serum free light chain (FLC) assay: involved FLC level greater or equal to 10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal • Bone marrow plasma cells >30% of total bone marrow cells, or other measurable bone disease (e.g., plasmacytomas measurable by PET or CT) (with medical monitor approval) Phase 2: • Serum M-protein greater or equal to 1.0 g/dL (10 g/L) • Urine M-protein greater or equal to 200 mg/24 h • Serum FLC assay: involved FLC level greater or equal to 10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal 5. Must have relapsed / refractory MM as defined by the following: Phase 1: • Received at least 3 prior lines of therapy, which must have contained a proteasome inhibitor and immunomodulatory agent (IMiD) OR • Received at least 2 prior lines of therapy if "double-refractory" to a proteasome inhibitor and IMiD, defined as progression on or within 60 days of treatment with these agents. Phase 2: • Received at least 3 prior lines of therapy which must have contained a proteasome inhibitor, an IMiD, and CD38 targeted therapy with at least 2 of the prior lines in the form of triplet combinations, and undergone ≥2 cycles of each line unless PD was the best response. AND • Refractory to the most recent line of therapy. AND • Undergone ASCT or not be a candidate for ASCT. *Note*: induction therapy, autologous stem cell transplant (ASCT), and maintenance therapy, if given sequentially without intervening progression, should be considered as single line. 6. Must be willing to practice birth control from the time of Screening and throughout the study (both males and females of childbearing potential). • Females on cohorts R, RP or RIT must commit either to abstain continuously from sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide and 12 months after last dose of rituximab. • Males in cohort R or RP must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide and for up to 4 weeks after discontinuing lenalidomide, even if they have undergone a successful vasectomy. Male patients taking lenalidomide must not donate sperm.

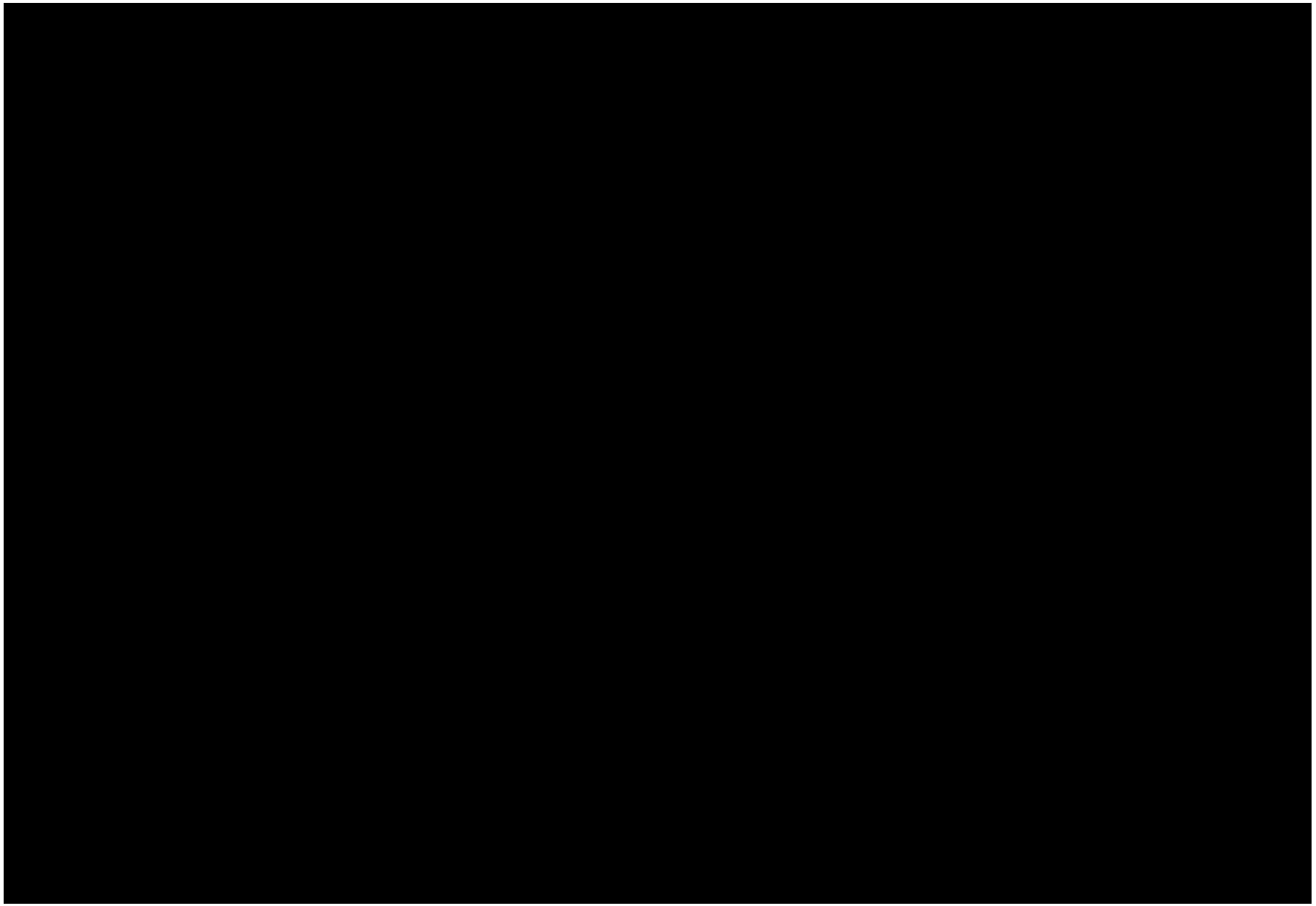
	7. Must have a negative serum pregnancy test at Screening and a negative urine test within 3 days prior to initiating the lymphodepletion chemotherapy regimen (females of childbearing potential). • Female subjects in cohort R and RP must have two negative pregnancy tests prior to initiating lenalidomide. The first test should be performed within 10-14 days and the second test within 24 hours prior to subject starting lenalidomide therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles. 8. Must be at least 90 days since autologous stem cell transplant, if performed. 9. Must have adequate vital organ function, defined as follows (or medical monitor approval): • Serum creatinine ≤2.0 mg/dL and estimated creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault formula and not dialysis-dependent. • Absolute neutrophil count ≥1000/µL and platelet count ≥50,000/µL (≥30,000/µL if bone marrow plasma cells are ≥50% of cellularity). • [redacted] • Hemoglobin >8 g/dL (transfusion and/or growth factor support is allowable). • Serum glutamic oxaloacetic transaminase (SGOT) ≤3 × the upper limit of normal and total bilirubin ≤2.0 mg/dL (unless there is a molecularly documented history of Gilbert's syndrome). • Left ventricular ejection fraction (LVEF) ≥45%. LVEF assessment must have been performed within 4 weeks of enrollment. 10. Must have recovered from toxicities due to prior therapies, with the exception of peripheral neuropathy, to Grade ≤2 according to the NCI CTCAE Version 4.03 criteria or to the subject's prior baseline. 11. Must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
Exclusion Criteria	1. Is pregnant or lactating 2. Has inadequate venous access and/or contraindications to leukapheresis. 3. Has active hemolytic anemia, plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), disseminated intravascular coagulation, leukostasis, or amyloidosis. 4. Has an active second malignancy (not disease-free for at least 5 years) in addition to MM, excluding low-risk neoplasms such as non-metastatic basal cell or squamous cell skin carcinoma. 5. Has active autoimmune disease, such as psoriasis, multiple sclerosis, lupus, rheumatoid arthritis, etc. (the medical monitor will determine if a disease is active and autoimmune). 6. Has a history of significant central nervous system (CNS) disease, such as stroke, epilepsy, etc. (the medical monitor will determine if significant). 7. Has an active systemic infection (e.g. causing fevers or requiring antimicrobial treatment).

	8. Has hepatitis B or C virus, human immunodeficiency virus (HIV), or human T-lymphotropic virus (HTLV) infection, or any immunodeficiency syndrome. 9. Has New York Heart Association (NYHA) Class III or IV heart failure, unstable angina, or a history of myocardial infarction or significant arrhythmia (e.g. atrial fibrillation, sustained [>30 seconds] ventricular tachyarrhythmias, etc.). 10. Has any psychiatric or medical disorder (e.g. cardiovascular, endocrine, renal, gastrointestinal, genitourinary, immunodeficiency or pulmonary disorder not otherwise specified) that would, in the opinion of the Investigator or medical monitor, preclude safe participation in and/or adherence to the protocol (including medical conditions or laboratory findings that indicate a significant probability of not qualifying for or being unable to undergo adequate leukapheresis, conditioning chemotherapy and/or CAR-T cell administration). 11. Has received prior gene therapy or gene-modified cellular immunotherapy (or have approval of the medical monitor). Subject may have received non-gene-modified autologous T-cells or stem cells in association with an anti-myeloma treatment. 12. Has received anti-cancer medications within 2 weeks or 5 half-lives (whichever is longer or have medical monitor approval) of the time of initiating conditioning chemotherapy. 13. Has received immunosuppressive medications within 2 weeks of the time of initiating leukapheresis, and/or expected to require them while on study (the medical monitor will determine if a medication is considered immunosuppressive). Generally, all non-essential medications (including supplements, herbal medications, etc.) should be discontinued from 2 weeks before leukapheresis until 2 months after P-BCMA-101 administration due to the potential for unappreciated immunosuppressive effects. 14. Has received systemic corticosteroid therapy ≥5 mg/day of prednisone or equivalent dose of another corticosteroid within 2 weeks of either the required leukapheresis or 1 week or 5 half-lives (whichever is shorter) of the administration of P-BCMA-101 or is expected to require it during the course of the study. (Topical and inhaled steroids are permitted. Systemic corticosteroids are contraindicated after receiving P-BCMA-101 cells outside of study-specific guidance). 15. Has CNS metastases or symptomatic CNS involvement (including leptomeningeal carcinomatosis, cranial neuropathies or mass lesions and spinal cord compression) of their myeloma. 16. Has a history of severe immediate hypersensitivity reaction to any of the agents used in this study. 17. Has a history of having undergone allogeneic stem cell transplantation, or any other allogeneic or xenogeneic transplant, or has undergone autologous transplantation within 90 days. 18. Unable to take acetylsalicylic acid (ASA) (325 mg) daily as prophylactic anticoagulation. Patients intolerant to ASA may use warfarin or low molecular weight heparin) (Cohorts R and RP only). 19. History of thromboembolic disease within the past 6 months, regardless of anticoagulation (Cohorts R and RP only).

Duration of Study	Subjects will be followed for up to 2 years after the last dose in this study, following which consenting subjects will roll over into a long-term safety follow-up protocol for a total of 15 years follow-up post-last dose.
Schedule of Events	See Table 2, for single administration Schedule of Events – Screening through Conditioning Chemotherapy, and Table 3, Schedule of Events – P-BCMA-101 Administration and Follow-Up. The Schedules of Events for retreatment of subjects with P-BCMA-101 is described in Table 9 and Table 10 (see Section 15.4). For rimiducid treatment see the Schedule of Events in Table 8. The Schedule of Events for subjects in Cycle Administration cohorts is described in Table 11, Table 12, Table 13, and Table 14 (see Section 15.5). The Schedule of Events for subjects in Combination Administration cohorts is described in Table 15 and Table 16 (see Section 15.6).
Criteria for pausing dosing or stopping the study	If a study-defined DLT or any treatment related death occurs, dosing of new subjects will be paused until the Safety Committee meets, reviews the event(s), and determines forward plans, which might include stopping the study, reducing subsequent dose levels, instituting additional safety procedures or a study amendment, continuing the study as planned or other measures as appropriate to the event. As described above, if 2 or more subjects have DLTs in a cohort during Phase 1, and a ≥10% incidence of ≥ Grade 4 or ≥30% incidence of ≥Grade 3 CRS or neurotoxicity at or below a corresponding dose level in Phase 2 with >10 patients treated, that dose level will have exceeded the MTD and any further dosing would take place at a lower dose level.
Statistical Methodology	The demographic and baseline characteristics, safety, and efficacy data will be summarized using appropriate descriptive statistics. Data analyses will be provided by dose cohort, as well as for all subjects combined where appropriate. Descriptive statistics including means, medians, standard deviations, and ranges will be calculated for continuous variables, and categorical data will be summarized using counts and percentages. For response rate endpoints, point estimates and two-sided exact binomial 95% confidence intervals will be computed. Time-to-event variables will be summarized using the Kaplan-Meier method. Treatment-emergent AEs (TEAEs) will be summarized using counts and percentages of subjects by cohort, and for all subjects combined. TEAEs will also be summarized by severity and relationship. Concomitant medications will be summarized using counts and percentages of subjects by dose cohort. Vital signs, electrocardiogram (ECG) measurements, and laboratory results will be summarized using descriptive statistics for observed values and change from baseline values by cohort. Laboratory results will also be summarized relative to the normal range (below, within, or above) by cohort. The Phase 1 part of the study is a standard 3+3 design of dose cohorts intended to determine a dose below which a 33% incidence of DLTs occurs. Thus, up to 120 subjects may be enrolled to include the possibility of 18 cohorts of 6 subjects during dose escalation, cycle administration and combination administration, as well as subjects who might be enrolled to replace those who discontinue prior to completion of the DLT evaluation period or further assess findings in a cohort. For the Phase 2 part of the study response rate endpoints will be tested to exclude a response rate of ≤30% as obtained with the recently approved standard of care agent daratumumab at $p<0.05$. Time-to-event variables will be summarized using the Kaplan-Meier method. With a 100-subject sample, the Phase 2 part of the trial

	will have 90% power to detect a 15-percentage point improvement over a 30% response rate. This power calculation is based on an exact test for a binomial proportion with a 1-sided 0.05 significance level. A futility analysis will be conducted once 35 subjects are enrolled, received P-BCMA-101, and followed up for 4 months or progressed prior to 4-month follow-up. This analysis set is called Futility Analysis Set (FAS). The futility analysis will use Futility Index (FI) which is equal to 1 minus the Conditional Power (CP) based on the observed proportion of BOR in FAS. The study may be stopped if FI is above 0.80 (that is, if CP falls below 0.20). Subjects who receive additional infusions of P-BCMA-101 will also be analyzed as separate subgroups for all outcomes afterwards.





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LIST OF DEFINITIONS AND ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
ASCT	autologous stem cell transplant
BCMA	B-cell maturation antigen
BP	blood pressure
CAR	chimeric antigen receptor (CAR + cells = P-BCMA-101 cells)
CARTyrin	anti-BCMA Centyrin CAR
CNS	central nervous system
CP	conditional power
CR	complete response
CRO	Contract Research Organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DHFR	dihydrofolate reductase
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
FAS	futility analysis set
FDA	Food and Drug Administration
FI	Futility index
FKBP12	FK506-binding protein 12
FLC	free light chain
GCP	Good Clinical Practice

GVHD	Graft Versus Host Disease
HDAC	histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HTLV	human T-lymphotropic virus
iCasp9	inducible caspase 9
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IgG	immunoglobulin G
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent-to-Treat
IV	intravenous(ly)
Kg	Kilogram
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MMSE	Mini Mental Status Exam
MR	minimal response
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institute of Health
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
ORR	overall response rate

OS	overall survival
PB	piggyBac™
PBMC	peripheral blood mononuclear cells
PET	positron emission tomography
PFS	progression free survival
PHI	protected health information
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PD	progressive disease
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
RNA	ribonucleic acid
RR	respiratory rate
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SIFE	serum immunofixation
SPB	Super piggyBac™ transposase
SPEP	serum protein electrophoresis
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TNF-α	tumor necrosis factor alpha
Tscm	T stem cell memory
TTR	time to response
UIFE	urine immunofixation
UPEP	urine protein electrophoresis
VGPR	very good partial response
WHO	World Health Organization

1. INTRODUCTION

Multiple myeloma (MM) is generally an incurable and fatal disease which typically runs a course of multiple relapses and recurrences. Currently available therapies are inadequate and there remains an unmet need for an effective and durable MM therapy. Chimeric antigen receptor T cell (CAR-T) immunotherapy is emerging as an important potential therapeutic approach for cancer, including MM. B-cell maturation antigen (BCMA) is an attractive target given that BCMA is expressed in MM cells, but among non-malignant cells, BCMA expression is largely restricted to plasma cells and a subset of B cells. Clinical data in MM patients has recently been published using two similar BCMA-targeted CAR-T cell products (NCI/NIH, University of Pennsylvania and BlueBird Bio studies) demonstrating the safety and efficacy of the approach (Ali, 2016; Cohen, 2016; Berdeja, 2016). *In vitro* and *in vivo* studies have shown that the P-BCMA-101 T cells bind to BCMA+ tumor lines with high affinity and specificity, resulting in robust degranulation and cytotoxicity. The unmet medical need, when taken together with the available preclinical and clinical data, and the potential safety and efficacy advantages of this construct, provide the rationale for evaluating P-BCMA-101 in patients with recurrent or relapsing MM. The information below is also described in detail in the Investigator's Brochure.

1.1. Multiple Myeloma

Multiple myeloma (MM) is a treatable but typically incurable plasma cell malignancy that often runs an aggressive and lethal clinical course. It is estimated that about 26,850 new cases of MM occurred in the U.S. in 2015 with approximately 11,240 deaths. The diagnosis is most common in the 6th and 7th decades of life (Howlader, 2015).

The hallmark feature of MM is monoclonal expansion of plasma cells in the bone marrow with accompanying excessive production of monoclonal antibodies (mAbs) that produce an "M spike" on serum protein electrophoresis (Raab, 2009). The clinical features of the disease result from bone marrow infiltration by the malignant clone, high levels of circulating monoclonal antibody (mAb) and/or free light chains, depressed immunity and end-organ damage. The classic signs and symptoms of MM include anemia, bleeding due to thrombocytopenia, frequent infections due to leukopenia and low antibody production, bone pain due to bone lesions and fractures and renal impairment due to high levels of M protein accumulation and hypercalcemia.

Recent advances in the understanding of MM's pathophysiology and the introduction of novel therapeutic agents have contributed toward the management of this disease with dramatic improvements in survival observed in the last 2 decades. Median survival increased from about 2 years in the 1980s up to 5-6 years or more today (Engelhardt, 2010). Treatment regimens tend to be comprised of two to three agents; most all patients receive a proteasome inhibitor (bortezomib or carfilzomib) and an immunomodulatory agent (IMiD) (lenalidomide, pomalidomide, thalidomide) both early and late in the course of treatment of their disease. In addition, eligible patients may undergo autologous hematopoietic stem cell transplantation and/or, less frequently, allogeneic hematopoietic stem cell transplantation. In 2015, several new therapies were approved in the United States including 2 mAbs (daratumumab and elotuzumab), a pan histone deacetylase (HDAC) inhibitor (panabinostat), and an oral proteasome inhibitor (ixazomib). The long-term impact of these recent approvals remains to be determined, but they do not appear to produce cures in the relapsed and/or refractory setting, and most patients will ultimately relapse and die (Kumar, 2008). Tumors that relapse tend to recur more aggressively with each relapse.

Responses to treatment are less durable with subsequent disease progression resulting in treatment-refractory disease associated with shortened survival times (Kumar, 2012).

1.2. Rationale for P-BCMA-101 T Cell Therapy in Multiple Myeloma

1.2.1. P-BCMA-101 T Cell Therapy

P-BCMA-101 is an autologous Centyrin-based CAR-T cell therapy, referred to as CARTyrin T cells. It is a biologic product designed to target MM cells expressing the cell surface antigen BCMA and to direct cytotoxic effects to the targeted cell (Tai, 2015). The mechanism of action of P-BCMA-101 is the same as that of other CAR-T approaches (e.g. Ali, 2016; Berdeja, 2016). Each patient's peripheral blood mononuclear cells (PBMCs) will be harvested by leukapheresis, then will be used to generate the PBCMA-101 investigational product for that individual patient via electroporation of transposase ribonucleic acid (RNA) along with a DNA plasmid encoding a PB transposon carrying the CARTyrin (i.e. the piggyBac™ (PB) DNA modification system), followed by culture/expansion.

As of 14 July 2019, 36 subjects had been treated with P-BCMA-101 cells (34 in Phase 1 and 2 in Phase 2), 3 of whom have received a second administration of P-BCMA-101. All Phase 1 dose escalation cohorts (1-5: 0.75-15 × 10^6 P-BCMA-101 cells/kg/dose) had successfully been completed with good safety and efficacy reported through the highest dose level. No DLTs had been reported and enrollment of new subjects is continuing in expansions of cohorts, suggesting additional cohorts should be assessed. Patients were heavily pre-treated (3-18 prior therapies), most had failed IMiDs, proteasome inhibitors, daratumumab and ASCT. Patients were treated with 48-1545 × 10^6 total P-BCMA-101 cells/kg. Circulating P-BCMA-101 cells have been detected in the blood of patients by PCR, with expansion peaking at 2-3 weeks. Above a threshold level reached in Cohorts 2-3, greater response appears to occur in patients with broader peaks, suggesting there may be additional benefit in repeat or fractionated dosing. Although of

unknown significance, indications of anti-CAR-T antibodies have been seen in some patients. The most common TEAEs (>30%) were neutropenia, WBC decreased, thrombocytopenia, anemia, nausea, constipation and febrile neutropenia. Only 4 subjects had cases of CRS (1 subject had Grade 2 at 2×10^6 cells/kg and 3 subjects had Grade 2 at 15×10^6 cells/kg) and 1 case of CRES (Grade 2 at 6×10^6 cells/kg, transient confusion) had been reported. Repeat administrations of P-BCMA-101 were also well tolerated. Twenty-nine of the Phase 1 subjects were evaluable for response by IMWG criteria and had completed at least one myeloma response assessment, with 17 thus far demonstrating a response (1/2 at ~0.75×10^6 cells/kg, 5/7 at ~2×10^6 cells/kg, 4/9 (+ 2 MR) at ~6×10^6 cells/kg, 3/4 (+ 1 MR) at ~10×10^6 cells/kg, and 4/7 at ~15×10^6 cells/kg). Based on these results the study was further expanded with a Phase 2 portion to further characterize the safety and efficacy at dose levels 3-5.

1.2.2. BCMA as a Therapeutic Target for CAR-T cells

Myeloma has several characteristics that make it suitable to treat with adoptive T cell therapy. First, myeloma is primarily a disease of the bone marrow and adoptive T cell therapy targeting CD19 has been particularly successful in bone marrow-predominant diseases, such as acute lymphoblastic leukemia (ALL) (Brentjens, 2013). Second, autologous stem cell transplantation is the standard of care in myeloma, and lymphodepletion may enhance the efficacy of adoptive T cell therapy (Brentjens, 2011; Pegram, 2012). Third, unlike all other treatments for myeloma, an allo-SCT is potentially curative, however, its application is limited by transplant-associated toxicity, mortality, patient eligibility and availability of suitable donors. CAR-T cell therapy has the potential to be a safer way to achieve such anti-tumor efficacy (Milone, 2015).

The utility of CD19 as a target is limited by the fact that it is infrequently expressed on the malignant plasma cells of MM; therefore, other antigens have been explored, with particular attention to antigens expressed by tumor cells but not normal tissues. One attractive target is BCMA. The rationale for selecting this target is that BCMA is detected in MM cells, but among non-malignant cells, BCMA expression is largely restricted to plasma cells and a subset of B cells, and therefore may have less potential for on-target, off-tumor effects.

MM tumor cell recognition occurs when the BCMA-specific CAR expressed on the surface of a P-BCMA-101 T cell binds to BCMA antigen expressed on the surface of a MM tumor cell. Signaling and activation is mediated by the intracytoplasmic signaling domains 4-1BB and CD3ζ encoded within the CAR. Activation can lead to direct cytotoxicity of MM tumor targeted by CAR-T cell-mediated release of granzyme and perforin. Tumor killing can also be mediated by activation of other components of the immune system through release of cytokines by CD4+ T cells. Long-term eradication and prevention against tumor relapse may be provided either by immediate tumor ablation or by long-term memory CAR-T cells that remain after the initial tumor response. Thus, there may be particular advantage to having CAR-T cells that are of the T stem cell memory phenotype (Tscm) and T central memory phenotype (Tcm). In addition, release of non-BMCA tumor-associated antigens during CAR-T-mediated tumor cell lysis may lead to the priming and/or reactivation of non-engineered tumor-specific cells of the adaptive immune system, a phenomenon termed ‘epitope-spreading’, that may also assist in the long-term eradication and prevention against tumor relapse.

In a nonclinical study conducted by Carpenter, et al. (Carpenter, 2013) anti-BCMA-CAR T cells exhibited specific anti-BCMA functions, including cytokine production, proliferation,

cytotoxicity, and *in vivo* tumor eradication. Importantly, anti-BCMA-CAR T cells recognized and killed primary MM cells. The authors concluded that BCMA is a suitable target for CAR-expressing T cells, and adoptive transfer of anti-BCMA-CAR T cells is a promising new strategy for treating MM (Carpenter, 2013).

Data was published that demonstrated the first clinical proof of concept for T cells expressing anti-BCMA CAR in subjects with relapsed/refractory MM from a study performed at the National Cancer Institute (NCI). Patients (N=16) were enrolled at 4 dose levels, including: 0.3×10^6; 1×10^6; 3×10^6 and 9×10^6 cells/kg-body wt. Responses were dose-dependent and included partial response (N=3), very good partial response (N=4) and stringent complete response (N=1). At the highest dose level, the response rate was 100%. Data on duration of response is not yet available. Tolerability was consistent with expectations from other CAR-T studies. Toxicities attributable to anti-BCMA CAR-T cells were minimal in patients treated at the low dose level. Subsequently, patients exhibited signs of CRS correlating with dose level. No unexpected damage to non-hematopoietic organs was observed (Ali, 2016; Kochenderfer, 2016). Initial results of another study utilizing anti-BCMA CAR-T cells by Cohen et al. (Cohen, 2016) have recently been presented. In this study, 6 patients were treated with $1\text{-}5 \times 10^8$ CAR-T cells. Four patients responded: minimal response (N=2), very good partial response (N=1) and minimal residual disease negative (MRD negative) stringent complete response (N=1). Five patients developed CRS, of which 1 was Grade 3 with neurotoxicity that responded to treatment without sequelae. CAR-T cell expansion appeared to correlate with efficacy. In an ongoing study of a third anti-BCMA CAR-T construct presented by Berdeja et al., 11 patients were enrolled at 3 fixed dose levels; 5×10^7; 15×10^7 and 45×10^7 CAR-T+ cells per patient (80×10^7 and 120×10^7 CAR-T+ cells per patient are planned for upcoming cohorts). The response rate was impressive and dose-dependent, including partial response (N=4), very good partial response (N=1) and stringent complete response (N=2), with 2 patients becoming MRD negative. Tolerability was better than what has been reported in other CAR-T studies. CRS was seen in 70-80% of the patients, but it was limited to Grade 1-2. No neurotoxicity or other significant or unexpected toxicities were reported (Berdeja, 2016). The relative paucity of toxicity in these studies has been variously attributed to use of the 4-1BB costimulatory domain, lessened disease burden and/or more gradual exposure of the T-cells to myeloma cells, compared to the anti-CD19 products used in leukemias which have generated the most publications.

Lenalidomide (Lenalidomide, 2019) is a member of the class of immunomodulatory imide drugs (IMiDs) known for significant activity against myeloma as well as pleiotropic effects on the immune system, and is approved for the treatment of myeloma, myelodysplastic syndrome and lymphomas in the United States **(**Moreau, 2019; Fink, 2015**)**. In addition to its direct anti-myeloma properties, it is hypothesized lenalidomide could enhance the efficacy of CAR-T cells such as P-BCMA-101. Lenalidomide treatment increases the frequency of naïve and stem cell memory T cells, and not only are these two T subsets the preferred starting material for the P-BCMA-101 manufacturing process, but they have also been associated with improved clinical outcome in CAR-T cell products (Fostier, 2018; Barnett, 2016a; Cohen, 2019). Inclusion of lenalidomide directly in the manufacturing process is not being proposed as this approach may increase the number and effector function of CAR-T cells produced (Wang, 2018). Thus, including lenalidomide treatment prior to apheresis is hypothesized to improve the quality of the T cells in the input material and, subsequently, the manufactured CAR-T cell product. Co-administration of lenalidomide with CAR-T cells is being proposed as it has been shown to

augment CAR-T cell effector functions and overall anti-myeloma activity both in vitro and in mouse models (Otáhal, 2016; Wang, 2018; Works, 2019). Moreover, a similar combination with lenalidomide and an anti-BCMA CAR-T cell product is currently being explored in at least one other clinical trial (NCT03070327).

[redacted]

1.2.3. P-BCMA-101 Design and Rationale

As described above, P-BCMA-101 cells are designed to express 3 major components: an anti-BCMA Centyrin chimeric antigen receptor (CARTyrin) gene, a dihydrofolate reductase (DHFR) resistance gene, and an inducible caspase 9 (iCasp9)-based safety switch gene (Hermanson, 2016). Binding of BCMA antigen expressed on the surface of a MM tumor cell by the BCMA-specific CARTyrin triggers signaling and activation within the P-BCMA-101 cells that is mediated by the CARTyrin-encoded intracytoplasmic signaling domains. [redacted]

Whereas genetic modification of autologous T cells for expression of CAR molecules is generally accomplished via lentivirus or γ–retrovirus transduction, P-BCMA-101 is manufactured using an electroporation-based non-viral (DNA transposon) gene delivery system called the piggyBac (PB) DNA modification system (Nakazawa, 2013) which efficiently moves DNA from a plasmid to a chromosome via a "cut and paste" mechanism and have been used extensively as a human gene transfer method, including CAR-T production (Woodard, 2015; Fraser, 1996; Singh, 2013; Huls, 2013). Compared to viral-based delivery, PB offers advantages, including a safer insertion profile (Cunningham, 2015), larger transgene capacity (enabling the delivery of genetic components to enhance safety and efficacy), higher level and more stable transgene expression (Cunningham, 2015), longer duration transgene expression (Mossine, 2013) as well as a preponderance of the highly favorable T_{SCM} phenotype. [redacted]

1.2.4. Summary of Nonclinical Studies with P-BCMA-101

1.2.4.1. Product Candidate Screening and Selection

1.2.4.1.1. *In vitro* Screening

[redacted]

1.2.4.1.2. *In vivo* Screening in MM Xenograft Models

[redacted]

[redacted]

1.2.4.2. P-BCMA-101 Preclinical Toxicology

1.2.4.2.1. *In vitro* Binding of the P-BCMA-101 Centyrin to a Human Protein Panel

[redacted]

1.2.4.2.2. P-BCMA-101 Reactivity Against Normal Human Tissues

[redacted]

1.2.4.2.3. Single-Dose GLP Safety and Efficacy Study of P-BCMA-101 CAR-T Cells in MM1.S Myeloma Tumor-bearing NSG Mice

[redacted]

1.3. Potential Risks and Benefits

1.3.1. Benefit Assessment

Based on data with P-BCMA-101 and other CAR-T cells (including anti-BCMA CAR-T cells) it is reasonable to expect that P-BCMA-101 may exert an anti-tumor effect.

1.3.2. Risk Assessment

Participation in this study will expose the subject to genetically engineered autologous T cells. The risk is acceptable based on clinical experience with similar products. The potential safety concerns for P-BCMA-101 are effectively the same as for other CAR-T cell products. The primary adverse effect seen in CAR-T cell studies is CRS and associated symptoms related to the activation of the CAR-T cells through their intended mechanism of action (significant increases in cytokines have also been reported to correlate with efficacy). Descriptions and guidelines for management of these toxicities are provided in Section 6.3. Although not yet reported with

BCMA-targeted CAR-T cells, other theoretical concerns with CAR-T cells include: 1) "on-target/on-tumor" toxicity, manifest as tumor lysis syndrome (TLS) through rapid destruction of myeloma tumor cells; 2) "on-target/off-tumor" toxicity related to destruction of BCMA+ non-tumor cells in healthy tissues (other than hypogammaglobulinemia); 3) "off-target" toxicity due to potential cross-reactivity of the BCMA-binding domain with BCMA-negative targets; and; 4) immune-related reactions secondary to the development of anti-CAR-T antibodies. Many of these questions are addressed in the data in Section 1.2. The potential for tumorigenicity is another hypothetical risk that is considered negligible (Tey, 2014; Hackett, 2013), based upon the terminal differentiation of these cells, insertion profile and character of the gene addition materials and process, as well as the extensive clinical experience to date with long-term follow up of patients receiving other CAR-T cell products (Jena, 2010). At least one previous CAR-T study used a similar DNA transposon approach, and was found to be well-tolerated in a Phase 1 clinical trial at doses up 1.2×10^9 total CAR-T cells (Singh, 2013; Huls, 2013). Potential risks of the moderate conditioning chemotherapy regimen utilized in this protocol are expected to be typical for these agents, in particular cytopenias, gastrointestinal effects, and infertility. Hemorrhagic cystitis, pulmonary, cardiac and neurologic effects have also been reported.

The proposed starting dose (0.75×10^6 CAR-T cells/kg) in this Phase 1 study is ~3-fold lower than that reported in one clinical trial of CAR-T cells targeting BCMA (Cohen 2016) and approximately the same as others (Ali, 2016; Berdeja, 2016) who described toxicity as mild through doses up to 10-fold higher. [redacted] further supporting a large margin of safety for the proposed FIH trial. [redacted]

As described above, P-BCMA-101 was designed with a number of features to increase safety, [redacted]

This study incorporates several further measures to address potential risks, including the following: step-wise escalation of the T cell dose, staggered enrollment of subjects, treatment in specialized academic centers experienced with management of toxicities associated with autologous T cell therapies, guidelines for management of toxicities, and a Safety Review Committee to evaluate safety throughout the study. As of 14 July 2019, the most common TEAEs (>30%) in Phase 1 were neutropenia, WBC decreased, thrombocytopenia, anemia, nausea, constipation, and febrile neutropenia. Only 4 subjects had cases of CRS (1 subject had Grade 2 at 2×10^6 cells/kg and 3 subjects had Grade 2 at 15×10^6 cells/kg) and 1 case of CRES (Grade 2 at 6×10^6 cells/kg) had been reported.

1.3.3. Overall Benefit: Risk Conclusion

The known and potential risks anticipated with P-BCMA-101 T cell therapy appear justified by the potential benefits that may be afforded to subjects with relapsed/refractory MM, a fatal malignancy.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
The primary objective of this study is: **Phase 1:** To determine the safety and maximum tolerated dose (MTD) of P-BCMA-101 based on dose limiting toxicities (DLT) **Phase 2:** To assess the safety and efficacy of P-BCMA-101	**Phase 1:** Number of subjects with DLT at each dose level to define an MTD **Phase 2:** • Safety and tolerability based on adverse events (AEs), examinations, and standard laboratory studies • Overall response rate (ORR) and duration of response (DOR) by International Myeloma Working Group Criteria (Kumar, 2016) as assessed by an independent review committee (IRC)
Secondary	

Secondary objectives of this study are to evaluate:
Phase 1:
• The safety and feasibility of P-BCMA-101
• The anti-myeloma effect of P-BCMA-101
• The effect of cell dose to guide selection of doses for further assessment in Phase 2/ 3 studies
Phase 2:
• Incidence and severity of CRS
• Additional efficacy endpoints
	The following secondary endpoints will be evaluated:
	Phase 1:
	• Ability to generate the protocol-proscribed doses of P-BCMA-101
	• Safety and tolerability based on AEs, examinations, and standard laboratory studies
	• CRS graded using Lee criteria (Lee, 2014)
	• Efficacy based on International Myeloma Working Group (IMWG) Uniform Response Criteria (Rajkumar, 2011; Kumar, 2016; Cavo, 2017)
	  ○ Overall response rate (ORR)
	  ○ Time to response (TTR)
	  ○ Duration of response (DOR)
	  ○ Progression free survival (PFS)
	  ○ Overall survival (OS)
	Phase 2:
	• CRS graded using Lee criteria (Lee, 2014)
	• Rate of IL-6 antagonist, corticosteroid, and rimiducid use
	• OS, PFS, TTR, MRD negative rate

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

The study will be conducted in multiple parts: a Phase 1, open-label, SAD phase; a Phase 1, multiple dose cycle administration phase; a Phase 1, combination administration phase; and a Phase 2 open-label efficacy and safety phase, in adult subjects with relapsed / refractory MM. A schematic of the study design for single dose administration is shown in Figure 3. Schematics for the Phase 1 cycle administration cohorts are shown in Figure 5 and Figure 6 in Section 15.5. A schematic of the study design for combination administration is shown in Figure 7 in Section 15.6.

Only sites that are experienced in managing oncology subjects and stem-cell/bone marrow transplant with the resources to manage the types of acute emergent events expected with CAR-T cell administration will be selected to participate in this study. A Safety Committee will meet regularly to review data throughout the study.

Subjects meeting the protocol entry criteria will be eligible to enroll in the study and will follow the procedures outlined in Table 2 for single administration cohorts. Procedures for cycle administration cohorts are detailed in Section 15.5. Procedures for the Phase 1 combination administration are detailed in Section 15.6. After a subject enrolls, leukapheresis will be performed to obtain PBMCs which will be sent to a manufacturing site to produce P-BCMA-101 CARTyrin-T cells. Allowing approximately 4 weeks for P-BCMA-101 manufacturing, subjects are intended to return for conditioning chemotherapy and P-BCMA-101 administration approximately 4 weeks from the Leukapheresis Visit (this period may be extended as deemed necessary by the Investigator).

Before dosing with the P-BCMA-101 cell infusion, subjects will receive a lymphodepletion chemotherapy regimen of 300 mg/m^2 of cyclophosphamide and 30 mg/m^2 of fludarabine, with each agent given daily for 3 consecutive days starting at Day -5. Subjects may be maintained as an inpatient during lymphodepleting chemotherapy as the Investigator deems appropriate.

After 2 rest days following the lymphodepletion chemotherapy regimen, subjects will be dosed with P-BCMA-101 cells administered IV over approximately 5 to 20 mins on Day 0. Prior studies conducted with other CAR-T therapies have observed peak toxicity to occur within 3-7 days of investigational product administration. Study subjects will be closely monitored during and after the infusion and for approximately 7 days afterwards. This observation period will include serial assessments of adverse events (AEs), including the emergence of P-BCMA-101 cell-related toxicities, including CRS for all subjects. CRS will be graded using the Lee criteria (Lee, 2014).

Subjects may be admitted to the hospital for the P-BCMA-101 administration based on the Investigator's assessment of the individual patient's risks. Admission is not required, but subjects should remain within 50 miles of the hospital through approximately 14 days after last dose of P-BCMA-101 and assessed for admission in case of symptoms of CRS or neurotoxicity such as fever. If admitted, subjects will not be discharged until they are assessed as stable by the Investigator. Subjects may be maintained as an inpatient during lymphodepleting chemotherapy or after the above criteria are met as the Investigator deems appropriate.

Subjects will return for regular follow up and will undergo serial assessment of safety, tolerability and anti-myeloma response, as specified in the Schedule of Events (Table 3). Post-treatment follow-up visits in both Phase 1 and Phase 2 will occur at Day 10, Weeks 2, 3, 4, 6, 8, Months 3, 4, 5, 6, 7, 8, 9, and then every 3 months thereafter for up to 24 months after P-BCMA-101 administration. Follow-up procedures for cycle administration cohorts are detailed in Section 15.5. Follow-up procedures for combination administration cohorts are detailed in Section 15.6.

All consenting subjects who receive P-BCMA-101 and who complete or withdraw from the study will be encouraged to enter a long-term follow-up (LTFU) protocol (P-BCMA-101-002). Between this study and the LTFU study, a subject will be followed for 15 years from the time of the last P-BCMA-101 infusion. This LTFU is for observation of delayed AEs in accordance with FDA (FDA, 2006) requirements for gene therapy clinical trials. Subjects will continue to be followed for overall survival during the LTFU phase.

Figure 3: Schematic for Study P-BCMA-101-001 – Single Administration

3.2. Study Dosing

3.2.1. Dose Escalation Guidelines for Phase 1

Phase 1 of the study is an open-label, multi-center, SAD multiple cohort study, a multiple dose cycle administration cohort study, and a combination administration study in approximately 120 adult subjects. Initially, up to 6 dose levels of P-BCMA-101 will be administered intravenously as a single dose.

Proposed Doses (P-BCMA-101 cells/kg/dose) include:

Cohort minus 1: 0.25×10^6
Cohort 1: 0.75×10^6
Cohort 2: 2×10^6
Cohort 3: 6×10^6
Cohort 4: 10×10^6
Cohort 5: 15×10^6

Phase 1 of the study will follow a 3 + 3 design of dose-escalating cohorts, wherein 3 subjects are initially planned to be dosed with P-BCMA-101 T cells for each cohort. Additional subjects may be dosed in a cohort depending on the outcomes observed in those subjects.

For each of the first 2 cohorts, dosing of the first 3 subjects will be staggered rather than concurrently, with at least a 14-day interval between subjects to assess safety, as the peak of toxicity in CAR-T studies occurs in 3-7 days of administration, with the vast majority within 2 weeks and resolving by 2-3 weeks (Frey, 2016).

At the discretion of the Safety Committee, beginning with the 3rd cohort, dosing of the first and second subject in each cohort will be staggered.

Dose escalation guidelines are outlined in Table 4.

Table 4: Dose Escalation Guidelines

Outcome: **(# subjects with DLT)**	***Action:***
0 out of 3 subjects	Escalate dose for next cohort of 3 subjects
1 out of 3 subjects	Treat next 3 subjects at the same dose
≥2 out of 3 subjects	Halt dose escalation; treat at least 6 subjects at a lower dose to determine the MTD[1]
1 out of 6 subjects	Escalate dose for next cohort of 3 subjects
≥2 out of 6 subjects	Halt dose escalation; treat at least 6 subjects at a lower dose to determine the MTD[1]

1. MTD – the highest dose for which no more than 1 of 6 treated subjects exhibits DLT

Administration of P-BCMA-101 cells will be conducted in escalating dose cohorts in a 3+3 design. Beginning with Cohort 1, at least 3 subjects will be dosed in the cohort. If no P-BCMA-101 cell-related DLT through Day 28 is observed in the first 3 subjects, then escalation may proceed to the next cohort. If a P-BCMA-101 cell-related DLT is observed in 1 of the first 3 subjects, then at least 3 additional subjects will be treated at this dose level. If DLTs are observed in 2 or more subjects, the MTD will be considered to be at or below the next lower dose level and further enrollment may take place at a lower dose level, or an intermediate dose level may be tested at the discretion of the Safety Committee, otherwise escalation may proceed (i.e. the MTD is the highest dose cohort assessed in which this has not occurred). In the event that 2 or more subjects experience DLTs in Cohort 1, the Safety Committee, after review of all available data, may elect to dose 3 subjects in Cohort -1 with the same 3+3 expansion rules. In the event that 2 or more subjects experience DLTs in Cohort -1, the Safety Committee, based on consideration of safety and efficacy data to assess risk vs. benefit, may elect to dose 3 subjects at a lower dose with the same 3+3 expansion rules or discontinue the study.

Additional subjects may be added to a cohort by the Safety Committee based on the safety and efficacy data from that cohort to further evaluate the safety and anti-myeloma effects of P-BCMA-101, provided the dose does not exceed the MTD. If Cohort 5 is completed without concluding an overall MTD, the Safety Committee may elect to assess further escalation cohorts in 5-10 × 10^6 P-BCMA-101 cells/kg increments.

3.2.2. Dosing in Cycle Administration

In Phase 1 – Cycle Administration, multiple doses of P-BCMA-101 will be administered intravenously in 2 cycles (Cohort A and Cohort C) or 3 cycles (Cohort B) of 2 weeks each. The total dose administered will follow the 3+3 design starting at ≤ the MTD as determined during single administration escalation. In the first cycle 1/3 the total dose will be administered. In Cohort A up to 2/3 the total dose will be administered in the 2nd cycle. In Cohort B up to 1/3 the total dose will be administered in each of the 2nd and 3rd cycles. In Cohort C up to 2/3 the total dose will be administered in the 1st cycle and up to 1/3 the total dose will be administered in the 2nd cycle. Details of the procedures are provided in Section 15.5. Prior to each infusion Serum creatinine should be ≤2.0 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) ≤3 × the upper limit of normal and total bilirubin ≤2.0 mg/dL or have medical monitor approval to proceed with P-BCMA-101 infusion.

3.2.3. Dosing in Combination Administration

In Phase 1 – Combination Administration, P-BCMA-101 will be administered in combination with approved therapies:

Lenalidomide

Cohort R: lenalidomide [redacted] before P-BCMA-101 infusion; and

Cohort RP: lenalidomide [redacted] before apheresis [redacted] before P-BCMA-101 infusion.

Dosing with lenalidomide will continue for Cohort R and Cohort RP unless disease progresses. Refer to the lenalidomide package insert for prescribing information (Lenalidomide, 2019) (note particularly that lenalidomide is a presumed teratogen, pregnancy avoidance and monitoring is necessary). The following are additional recommendations specific to this protocol. If no DLTs are reported and platelets are ≥50,000/μL and neutrophils ≥1000/μL 28 days after P-BCMA-101 administration [redacted] If <2 DLTs are reported in the first 6 patients treated at this dose, the starting dose in all patients may [redacted] at the determination of the Safety Committee. During treatment if neutrophils decrease to <1000/μL hold lenalidomide until they are ≥1000/μL, [redacted] During treatment if platelets decrease to <30,000/μL hold lenalidomide until they are ≥30,000/μL, [redacted] If creatinine clearance is 30-60 mL/min the maximum lenalidomide dose [redacted] If creatinine clearance is <30 mL/min hold lenalidomide. Lenalidomide should be discontinued in case of DLT. The lowest dose allowed on this study [redacted] The investigator and Safety Committee may decide to discontinue lenalidomide at time based on other safety findings.

Patients should receive concomitant anticoagulation as indicated (eg. aspirin 325 mg orally daily). Do not administer glucocorticoids with lenalidomide.

Rituximab

Cohort RIT: [redacted]. Refer to the rituximab package insert for prescribing information (Rituximab, 2019). The following are additional recommendations specific to this protocol. Rituximab should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur. [redacted] Administer only as an intravenous infusion. Do not administer as an intravenous push or bolus. Premedicate before each infusion with acetaminophen, an antihistamine, and 100 mg intravenous methylprednisolone to be completed 30 minutes prior to each infusion. Rituximab should be discontinued in case of infusion reaction or DLT. The investigator and Safety Committee may decide to discontinue rituximab at any time based on other safety findings. Prophylaxis and observation for infectious diseases such as *Pneumocystis* pneumonia (PCP) should be considered for patients during and following treatment per rituximab prescribing information.

The dose of P-BCMA-101 administered will escalate or de-escalate following the 3+3 design starting at ≤ the MTD as determined during dose escalation. Details of the procedures are provided in Section 15.6.

3.2.4. Dosing in Phase 2

Phase 2 of the study is an open-label, multi-center study in approximately 100 adult subjects with relapsed/refractory MM. Subjects in Phase 2 will receive a total dose of 6-15 × 10^6 cells/kg (per the schedule determined in Phase 1).

3.2.5. Repeat Dosing

If sufficient P-BCMA-101 cells remain from manufacturing when a subject's disease progresses, with Safety Committee approval additional cells may be administered up to the highest dose level that has successfully completed dose-limiting toxicity assessment. In order to receive an additional P-BCMA-101 T-cell infusion, subjects will be assigned a new subject identification number, they will have to meet all eligibility criteria as described for the initial dosing, and will undergo the same screening, enrollment, conditioning chemotherapy, and follow-up procedures except for leukapheresis. Details regarding retreatment procedures are provided in Section 15.4.

3.3. Evaluation of Dose-Limiting Toxicity

DLT is defined as any National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥3 event at least possibly related to P-BCMA-101 cell therapy, including uncontrollable expansion of P-BCMA-101 cells, and not attributable to the underlying

disease or lymphodepleting chemotherapy regimen with onset within the first 28 days following the last P-BCMA-101 cell infusion with the following exceptions:

- Grade 3 or 4 neutropenia with or without neutropenic fever resolving within 28 days following the last P-BCMA-101 cell infusion
- Grade 3 fever
- Grade 3 or 4 thrombocytopenia, with or without bleeding due to thrombocytopenia, resolving within 28 days following the last P-BCMA-101 cell infusion
- Grade 3 or 4 anemia and lymphopenia
- Grade 3 or 4 hypogammaglobulinemia
- Alopecia
- Grade 3 or 4 nausea, vomiting, or diarrhea which responds to medical treatment within 24 hours
- Immediate hypersensitivity reactions (fever, rash, bronchospasm) occurring within 2 hours of cell infusion (related to cell infusion) that are reversible to a Grade 2 or less within 6 hours of cell administration with standard antihistamine based therapy
- Grade 3 encephalopathy that recovers to less than Grade 2 within 28 days
- Grade 3 CRS per Lee criteria (Lee, 2014) that resolves within 14 days
- Grade 3 non-hematological laboratory abnormalities that recover to ≤Grade 2 in 14 days
- Grade 4 non-hematological laboratory abnormalities that recover to ≤Grade 2 in 7 days

3.4. Number of Subjects and Duration of Study

In Phase 1, up to 120 subjects at up to 20 sites are planned to be enrolled. In Phase 2, approximately 100 subjects at up to 20 sites are planned to be enrolled. Enrolled subjects will undergo serial measurements of safety, tolerability and response (myeloma staging). These measures will be obtained during a period between Screening and up to 24 months after P-BCMA-101 administration according to the schedule of events described in Table 2 and Table 3 for single administration, and in Section 15.5 for cycle administration cohorts and Section 15.6 for combination administration cohorts. Subjects who experience disease progression may receive an additional infusion of P-BCMA-101 according to the schedule of events described in Table 9 and Table 10.

After completing or withdrawing from this protocol, consenting subjects who have received P-BCMA-101 will be encouraged to enroll in a separate protocol (P-BCMA-101-002) that allows for continued follow-up for a total of 15 years after the last dosing to evaluate long-term safety.

4. SELECTION OF STUDY POPULATION, WITHDRAWAL, COMPLETION, AND STOPPING CRITERIA

4.1. Inclusion Criteria

A subject must meet the following inclusion criteria to be eligible for participation in this study:

1. Must have signed written, informed consent.
2. Males or females, ≥18 years of age.
3. Must have a confirmed diagnosis of active MM as defined by the IMWG criteria at initial diagnosis (Rajkumar, 2014).
4. Must have measurable MM as defined by at least 1 of the following criteria:

   Phase 1:

   - Serum M-protein greater or equal to 0.5 g/dL (5 g/L)
   - Urine M-protein greater or equal to 200 mg/24 h
   - Serum free light chain (FLC) assay: involved FLC level greater or equal to 10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal
   - Bone marrow plasma cells >30% of total bone marrow cells, or other measurable bone disease (e.g., plasmacytomas measurable by PET or CT) (with medical monitor approval)

   Phase 2:

   - Serum M-protein greater or equal to 1.0 g/dL (10 g/L)
   - Urine M-protein greater or equal to 200 mg/24 h
   - Serum FLC assay: involved FLC level greater or equal to 10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal
5. Must have relapsed / refractory MM as defined by the following:

   Phase 1:

   - Received at least 3 prior lines of therapy, which must have contained a proteasome inhibitor and immunomodulatory agent (IMiD)

   OR

   - Received at least 2 prior lines of therapy if "double-refractory" to a proteasome inhibitor and IMiD, defined as progression on or within 60 days of treatment with these agents.

   Phase 2:

   - Received at least 3 prior lines of therapy which must have contained a proteasome inhibitor, an IMiD, and CD38 targeted therapy with at least 2 of the lines in the form of triplet combinations, and undergone ≥2 cycles of each line unless PD was the best response.

   AND

- Refractory to the most recent line of therapy.

AND

- Undergone ASCT or not be a candidate for ASCT.

  Note: induction therapy, autologous stem cell transplant, and maintenance therapy, if given sequentially without intervening progression, should be considered as single line.

6. Must be willing to practice birth control from the time of Screening and for the duration of the study (both males and females of childbearing potential).
   - Females on cohorts R, RP or RIT must commit either to abstain continuously from sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide and 12 months after last dose of rituximab.
   - Males in cohort R or RP must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide and for up to 4 weeks after discontinuing lenalidomide, even if they have undergone a successful vasectomy. Male patients taking lenalidomide must not donate sperm.
7. Must have a negative serum pregnancy test at Screening and a negative urine pregnancy test within 3 days prior to initiating the lymphodepletion chemotherapy regimen (females of childbearing potential).
   - Female subjects in cohort R and RP must have two negative pregnancy tests prior to initiating lenalidomide. The first test should be performed within 10-14 days and the second test within 24 hours prior to subject starting lenalidomide therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles
8. Must be at least 90 days since autologous stem cell transplant, if performed.
9. Must have adequate vital organ function, defined as follows (or medical monitor approval):
   - Serum creatinine ≤2.0 mg/dL and estimated creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault formula and not dialysis-dependent.
   - Absolute neutrophil count ≥1000/μL and platelet count ≥50,000/μL (≥30,000/μL if bone marrow plasma cells are ≥50% of cellularity).

     [redacted]
   - Hemoglobin >8 g/dL (transfusion and/or growth factor support is allowable).
   - Serum glutamic oxaloacetic transaminase (SGOT) ≤3 × the upper limit of normal and total bilirubin ≤2.0 mg/dL (unless there is a molecularly documented history of Gilbert's syndrome).
   - Left ventricular ejection fraction (LVEF) ≥45%. LVEF assessment must have been performed within 4 weeks of enrollment.

10. Must have recovered from toxicities due to prior therapies, with the exception of peripheral neuropathy, to Grade ≤2 according to the NCI CTCAE version 4.03 criteria or to the subject's prior baseline.
11. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

4.2. Exclusion Criteria

1. Is pregnant or lactating
2. Has inadequate venous access and/or contraindications to leukapheresis.
3. Has active hemolytic anemia, plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), disseminated intravascular coagulation, leukostasis, or amyloidosis.
4. Has an active second malignancy (not disease-free for at least 5 years) in addition to MM, excluding low-risk neoplasms such as non-metastatic basal cell or squamous cell skin carcinoma.
5. Has active autoimmune disease, such as psoriasis, multiple sclerosis, lupus, rheumatoid arthritis, etc. (the medical monitor will determine if a disease is active and autoimmune).
6. Has a history of significant central nervous system (CNS) disease, such as stroke, epilepsy, etc. (the medical monitor will determine if significant).
7. Has an active systemic infection (e.g. causing fevers or requiring antimicrobial treatment).
8. Has hepatitis B or C virus, human immunodeficiency virus (HIV) or human T-lymphotropic virus (HTLV) infection, or any immunodeficiency syndrome.
9. Has New York Heart Association (NYHA) Class III or IV heart failure, unstable angina, or a history of myocardial infarction or significant arrhythmia (e.g. atrial fibrillation, sustained [>30 seconds] ventricular tachyarrhythmias, etc.)
10. Has any psychiatric or medical disorder (e.g. cardiovascular, endocrine, renal, gastrointestinal, genitourinary, immunodeficiency or pulmonary disorder not otherwise specified) that would, in the opinion of the Investigator or medical monitor, preclude safe participation in and/or adherence to the protocol (including medical conditions or laboratory findings that indicate a significant probability of not qualifying for or being unable to undergo adequate leukapheresis, conditioning chemotherapy and/or CAR-T cell administration).
11. Has received prior gene therapy or gene-modified cellular immunotherapy (or have approval of the medical monitor). Subject may have received non-gene-modified autologous T-cells or stem cells in association with an anti-myeloma treatment.
12. Has received anti-cancer medications within 2 weeks or 5 half-lives (whichever is longer or have medical monitor approval) of the time of initiating conditioning chemotherapy.

13. Has received immunosuppressive medications within 2 weeks of the time of initiating leukapheresis, and/or expected to require them while on study (the medical monitor will determine if a medication is considered immunosuppressive). Generally, all non-essential medications (including supplements, herbal medications, etc.) should be discontinued from 2 weeks before leukapheresis until 2 months after P-BCMA-101 administration due to the potential for unappreciated immunosuppressive effects.
14. Has received systemic corticosteroid therapy ≥5 mg/day of prednisone or equivalent dose of another corticosteroid within 2 weeks of either the required leukapheresis or 1 week or 5 half-lives (whichever is shorter) of the administration of P-BCMA-101 or is expected to require it during the course of the study. (Topical and inhaled steroids are permitted. Systemic corticosteroids are contraindicated after receiving P-BCMA-101 cells outside of study specific guidance).
15. Has CNS metastases or symptomatic CNS involvement (including leptomeningeal carcinomatosis, cranial neuropathies or mass lesions and spinal cord compression) of their myeloma.
16. Has a history of severe immediate hypersensitivity reaction to any of the agents used in this study.
17. Has a history of having undergone allogeneic stem cell transplantation, or any other allogenic or xenogeneic transplant, or has undergone autologous transplantation within 90 days.
18. Unable to take acetylsalicylic acid (ASA) (325 mg) daily as prophylactic anticoagulation. Patients intolerant to ASA may use warfarin or low molecular weight heparin) (Cohorts R and RP only).
19. History of thromboembolic disease within the past 6 months, regardless of anticoagulation (Cohorts R and RP only).

4.3. Subject Withdrawal

Subjects who are enrolled and do not complete the study protocol will be considered to have prematurely discontinued the study. The reasons for premature discontinuation (for example, voluntary withdrawal, toxicity, death) must be recorded on the case report form. Final study evaluations will be completed at the time of discontinuation. If a subject discontinues from this study, the events for the next visit scheduled should be performed (including all safety and efficacy evaluations) prior to initiating alternative medical, radiation or surgical intervention and recorded as an end-of-study visit for this study. Subjects who withdraw from the protocol after having received P-BCMA-101 will be encouraged to enroll in the companion long-term follow-up protocol P-BCMA-101-002. Potential reasons for premature discontinuation include:

1. The subject is lost to follow-up.
2. The judgment of the Investigator is that the subject is too ill to continue.
3. Subject noncompliance with study therapy and/or clinic appointments.
4. Pregnancy

5. Voluntary withdrawal; a subject may remove himself/herself from the study at any time without prejudice. A subject may withdraw from the study at any time they wish to withdraw consent.
6. Significant progression of malignancy, requiring alternative medical, radiation or surgical intervention. If disease markers decrease from P-BCMA-101 cell activity after reaching progressive disease instead of confirming a prior increase, they should subsequently increase from that level for consideration of progressive disease to discontinue the subject from the protocol unless another systemic myeloma therapy is indicated.
7. Technical difficulties are encountered in the T cell genetic modification and expansion procedure that precludes the generation of clinical cell doses that meet all Quality Control criteria.
8. Termination of the study by the Principal Investigator, the sponsor, the study funder, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or the Food and Drug Administration (FDA).

4.4. Study Termination

The Sponsor may suspend or terminate the study at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure applicable sites, regulatory agencies and IRBs/IECs are notified as appropriate.

If the Investigator stops/terminates the study at their site the Sponsor must be notified. The Sponsor will ensure Regulatory Agencies and IRBs/IECs are notified as appropriate.

The Sponsor will ensure appropriate end of study declarations are made to the relevant Regulatory Agencies/IECs in accordance with local regulations.

5. STUDY TREATMENTS

5.1. Leukapheresis

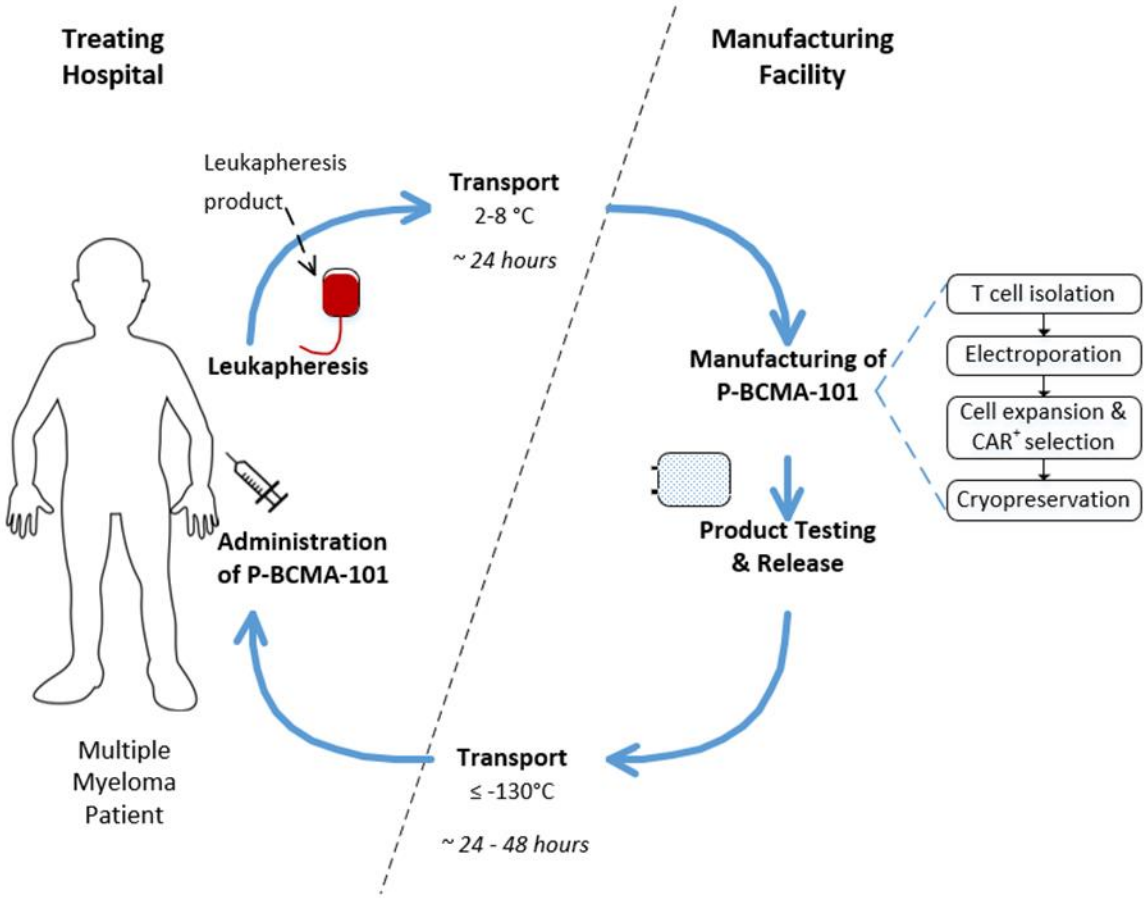
Subjects who complete all screening procedures and meet all eligibility criteria will undergo leukapheresis to harvest peripheral blood mononuclear cells (PBMCs) for the manufacture of P-BCMA-101. This visit should occur within ~28 days of the Screening Visit. Subjects enrolled in the study will undergo standard leukapheresis procedure using Spectra Optia system (Terumo BCT), or equivalent leukapheresis machine, at the enrolling hospital. Immediately following the procedure, leukapheresed cells will be shipped in validated, temperature-controlled conditions to the manufacturing and analytic sites. The intent is to perform a 10-15 liter (minimum and maximum defined by site policies) apheresis and harvest a target [redacted] white blood cells (WBC) (count is also acceptable as total nucleated cells [TNC]). For additional detail, please refer to the Study Reference Manual (Apheresis Center Manual). As it is recognized that volume, cell number and other output parameters reached at the end of apheresis will vary between patients, machines, methods and operators, this is provided as guidance as opposed to absolute requirements.

The manufacturing of P-BCMA-101 is diagramed in Figure 4 below. The collected apheresis products will be transported by courier to the manufacturer for immediate manufacturing. Manufacturing of P-BCMA-101, which includes T cell isolation, electroporation with piggyBac DNA plasmid (P-BCMA-101 plasmid encoding anti-BCMA CARTyrin) and Super piggyBac transposase mRNA (SPB mRNA), CARTyrin^{+} T cell selection, and cell expansion, will be completed [redacted]

Following product release for infusion, frozen P-BCMA-101 product will be shipped by courier to the pharmacy or applicable cell therapy facility of the enrolling study center. P-BCMA-101 will be stored there at ≤-130°C until time of administration.

If P-BCMA-101 cells that meet release criteria cannot be manufactured from the leukapheresis sample, a second leukapheresis and manufacturing may be attempted. If the second attempt also fails, the subject will be withdrawn from the study and considered not to have undergone study treatment. If sufficient P-BCMA-101 cells remain from manufacturing when a subject's disease progresses, with Safety Committee approval additional cells may be administered up to the highest dose level that has successfully completed dose-limiting toxicity assessment.

Figure 4: Clinical Product Manufacturing and Process Diagram



Once the product is manufactured, subjects will return to the clinic for the Conditioning Chemotherapy and P-BCMA-101 Administration Periods approximately 4 weeks (this period may be extended at the discretion of the Investigator and medical monitor) after the Leukapheresis Visit.

Subjects who experience rapid disease progression following the Leukapheresis Visit and prior to admission for the Conditioning Chemotherapy and P-BCMA-101 Administration Period may be administered salvage therapy at the discretion of the Investigator. Salvage therapy should not be used unless necessary and will be determined by the subject's clinical history (previously used agents are preferred, and medical monitor approval needed) at the discretion of the Investigator. If a subject receives salvage therapy, the Conditioning Chemotherapy and P-BCMA-101 Administration Period should be scheduled at least 2 weeks or 5 half-lives after the date of the last treatment of salvage therapy and the subject should meet the criteria described in Section 4 and Section 6 regarding entry criteria and concomitant medications. The subject's response to the salvage therapy will be evaluated by the Investigator and medical monitor in order to determine whether the subject will remain eligible to receive the Investigational Product.

Subjects will be permitted to receive radiation therapy or plasmapheresis and exchange for palliative purposes throughout the study period.

5.2. Conditioning Chemotherapy

Before dosing with the P-BCMA-101 cell infusion, subjects will receive a conditioning lymphodepletion chemotherapy regimen of 300 mg/m^2 of cyclophosphamide and 30 mg/m^2 of fludarabine, with each chemotherapy agent given sequentially IV over 30 minutes daily for 3 consecutive days (Day -5 through Day -3). Subjects should continue to meet entry criteria at the time of initiation of conditioning chemotherapy or have medical monitor approval. For subjects in Cohort R, Cohort RP and Cohort RIT, the combination therapy should be administered prior to conditioning chemotherapy on applicable days. The following assessments should be repeated within 72 hours prior to Day -5: Mini Mental Status Exam (MMSE), physical exam, vital signs, chemistry panel including electrolytes and magnesium, hematology including B and T cell counts, coagulation, assessment of circulating myeloma/plasma cells, and pregnancy test (if applicable). A baseline myeloma response assessment must be conducted within 7 days prior to initiating conditioning chemotherapy. Subjects may be admitted and treated as inpatients at this point at the discretion of the Investigator.

5.3. P-BCMA-101 Administration

5.3.1. Description

P-BCMA-101 is comprised of activated T cells genetically modified through an electroporation-based, non-viral (DNA transposon) gene delivery system called the piggyBac (PB) DNA modification system. The PB DNA modification system efficiently moves DNA from a plasmid to a chromosome via a "cut and paste" mechanism. [redacted]

5.3.2. Product Labeling

Each product bag will be labeled with product name (P-BCMA-101), date of product manufacturing, product lot number, storage conditions, part number, and at least two non-

personal subject identifiers (such as the subject's initials, birth date, and/or study subject identification number). In addition, the product bags will be labeled with the following for caution: "FOR AUTOLOGOUS USE ONLY", "NOT EVALUATED FOR INFECTIOUS SUBSTANCES", and "Caution: New Drug—Limited by Federal law to Investigational Use".

5.3.3. Storage

Upon receipt of the investigational product and any related study treatment supplies, an inventory must be performed, and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff inventories, counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable investigational product study drug in a given shipment will be documented in the study files. The Investigator must notify study sponsor or designee of any damaged or unusable study treatments that were supplied to the Investigator's site. P-BCMA-101 cells may require return to the sponsor or designee for various reasons, including but not limited to: 1) mislabeled product; 2) condition of subject prohibits infusion/injection, and 3) subject refuses infusion/injection. Overall, any unused product will be returned to the sponsor or designee.

Bags containing P-BCMA-101 cells will be stored at the site in blood bank conditions in a monitored ≤-130^{o}C freezer until the subject is ready for infusion.

5.3.4. Preparation

Recommended pre-medications prior to T cell infusion include 650 mg acetaminophen and 25-50 mg diphenhydramine hydrochloride. These medications may be given every 6 hours, as needed. Non-steroidal anti-inflammatory agents may be given for fever not controlled by acetaminophen, however, use should be carefully considered with regards to factors potentially impacting the subject's tolerance, such as bleeding risk and renal function. Evaluation for sepsis should be considered for fever of unexpected severity or duration, or other suggestive symptomology. Systemic corticosteroids should not be administered unless necessitated as described in supportive care guidance (Section 6.3), due to the potential for adverse impact on the efficacy of the T cell-based investigational product.

Subjects should continue to meet liver and renal laboratory entry requirements prior to dosing (i.e. prior to initiating conditioning chemotherapy). Additionally, there should continue to be no evidence of active infection, or significant cardiac (e.g. hypotension requiring pressor or uncontrollable arrhythmia) or pulmonary compromise (e.g. supplemental oxygen requirement or significant progressive infiltrates on chest x-ray).

5.3.5. Dosing and Administration

In Phase 1, dose levels of P-BCMA-101 will be administered intravenously as a single dose or multiple doses. Dose levels will be tested by cohort in the 3+3 escalation design described in the Dose Escalation Guidelines (Section 3.2). In Phase 2, subjects will receive a total dose of 6 to 15 × 10^{6} cells/kg (per the schedule determined in Phase 1).

Cryopreserved P-BCMA-101 is transported to the enrolling study center and stored at ≤-130^{o}C until infusion. If the label on a cryobag received for a subject indicates the contents are more than the assigned dose of P-BCMA-101 cells for the cohort [redacted] only a volume of the

[redacted] Immediately prior to infusion, P-BCMA-101 is thawed and infused as detailed below. No further processing of P-BCMA-101 will be needed prior to infusion. Cells should be logged in the investigational pharmacy or applicable cell therapy facility.

After 2 rest days following the lymphodepletion chemotherapy regimen, subjects will be dosed with P-BCMA-101 administered IV. Subjects may be admitted to the hospital for the P-BCMA-101 administration based on the investigator's assessment. Admission is not required, but subjects should remain within 50 miles of the hospital through approximately 14 days after last dose of P-BCMA-101 and assessed for admission in case of symptoms of CRS or neurotoxicity such as fever. Immediately prior to infusion, P-BCMA-101 cells are transferred at ≤-130ºC (in vapor phase liquid nitrogen) to the subject bedside. The cells will be thawed at the bedside just prior to infusing using a water bath maintained at 36°C to 38°C (thawing at a different location and transporting to bedside at 2-8°C must be pre-approved by the sponsor). The bag will be gently massaged until the cells have just thawed. There should be no frozen clumps left in the container. If the bag appears to be damaged or leaking, or otherwise compromised, it should not be infused, and should be returned to the sponsor or sponsor's designee. The infusion bag label will have at least 2 unique identifiers including the subject's study identification number and initials or birth date. Prior to the infusion, 2 individuals will independently verify all this information in the presence of the subject and so confirm that the information is correctly matched to the participant. Emergency medical equipment (i.e., emergency trolley) will be available during the infusion in case the subject has an allergic response, or severe hypotensive crisis, or any other reaction to the infusion. An intensive care unit should be within a reasonable distance of the study administration site.

The P-BCMA-101 cells will generally be provided in 250 mL infusion bags at a concentration ranging approximately from [redacted], dependent on the dose. They should be administered by intravenous infusion at a flow rate of approximately 1 mL to 20 mL per minute through an 18-gauge latex-free, Y-type blood set with a 3-way stopcock or butterfly needle as appropriate for the dose and volume. The duration of the infusion should be approximately 5-20 minutes, as appropriate for the volume. It is intended P-BCMA-101 cells be infused within 2 hours of thawing, and the maximum stability assessed is 4 hours. For additional detail, see also Study Reference Manual (Pharmacy and Administration Manual).

Vital signs (temperature, respiration rate, pulse, and blood pressure) will be taken before and after infusion, then every 15 minutes for at least one hour and until these signs are satisfactory and stable.

Empty bags and remaining cells should be disposed of per institutional biosafety guidelines. In case of unused or damage product/packaging, the sponsor should be contacted to determine disposition.

Prior studies conducted with other CAR-T therapies have observed peak toxicity to occur within 3-7 days of investigational product administration. Study subjects will be closely monitored during and after the infusion and for approximately 7 days afterwards. This observation period will include serial assessments of AEs, including the emergence of P-BCMA-101-related toxicities, such as CRS for all subjects.

If admitted, subjects will not be discharged until they are assessed as stable by the Investigator. Subjects may be maintained as an inpatient during lymphodepleting chemotherapy or after the above criteria are met as the Investigator deems appropriate. Subjects will return for regular follow up and will undergo serial assessment of safety, tolerability and anti-myeloma response as specified in the Schedule of Events tables.

6. CONCOMITANT MEDICATION AND TREATMENT

6.1. Prohibited Concomitant Medications and Treatments

- May not receive on study or have received anticancer/anti-myeloma medications after P-BCMA-101 administration or within 2 weeks or 5 half-lives (whichever is longer or have medical monitor approval) of the time of initiating leukapheresis or conditioning chemotherapy. Salvage treatment should not be used unless necessary but may be administered between leukapheresis and conditioning chemotherapy if deemed necessary by the Investigator and approved by the medical monitor. The intervals described in the exclusion criteria need to be met for the relevant agents.
- May not have received immunosuppressive medications within 2 weeks or 5 half-lives (whichever is longer) at the time of initiating leukapheresis, and/or is expected to require them while enrolled in the study, or receive them after P-BCMA-101 administration (the medical monitor will determine when and if a potentially immunosuppressive medication is allowed).
- May not have received systemic corticosteroid therapy ≥5 mg/day of prednisone or equivalent dose of another corticosteroid within 2 weeks of either the required leukapheresis or 1 week or 5 half-lives (whichever is shorter) of the administration of P-BCMA-101 or is expected to require it during the course of the study (topical, and inhaled steroids are permitted). Systemic corticosteroids are generally contraindicated after receiving P-BCMA-101 outside of study specific guidance regarding the management of AEs, directed use with combination therapies, or with medical monitor approval.
- May not receive G-CSF or GM-CSF within 2 weeks of the time of initiating leukapheresis, within 5 half-lives before planned administration of P-BCMA-101, or within 2 months after administration of P-BCMA-101 without medical monitor approval.
- Generally, all non-essential medications (including supplements, herbal medications, etc.) should be discontinued from 2 weeks before leukapheresis until 2 months after P-BCMA-101 administration due to the potential for unappreciated immunosuppressive effects.

6.2. Permitted Concomitant Medications and Treatments

Subjects will be permitted to receive radiation therapy or plasmapheresis and exchange for palliative purposes throughout the study period. Other diagnostics or treatments that the Investigator considers necessary for a subject's welfare may be conducted at the discretion of the Investigator in keeping with standards of medical care and in adherence to the protocol.

All prescription and nonprescription medication, vitamins, herbal and nutritional supplements, taken by the subject during the 30 days prior to Screening will be recorded at the Screening Visit. At every visit, concomitant medications will be recorded in the medical record and on the appropriate electronic Case Report Form (eCRF). Any additions, deletions, or changes of these medications will be documented.

6.3. Supportive Care Guidance

Recommended pre-medications prior to P-BCMA-101 infusion include 650 mg acetaminophen and 25 to 50 mg diphenhydramine hydrochloride. These medications may be given every 6 hours as needed. Non-steroidal anti-inflammatory agents may be given for fever not controlled by acetaminophen, however, use should be carefully considered with regards to factors potentially impacting the subjects' tolerance, such as bleeding risk and renal function. Work-up for sepsis should be considered for fever of unexpected severity or duration, or other suggestive symptomology. Systemic corticosteroids should not be administered unless necessitated by a severe or life-threatening AE as described below, due to the known adverse impact on the survival of the T cells and consequent efficacy of the T cell-based investigational product.

The Investigator must use appropriate medical judgment in the management of AEs, including expected events such as those of conditioning chemotherapy, as well as those of CAR-T cell therapies including CRS. CRS is perhaps the most common AE associated with CAR-T cell administration and is characterized by cytokines being released into circulation by active T-cells and the downstream effects on multiple organ systems. CRS has also been seen following the infusion of therapeutic monoclonal antibodies (mAbs), systemic interleukin-2 (IL-2), and the bispecific CD19-CD3 T-cell engaging antibody, blinatumomab. The incidence and severity of CRS has been reported to correlate with disease burden in patients with acute lymphoblastic leukemia. Clinical and laboratory measures range from mild CRS (e.g. constitutional symptoms, high fever) to severe CRS and/or potentially life threatening (e.g. high fever, malaise, fatigue, myalgia, nausea, anorexia, tachycardia/hypotension, hypoxia, capillary leak, cytopenias, cardiac dysfunction, renal impairment, hepatic failure, disseminated intravascular coagulation. Neurologic changes and/or cerebral edema have been associated with the potential for severe or fatal outcomes). The goal of CRS management in CAR-T cell therapy is to prevent life-threatening conditions while preserving the benefits of antitumor effects, thus therapy is generally carefully tailored to symptoms and/or markers of CRS. For example, corticosteroids and other aggressive immunosuppressive agents are effective treatments for CRS, but also frequently toxic the CAR-T cells. Suggested management of CRS is generally per Lee et al. (Lee, 2014) and Brudno et al. (Brudno, 2016). For detailed toxicity management recommendations see the Study Reference Manual (Toxicity Reference Manual). In summary: Symptomatic treatment of grade 1 CRS is suggested. CRS is defined as Grade 2 when the subject develops hypotension responsive to fluids or 1 low-dose vasopressor or mild respiratory symptoms responsive to low flow oxygen (40% FiO2) or Grade 2 organ toxicity. Because hypotension is a major driver of severity grading, it is imperative that a clear baseline blood pressure be established prior to initiation of therapy. The decision to intervene with immunosuppressive agents (tocilizumab +/- corticosteroids) for subjects with Grade 2 CRS is influenced by the degree to which the subject is judged to be able to tolerate the altered hemodynamics and organ stresses associated with the syndrome. In older subjects and subjects with significant comorbidities, depending on clinical judgment, it may be appropriate to intervene with immunosuppression in subjects with Grade 2 CRS. Subjects in whom fluid therapy and 1 low-dose vasopressor are not sufficient to reverse hypotension are classified as severe or Grade 3 CRS. Similarly, subjects who require more than low flow oxygen or show evidence for Grade 3 organ toxicity, including but not limited to coagulopathy, renal, or cardiac dysfunction, should be considered Grade 3. Subjects with Grade 3 CRS need to be monitored

very closely, likely in an intensive care unit with 1:1 nursing care. Importantly, in subjects with Grade 2 or higher CRS, careful attention should be paid to cardiac function, as cardiac decompensation may occur and may not be readily evident without careful monitoring. Frequent echocardiographic monitoring may be indicated in subjects in whom there is a concern of cardiac dysfunction. Subjects with Grade 3 CRS should be treated with immunosuppressive agents such as tocilizumab and corticosteroids (e.g. 10 mg dexamethasone IV every 6 hours) because of the risk for progression and the potential for irreversible organ dysfunction, with the goal of preventing progression to Grade 4. Grade 4 CRS occurs when subjects experience toxicity that is immediately life threatening, including a need for mechanical ventilation or Grade 4 organ toxicity. It is recommended that all subjects with Grade 4 CRS be treated with immunosuppressive and/or cytotoxic agents such as tocilizumab (typically 8 mg/kg daily for 1 to 2 days), corticosteroids (e.g. methylprednisolone 1g daily for 3 days), rimiducid (typically 0.4 mg/kg) and/or an aggressive immunosuppressive/cytotoxic agent such as cyclophosphamide (e.g. 1.5 g/m^2) (generally use of rimiducid would be prioritized over use of a systemically toxic cytotoxic agent) in an attempt to suppress the inflammatory cascade and to prevent irreversible organ dysfunction. These options may also be considered for Grade 3 toxicity unresponsive to other measures.

When indicated, tocilizumab is typically administered intravenously over 1 hour at a dose of 8 mg/kg, with an option to repeat the dose if clinical improvement does not occur within 24 to 48 hours. In subjects with CRS who respond to tocilizumab, fever and hypotension often resolve within a few hours, and pressors and other supportive care measures can potentially be weaned quickly thereafter. In some cases, however, symptoms may not completely resolve, and continued aggressive support may be necessary for several days.

If a subject develops uncontrollable P-BCMA-101 T cell expansion or other clinically significant Grade 3-4 toxicities possibly related to P-BCMA-101, it is recommended the Investigator review the clinical scenario and potential confounding factors, and consider treating with immunosuppressive and/or cytotoxic agents, such as corticosteroids (e.g. methylprednisolone 1g daily for 3 days), rimiducid (typically 0.4 mg/kg) and/or an aggressive immunosuppressive/cytotoxic agent such as cyclophosphamide (e.g. 1.5 g/m^2).

7. SCHEDULE OF ASSESSMENTS AND PROCEDURES

7.1. Schedule of Procedures

The Schedule of Procedures for this study will be the same for subjects in single administration, and is provided in Table 2 for procedures from Screening through conditioning chemotherapy and Table 3 for procedures from P-BCMA-101 administration through follow-up. The Schedule of Procedures tables for cycle administration cohorts are provided in Section 15.5. The Schedule of Procedures tables for combination administration are provided in Section 15.6. Following obtaining consent, screening and confirmation of eligibility, all subjects will undergo leukapheresis, conditioning chemotherapy, and P-BCMA-101 administration as described in Section 5.3. Subjects will return for regular follow up and will undergo serial assessment of safety, tolerability and anti-myeloma response as specified in each respective Schedule of Events table. Post-treatment follow-up visits will occur at Day 10, Weeks 2, 3, 4, 6, 8, Months 3, 4, 5, 6, 7, 8, 9, 12, 15, 18, 21, and 24.

7.2. Clinical Assessments

Clinical assessments and procedures to be performed throughout the study are outlined in the Schedule of Events tables. Assessment timing windows not described in these tables may be found in the Study Reference Manual.

7.2.1. Medical History

General medical history and demographics will be recorded at Screening, as well as any baseline symptoms or medical conditions that would be considered AEs on study. MM disease history, including results of MM assessments obtained in the 6 months prior to Screening, as described in Inclusion Criterion #4, will also be obtained. Myeloma response will be collected as described in Section 7.2.10.

7.2.2. Physical and Neurological Examination

A complete physical examination, including a neurological examination, will be performed at Screening; within 72 hours prior to start of conditioning chemotherapy; on Day -5, on Day 0 before and approximately 1 hour after P-BCMA-101 administration; on Days 1, 4, 7, 10; Weeks 2, 3, 4, 6, and 8, and starting at Month 3 every 3 months for 24 months. After administration of P-BCMA-101, physical examination, including a neurological examination (or any other assessments deemed appropriate by the Investigator) should be repeated as often as clinically indicated by the AEs observed or by the institution's standards, but at minimum once per study visit.

7.2.3. Vital Signs

Vital signs, including blood pressure, heart rate, respiration rate, O_2 saturation and temperature will be obtained at visits as outlined in the Schedule of Events tables. On Day 0, vital signs (temperature, respiration rate, heart rate, O_2 saturation and blood pressure) will be taken before and approximately one hour after P-BCMA-101 administration, then every 15 minutes (+/- 5 minutes) for at least one hour and until these signs are satisfactory and stable. Weight will be obtained at Screening, Enrollment and Leukapheresis. Height will be recorded only at Screening.

7.2.4. Performance Status

ECOG performance status will be assessed at Screening and Day -5 using the ECOG performance scale described in Appendix 15.1.

7.2.5. Clinical Safety Assessments

Subjects will be assessed for AEs throughout the study. AEs will be graded by the NCI CTCAE Version 4.03 criteria. Details on assessment and reporting of AEs and SAEs are provided in Section 8.

7.2.6. Cardiac Assessments

A 12-lead electrocardiogram (ECG) will be obtained at Screening, Days 0 (before and approximately 1 hour after P-BCMA-101 administration), 1, 4, 7, Week 4, and starting at Month 3 every 3 months for 24 months. Echocardiogram will be obtained at Screening only.

7.2.7. Laboratory Assessments

7.2.7.1. Clinical Chemistry and Hematology

Clinical chemistry and hematology laboratory evaluations will be performed as outlined in the Schedule of Events tables (Chemistry Panel, Hematology including B and T cells, Coagulation).

The chemistry panel will include sodium, potassium, chloride, magnesium, bicarbonate, blood urea nitrogen, creatinine, calcium, albumin, glucose, lactate dehydrogenase (LDH), total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST)/ Serum glutamic oxaloacetic transaminase (SGOT), bilirubin (total and direct), and alkaline phosphatase. Coagulation evaluations will include PTT (partial thromboplastin time) and PT (prothrombin time) or international normalized ratio (INR). Assessments for tumor lysis (uric acid and phosphate) will be performed at baseline and Days 1, 4, 7, then as clinically indicated.

On Day 0, chemistry panel, hematology including B and T cells, and coagulation evaluations should be obtained before and approximately 1 hour after P-BCMA-101 administration. After administration of P-BCMA-101, these (or any other assessments deemed appropriate by the Investigator) should be repeated as often as clinically indicated by the AEs observed or by the institution's standards, but at minimum once daily on Days 1, 4, 7 and 10 and as outlined in the Schedule of Events tables.

Hematology laboratory evaluation will include complete blood count, platelets, B (CD19) and T (CD3) cell counts and CD4 and CD8 (at all timepoints except Days -3 and -4), and assessment of circulating myeloma/plasma cells (e.g., by flow cytometry or CBC with manual differential) is required at timepoints prior to P-BCMA-101 administration. Contact the sponsor and refer to exclusion criteria #3 and #10 if circulating myeloma/plasma cells are identified in the Enrollment & Baseline sample.

7.2.7.2. Pregnancy Testing

Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test within 72 hours prior to initiating the conditioning

chemotherapy. Urine pregnancy tests will be performed prior to each dose of P-BCMA-101 and at subsequent post-treatment visits starting at Week 2.

Female subjects in cohort R and RP must have two negative pregnancy tests prior to initiating lenalidomide. The first test should be performed within 10-14 days and the second test within 24 hours prior to subject starting lenalidomide therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles.

7.2.7.3. Infectious Disease Screening

Laboratory test will be performed at Screening for the presence of HIV 1 and 2 antibody, hepatitis B surface antigen, hepatitis C antibody, and HTLV.

7.2.8. Cytokine Release Syndrome

Blood samples for detection of CRS markers: [redacted] will be obtained as indicated in the Schedule of Events tables.

7.2.9. Mini Mental Status Exam

Mini Mental Status Exam (MMSE) will be performed as indicated in the Schedule of Events tables. The MMSE should include a sample of the subject's handwriting at all timepoints.

7.2.10. Disease Response Assessments

7.2.10.1. PET-CT Assessment

Assessment of disease by PET-CT scan will be performed at the Baseline visit within 7 days prior to initiating conditioning chemotherapy, then as clinically indicated (e.g. every 8 weeks if soft tissue plasmacytomas are found at baseline that require imaging as part of response assessments or to confirm response).

7.2.10.2. Response and Response Rates

Laboratory samples for evaluation of myeloma response will be drawn at Screening, Baseline visit within 7 days of initiating conditioning chemotherapy, Day 0 (before P-BCMA-101 administration), Weeks 2, 3, 4, 6, 8, Months 3, 4, 5, 6, 7, 8, 9, 12, 15, 18, 21, and 24.

Myeloma response will be assessed per the International Myeloma Working Group criteria and based on the standard assessments, as clinically indicated (e.g., $\leq$1 week after an assessment demonstrating a response for confirmation), for each subject, such as serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), serum immunofixation (SIFE), urine immunofixation (UIFE), serum free light chains (FLC), PET/CT (Positron Emission Tomography / Computed Tomography, liver background) and/or bone marrow biopsy/aspirate. A baseline myeloma response assessment must be done within 7 days prior to initiating conditioning chemotherapy. Fresh bone marrow biopsy and aspirate must be collected at either screening or baseline (typically within 7 days of initiating conditioning chemotherapy) and at Week 4, Months 3, 6 and 12, then as clinically indicated, or have a medical monitor exemption.

Response rate will be determined as the number of subjects in each best overall response category divided by the number of subjects in the study population.

7.2.10.3. Time to Response

For subjects with a response, the time to response will be assessed from time of P-BCMA-101 administration to time of first documented response (partial response [PR] or better).

7.2.10.4. Duration of Response

For subjects with a response, the duration of response will be assessed from time of first documented response (PR or better) to time of confirmed disease progression (deaths from other causes will be censored).

7.2.10.5. Progression Free Survival

Progression Free Survival (PFS) from time of P-BCMA-101 administration to time of confirmed disease progression or death will be assessed for all subjects.

7.2.10.6. Overall Survival

Overall survival (OS) from time of P-BCMA-101 administration to time of death will be assessed for all subjects.

7.2.11. Long-Term Follow-up

All subjects treated with P-BCMA-101 in this study will be followed for up to 2 years in this study. After they discontinue this protocol, consenting subjects will roll over into a separate long-term safety follow-up protocol (P-BCMA-101-002) and be followed for a total of 15 years post-last dosing with P-BCMA-101.

8. RECORDING ADVERSE EVENTS

The Principal Investigators are responsible for detecting, documenting, and reporting events that meet the definition of an AE or a serious adverse event (SAE). Individual AEs should be evaluated by the Investigator and reported to the Sponsor via the eCRF. This includes the evaluation of the intensity, the causality between the investigational product and/or concomitant therapy and the AE, seriousness, etc.

8.1. Time Period for Collecting AE and SAE Information

All AEs and SAEs will be collected from enrollment until the Month 24 visit, or withdrawal from the protocol, whichever is shorter.

8.2. Definition of Adverse Event

In accordance with the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a subject or clinical investigation subject who receives a pharmaceutical product. The event does not necessarily have a causal relationship with study treatment to be an AE. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Preexisting conditions should only be reported as AEs if they worsen during the study. Progression of the cancer under study and symptoms thereof are not considered an AE unless it is considered to be drug related by the Investigator. New abnormal laboratory findings should only be considered AEs if they necessitate treatment or are considered clinically significant by the Investigator.

AEs should be recorded in the eCRF using a diagnosis or possible diagnosis, and rated for intensity, causality, and seriousness. In the absence of a diagnosis, individual symptoms or findings may be recorded and the eCRF updated to reflect a final diagnosis once additional information becomes available.

All AEs should be followed until:

- Resolved or improved to baseline.
- Investigator confirms no further improvement can be expected.

On completion or discontinuation from the study, AEs will be followed for 30 days or until one of the above criteria is met. Ongoing AEs will continue to be recorded and monitored into the long-term follow up study.

8.2.1. Assessment of Intensity

Adverse events will be graded according to the NCI CTCAE version 4.03. The Investigator will assess intensity of all AEs using this five-point scale (Grade 1-5) and record on the eCRF.

AEs not specifically listed on the NCI CTCAE should be graded according to Table 5:

Table 5: Grading of AEs Not Specified in NCI CTCAE version 4.03

NCI CTCAE Grade	Equivalent to	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity.
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; minimal medical intervention is indicated.
Grade 3	Severe	Incapacitating with inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk.
Grade 4	Life-threatening/ disabling	An immediate threat to life that requires urgent medical intervention.
Grade 5	Death	AE resulting in death.

8.2.2. Assessment of Causality

The Investigator will assess the causal relationship between the AE and investigational product (P-BCMA-101 and/or rimiducid, if administered) according to his/her best clinical judgement. An assessment of possibly/probably/definitely related is meant to convey there is evidence of a causal relationship, not that a relationship cannot be ruled out. The Investigator should consider alternative causes such as natural history of the underlying disease, lymphodepleting chemotherapy, concomitant medications, and other risk factors when making an assessment. The following scale will be used as guidance:

- **Not related** – The subject did not receive the investigational product; the temporal sequence of the AE onset relative to administration of the investigational product is not reasonable; or there is another highly likely cause of the AE.
- **Unlikely related** – The AE is not reasonably, temporally correlated with T-cell infusion; the AE is more likely explained by another cause or causes, but a theoretical impact of T cell infusion on the onset or severity of the event is remotely possible in a multi-factorial context
- **Possibly related** – There is evidence of exposure to the investigational product; the temporal sequence of the AE onset relative to T cell infusion is plausible; there is a reasonable explanation for the investigational product to have elicited the AE; and the investigational product is equally likely to have caused the AE as other explanations.
- **Probably related** – There is evidence of exposure to the investigational product; the temporal sequence of the AE onset relative to T cell infusion is plausible; the AE shows a pattern consistent with previous knowledge of the investigational product; or the AE is more likely explained by the investigational product than any other cause.

- **Definitely related** – There is evidence of exposure to the investigational product; the temporal sequence of the AE onset relative to T cell infusion is plausible; the AE shows a pattern consistent with previous knowledge of the investigational product, or the AE is most likely explained by the investigational product and any other cause is improbable.

The Investigator may change his/her opinion of causality if additional information is received and amend the AE eCRF accordingly. The Investigator causality assessment is one of the criteria the sponsor will use to determine regulatory reporting requirements for an SAE.

8.3. Reporting Serious Adverse Events (SAEs)

An SAE is any AE that:

- Results in death (NOTE: death should be recorded as the outcome, and initiating event leading to death as the event).
- Is life-threatening (NOTE: the term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- Requires hospitalization or prolongation of existing hospitalization, except for elective or diagnostic procedures associated with pre-existing conditions that have not worsened, including the disease under study (e.g. study specified procedures and hospitalization).
- Results in a persistent or significant incapacity.
- Is a congenital anomaly/birth defect.
- Is medically significant or requires intervention to prevent one or the outcomes listed above.

Medical and scientific judgment should be exercised in deciding if an AE is of significant enough medical importance to be classified as serious outside the above definitions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 and FDA Safety Reporting Requirements for INDs, 21 CFR 312.32.

8.4. Adverse Events of Special Interest (AESI)

AESIs are events that are of special interest with regards to CAR-T cell products and therefore have unique reporting requirements as described in Section 8.5.

AESI for P-BCMA-101 currently include:

1. Any death, regardless of attribution, that occurs within 30 days of the infusion of P-BCMA-101.
2. Grade 4 or greater product infusion reactions.
3. Grade 4 or greater cytokine release syndrome.
4. Grade 4 or greater neurologic toxicity.
5. New malignancies.
6. New incidence or exacerbation of a pre-existing neurological disorder.
7. New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder.
8. New incidence of hematologic disorder.

8.5. Regulatory Reporting Requirements for SAEs and AESIs

An SAE/ AESI must be reported to the Sponsor or designee by emailing or faxing a completed SAE/ AESI Report form within 24 hours of the study personnel's discovery of the event. The SAE/ AESI Report form will be the primary source of data for safety reporting. Reporting procedures are described in the Study Reference Manual. Shortly following the submission of the SAE/ AESI Report form, an eCRF entry within Medidata will be required for each event term. Data fields must match those reported on the SAE/AESI Report form.

8.6. Pregnancy

As described in the entry criteria, subjects must practice birth control from the time of Screening and throughout the study (both males and females of childbearing potential).

Females on cohorts R, RP or RIT must commit either to abstain continuously from sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide and 12 months after last dose of rituximab.

Lenalidomide can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy based on the mechanism of action and findings. Lenalidomide is present in the semen of patients receiving the drug. Therefore, males in cohort R or RP must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide and for up to 4 weeks after discontinuing lenalidomide, even if they have undergone a successful vasectomy. Male patients taking lenalidomide must not donate sperm.

There is no preclinical or clinical trial data of P-BCMA-101 or rimiducid in pregnant women; however, this overall treatment regimen could theoretically be embryotoxic. The effects on breast milk are unknown, therefore, breastfeeding should be discontinued for the duration of the study starting at Screening and for at least 12 months after receiving the last dose of investigational product (P-BCMA-101 or rimiducid, lenalidomide or rituximab), or four months after there is no evidence of persistence/gene modified cells in the subject's blood, whichever is longer.

Pregnancy (or pregnancy of a male subject's partner) is not considered an AE/SAE unless there is reason to believe the pregnancy may be the result of failure of a contraceptive due to interaction with the investigational product, or there is an adverse fetal outcome in the pregnancy. However, the Investigator shall report all pregnancies immediately to the Sponsor. A woman who becomes and remains pregnant during the study will be discontinued from the study and would enter into the LTFU study. The outcome of the pregnancy must also be reported to the Sponsor.

9. SAFETY MONITORING

9.1. Safety Committee

A Safety Committee comprised of the Investigators and a clinical representative of the sponsor will be established and will review data regularly for all subjects and following each cohort to determine dose escalation. The Safety Committee may recommend expansion of a cohort to further evaluate safety and, if DLT is observed in the first cohort, exploration of a lower dose during Phase 1 and continue to manage safety, stopping and pausing criteria during Phase 2.

9.2. Criteria for Pausing Dosing or Stopping the Study

If a study-defined DLT or any treatment-related death occurs, dosing of new subjects will be paused until the Safety Committee meets, reviews the event(s) and determines forward plans, which might include stopping the study, reducing subsequent dose levels, instituting additional safety procedures or a study amendment, continuing the study as planned or other measures as appropriate to the event. As previously described, if 2 or more of 6 subjects have DLTs in a cohort during Phase 1, and a ≥10% incidence of ≥Grade 4 or ≥30% incidence of ≥Grade 3 CRS or neurotoxicity at or below a corresponding dose level in Phase 2 with >10 patients treated, that dose level will have exceeded the MTD and any further dosing would take place at a lower dose level.

10. STATISTICAL AND DATA ANALYSIS

Phase 1 of this study is a standard 3 + 3 design of dose cohorts intended to determine a dose below which a 33% incidence of DLTs occurs.

Phase 2 of this study is an open-label, single dose, efficacy and safety evaluation. Details of the analyses for all endpoints will be provided in the Statistical Analysis Plan (SAP).

10.1. Study Populations

The Intent-to-Treat (ITT) population will include all subjects enrolled into the study.

The Safety population will include all subjects who receive P-BCMA-101 administration.

The Per Protocol population will include all subjects who receive the protocol directed dose of P-BCMA-101 (e.g., patients who receive less than the protocol directed dose would be analyzed as a separate subgroup).

10.2. Sample Size Calculation

The Phase 1 part of the study is a standard 3+3 design of dose cohorts intended to determine a dose below which a 33% incidence of DLTs occurs. Thus, up to 120 subjects may be enrolled to include the possibility of 18 cohorts of 6 subjects during dose escalation, cycle administration and combination administration as well as subjects who might be enrolled to replace those who discontinue prior to completion of the DLT evaluation period or further assess findings in a cohort.

For the Phase 2 part of the study, response rate endpoints will be tested to exclude a response rate of ≤30% as obtained with the recently approved standard of care agent daratumumab at $p<0.05$. With a 100-subject sample, the Phase 2 part of the study will have 90% power to detect a 15-percentage point improvement over a 30% response rate. This power calculation is based on an exact test for a binomial proportion with a 1-sided 0.05 significance level.

10.3. Statistical Methods

The demographic and baseline characteristics, safety, and efficacy data will be summarized using appropriate descriptive statistics. Data analyses will be provided by dose cohort, as well as for all subjects combined where appropriate. Descriptive statistics, including means, medians, standard deviations and ranges will be calculated for continuous variables, and categorical data will be summarized using counts and percentages. For response rate endpoints, point estimates and two-sided exact binomial 95% confidence intervals will be computed. Time-to-event variables will be summarized using the Kaplan-Meier method.

Treatment-emergent AEs (TEAEs) will be summarized using counts and percentages of subjects by cohort and for all subjects combined. TEAEs will also be summarized by severity and relationship. Concomitant medications will be summarized using counts and percentages of subjects by dose cohort.

Vital signs, ECG measurements and laboratory results will be summarized using descriptive statistics for observed values and change from baseline values by cohort. Laboratory results will also be summarized relative to the normal range (below, within, or above) by cohort.

Response rates will be determined by comparing each subject's best response after P-BCMA-101 administration to the corresponding baseline values per the International Myeloma Working Group Uniform Response Criteria (Appendix 15.2) (Rajkumar, 2011; Kumar, 2016; Cavo, 2017). The overall response rate (ORR) will be determined from subjects having received P-BCMA-101 and attaining a PR, very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), over all subjects having received P-BCMA-101. The response rate for each individual response category will also be determined. Likewise, rates of stable disease (SD) at 8 weeks, and minimal response (MR) will also be determined. Time to response and duration of response will be determined for subjects who have response. OS, and PFS will also be determined for all subjects per the International Myeloma Working Group criteria.

A futility analysis will be conducted once 35 subjects are enrolled, received P-BCMA-101, and followed up for 4 months or progressed prior to 4-month follow-up. This analysis set is called Futility Analysis Set (FAS). The futility analysis will use Futility Index (FI) which is equal to 1 minus the Conditional Power (CP) based on the observed proportion of BOR in FAS. The study may be stopped if FI is above 0.80 (that is, if CP falls below 0.20).

Subjects who receive additional infusions of P-BCMA-101 T cells will be analyzed as separate subgroups for all outcomes.

11. DATA HANDLING AND RECORD KEEPING

11.1. Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and any other applicable laws, regulation, and guidelines. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

11.2. Data Management

An EDC system will be used to collect data pertaining to this trial. Trial data will be captured through an eCRF. Within the EDC system the eCRF data will be entered by the site staff and all source document verification and data cleaning will be performed by the Sponsor or designee (e.g. Contract Research Organization [CRO]).

The specifications for the EDC system will be documented and approved before the EDC system is released for live use. The validation of the eCRF data will be defined in a Data Management Plan. As data are entered into the eCRF, the validation checks will be performed, and where necessary, queries will be raised. All queries raised will be held in the EDC database.

The EDC system is a validated software program that has been designed to comply with CFR21 Part 11 requirements. All users will access the system via unique username and password. A full audit history of all actions performed within the system is maintained. User accounts ensure that each user can only perform the tasks applicable to their role and only have access to the data applicable to their role.

Standard coding dictionaries, World Health Organization (WHO) Drug and Medical Dictionary for Regulatory Activities (MedDRA) will be used to code medications, AEs and medical history.

When all data have been entered and all data cleaning is complete the data will be locked and made available for analysis and reporting.

On completion of the study, all eCRF data, including all associated queries and audit history, will be made available on a CD or USB drive to both the study Sponsor and the sites.

11.3. Source Documents

Source data is all information, original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial, etc.

The Investigator must ensure the availability of source documents from which the information on the eCRF was derived.

The Investigator must permit authorized representatives of the Sponsor, the respective national, local or foreign regulatory authorities, the IRB/IEC and auditors to inspect facilities and to have direct access to the Investigator Site File and all source documents relevant to this study regardless of the type of media.

11.4. Case Report Forms

For each subject enrolled, the completed eCRF must be reviewed and signed by the Principal Investigator or authorized delegate. If a subject withdraws from the study, the reason must be noted on the eCRF.

The Investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

11.5. Records Retention

It is the Investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

12. STUDY MONITORING, AUDITING, AND INSPECTING

12.1. Study Monitoring Plan

This study will be monitored according to a written monitoring plan. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.) and has adequate space to conduct the monitoring visit.

12.2. Audits and Inspections

The Investigator will permit study-related monitoring, audits, and inspections by the IRB/IEC, the sponsor, government regulatory bodies, and university compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable university compliance and quality assurance offices.

13. REGULATORY AND ETHICAL CONSIDERATIONS

13.1. Institutional Review Board/Independent Ethics Committees

The final study protocol and subject informed consent documentation will be approved by the IRB/IEC and any other site-level committee deemed appropriate by the Institution. Approval from each applicable committee will be received in writing before initiation of the study.

Protocol amendments must also be approved by the IRB/IEC (and other committees, as applicable) before implementation, except in the case of changes made to protect subjects from immediate hazard, which may be implemented immediately.

13.2. Ethical Considerations

The Investigator will ensure this study is conducted in full compliance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the subject. The study must fully adhere to the principles outlined in the current ICH "Guideline for Good Clinical Practice" or with local law if it affords greater protection to the subject.

13.3. Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study subjects prior to any study-related procedures being performed. All consent documentation must be in accordance with applicable regulations and ICH GCP. Documentation must include the dated signature of both the subject (or the subject's legally authorized representative as applicable) and the person conducting the consent discussion. If the subject is illiterate, an

impartial witness should be present during the consent discussion, and the consent signed and dated by the witness, the subject, and the person conducting the consent discussion. The consent form should be translated and communicated to the subject in a language that is understandable to the subject. Certified translations of the informed consent documentation will be provided as applicable.

A copy of the signed and dated informed consent should be provided to the subject before participation in the study.

Tests performed as standard-of-care prior to documentation of consent may be used for screening results as appropriate.

13.4. Protocol Adherence

The Investigator must sign the protocol to confirm acceptance and willingness to comply with the study protocol.

The Investigator or designee will not deviate from the protocol unless necessary to eliminate an apparent immediate hazard to the safety, rights or welfare of any study subject. In the event of a protocol deviation for any reason, the Investigator will promptly report the deviation to the Sponsor or designee via the eCRF.

13.5. Public Posting of Study Information

The Sponsor is responsible for posting appropriate study information on applicable clinical study registry websites. Information included in clinical study registries may include participating Investigator's names and contact information.

13.6. Clinical Study Report

The results of the study will be presented in an integrated Clinical Study Report (CSR) according to ICH guideline E3: Structure and Content of Clinical Study Reports.

13.7. Publication Policy

The Investigator may not submit the results of the study for publication or present the results of the study without the prior written agreement of the Sponsor in accordance with the Clinical Trial Agreement. Interim publications of data from the study may be made if mutually agreed between the Sponsor and the Investigators. Agreement will not be provided by the Sponsor where in the Sponsor's view interim publications would introduce bias or lead to any misrepresentation or inaccuracies in data.

Authorship will be determined in conformance with the International Committee of Medical Journal Editors (ICMJE) guidelines and/or publication guidelines if applicable.

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15. APPENDICES

15.1. ECOG Performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease 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 house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

15.2. IMWG Uniform Response Criteria

IMWG uniform response criteria by response subcategory for multiple myeloma (Kumar, 2016**)*‖**

CR	Stringent complete response (sCR)	VGPR	PR	Minimal Response (MR)	SD	PD¶¶,‖‖
Negative immunofixation of serum and urine, *and*	CR as defined, *plus*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or*	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours	≥ 25% but ≤ 49% reduction of serum M protein or urine M-protein by 50%-89%	Not meeting criteria for CR, VGPR, PR, MR or PD	Increase of 25% from lowest confirmed response value in any of the following:
Disappearance of any soft tissue plasmacytomas, *and*	Normal FLC ratio** *and*	≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 h	If the serum and urine M-protein are unmeasurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria	In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required		Serum M-protein (absolute increase must be ≥ 0.5 g/dL), *and/or* Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL
< 5% PCs in bone marrow aspirates	Absence of clonal PCs in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells) ††		If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30%			Urine M-protein (absolute increase must be ≥ 200 mg/24 h), *and/or*

CR	Stringent complete response (sCR)	VGPR	PR	Minimal Response (MR)	SD	PD¶¶,‖‖
			In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required			Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
						Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%)

CR	Stringent complete response (sCR)	VGPR	PR	Minimal Response (MR)	SD	PD¶¶,||||
						Appearance of a 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 of 200 cells per μL) if this is the only measure of disease

IMWG=International Myeloma Working Group. MRD=minimal residual disease. FLC=free light chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. SUV_{max}=maximum standardised uptake value. ^{18}F-FDG PET=^{18}F-fluorodeoxyglucose PET. *All response categories require two consecutive assessments made any time before starting any new therapy. ||Derived from international uniform response criteria for multiple myeloma (see Durie *et al.*, *Leukemia* 2006; 20: 1467-73). When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response. **All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK). ††Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2. §§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, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD. ¶¶Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival. ||||In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

15.3. Rimiducid

15.3.1. Introduction

Rimiducid (a.k.a. AP1903) (See also Rimiducid Investigator's Brochure) is an investigational small molecule drug that has been previously evaluated in Phase 1 human studies as the activation agent for cell therapies transduced with an inducible caspase 9 (iCasp9) safety switch gene. Rimiducid is a member of a class of compounds termed dimerizer drugs that act by inducing clustering of engineered proteins inside cells. Rimiducid-inducible cell death is achieved by expressing a chimeric protein comprising a human FK506-binding protein 12 (FKBP12) domain linked via a flexible linker to human delta caspase-9. Rimiducid is a cell-permeable synthetic ligand that binds to an engineered high-affinity version of FKBP12 that interacts minimally with endogenous FKBP. This chimeric protein is quiescent inside cells until administration of rimiducid, which cross-links the FKBP12 domains, initiating dimerization of the modified caspase-9 molecule, and results in cell apoptosis (Zhou, 2015a). A single intravenous infusion of rimiducid triggers apoptosis and eventual cell death in cells expressing the iCasp9 gene but does not affect non-transduced cells and has no therapeutic benefit on its own. [redacted] P-BCMA-101 is a proprietary CAR-T product that consists of autologous T-cells that have been genetically altered to target and eliminate myeloma cancer cells expressing BCMA, and these T cells also carry an iCasp9-based safety switch gene. Rimiducid is administered as a single intravenous dose of 0.4 mg/kg. Rimiducid drug product is supplied as a sterile solution for injection that contains 40 mg of rimiducid in 8 mL of solution (5 mg/mL) and is then further diluted in 0.9% normal sterile saline for injection prior to infusion administration.

Nonclinical studies with rimiducid demonstrated that primary human T lymphocytes transduced with the rimiducid-based safety switch; (1) retain their function, and (2) can be eliminated by exposure to rimiducid with high efficiency, potency, and specificity (Thomis, 2001). [redacted]

Rimiducid has previously been evaluated in phase 1 clinical studies, including healthy volunteers, and for Graft versus Host Disease (GVHD) in transplant patients treated with other genetically modified T cell products carrying an iCasp9-based safety switch gene, which support the potential for clinical use of rimiducid in conjunction with P-BCMA-101. In clinical studies published to date with rimiducid, there were no significant adverse events and no clinically significant changes in vital signs, ECGs, serum biochemistry, hematology, coagulation parameters, or urinalysis results. In subjects who developed GVHD and received 0.4 mg/kg of rimiducid as a 2-hour infusion, 90% of the modified T cells were eliminated within 30 minutes following rimiducid infusion, with a further log depletion during the next 24 hours. GVHD

completely resolved in these patients without recurrence (Zhou, 2015b; Iuliucci, 2001; Di Stasi, 2011; Kapoor, 2016; Zhou, 2016).

[redacted]

15.3.2. Investigational Use

Rimiducid may be used for subjects that experience significant adverse reactions to P-BCMA-101 as described in Section 6.3 and the Study Reference Manual (Toxicity Reference Manual). Generally, subjects with Grade 4 CRS may be treated with rimiducid in addition to other standard measures (e.g. tocilizumab, steroids and/or cytotoxic/immunosuppressive agents) (generally, use of rimiducid would be prioritized over use of a systemically toxic cytotoxic agent). This option may also be considered for Grade 3 toxicity unresponsive to other measures. Rimiducid use would also be considered in addition to other standard measures if subject develops uncontrollable P-BCMA-101 T cell expansion or other clinically significant Grade 3-4 toxicities possibly related to P-BCMA-101. It is recommended the Investigator review the clinical scenario and potential confounding factors before administration. The study medical monitor should be consulted if time permits and a rimiducid use form completed. There are no absolute predefined inclusion or exclusion criteria.

15.3.3. Study Treatments

15.3.3.1. Rimiducid Administration

15.3.3.1.1. Description

The dosage form for the rimiducid drug product is a sterile solution for injection. The drug product contains 40 mg of rimiducid and is intended to be further diluted in 0.9% normal sterile saline for injection prior to administration by intravenous infusion.

The sterile rimiducid solution, 5 mg/mL, is provided as an 8 ml fill in a Type 1 glass 10 mL vial, with a gray butyl stopper and aluminum overseal. The quantitative composition of rimiducid injection, 5 mg/mL is provided in Table 6.

Table 6: Qualitative and Quantitative Composition of Rimiducid Drug Product

Component	Quality Reference	Function	Quantity/Unit Dose (mg/vial)
Rimiducid	In-house	Active Ingredient	40.0[a]
Polyoxyl 15 hydroxystearate[b]	USP	Surfactant	2000
Water for Injection	USP	Diluent	QS to 8 mL

a. The actual quantity will be adjusted based on the purity of the drug substance.
b. Also referred to as Kollilphor^{R} HS 15 or solutol HS 15.

15.3.3.1.2. Supply and Storage

The drug product should be stored refrigerated at 2-8°C. Prior to dilution and administration, the drug product should be brought to room temperature and mixed several times by inversion to ensure a clear and homogenous solution, in accordance with protocol directions below.

15.3.3.1.4. Dosing and Administration

If indicated, rimiducid should be administered at a dose of 0.4 mg/kg as a ~2-hour intravenous infusion.

15.3.4. Concomitant Medications and Treatment

There are no limitations or requirements for concomitant medications and treatments with rimiducid.

15.3.5. Schedule of Assessments and Procedures

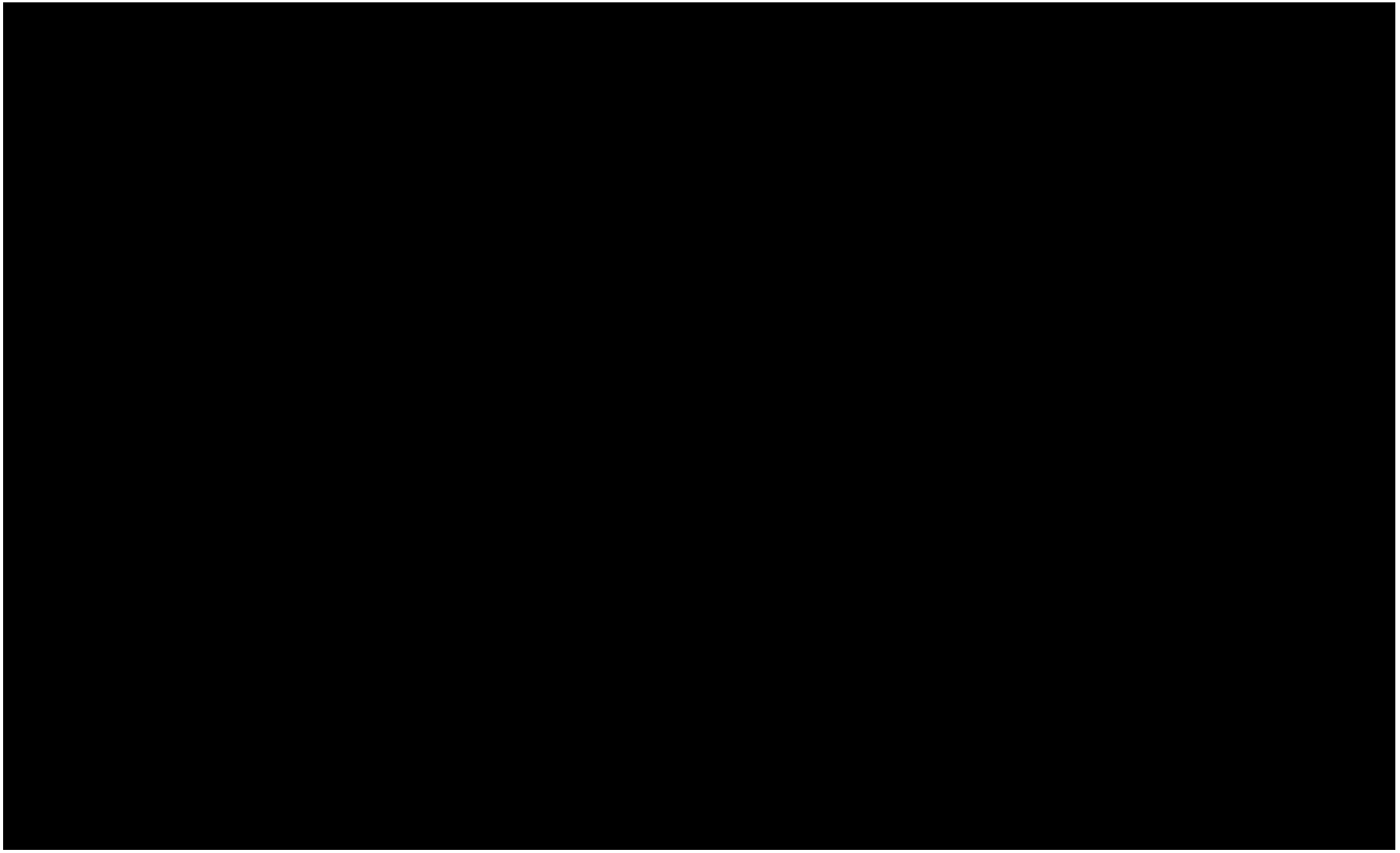
The schedule of events and procedures to be followed in case of the use of rimiducid is shown in Table 8.

In the event of the occurrence of a specific AE as described in Section 6.3, the use of rimiducid should be considered. The rimiducid use form is to be completed and, if time permits, reviewed and approved by the Medical Monitor. The consent for rimiducid will be included in the main study ICF.

[redacted]

15.3.6. Recording Adverse Events

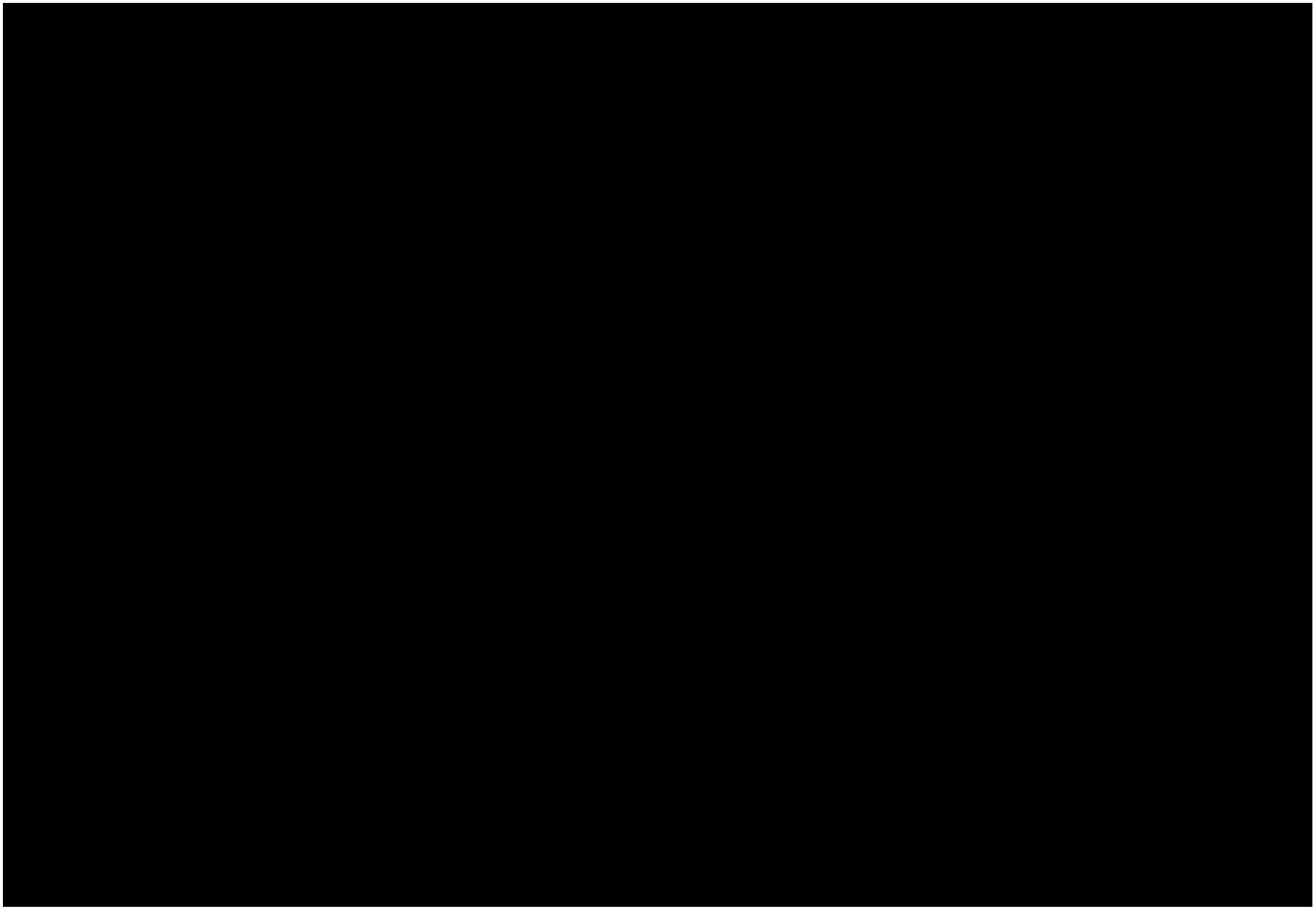
See Section 8 for procedures for recording adverse events. Adverse events are to be recorded on study CRFs and marked with attribution assigned to rimiducid if appropriate.

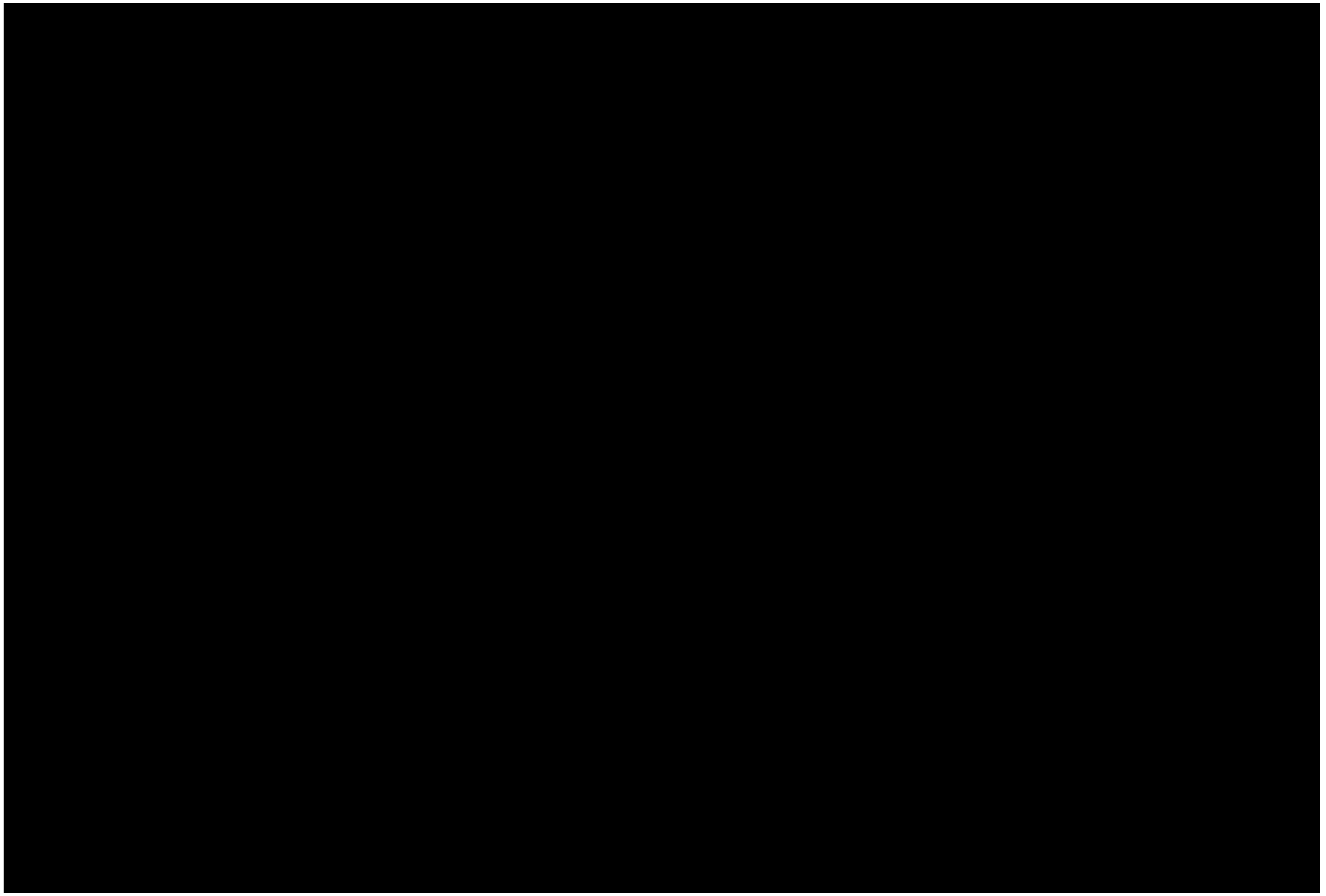


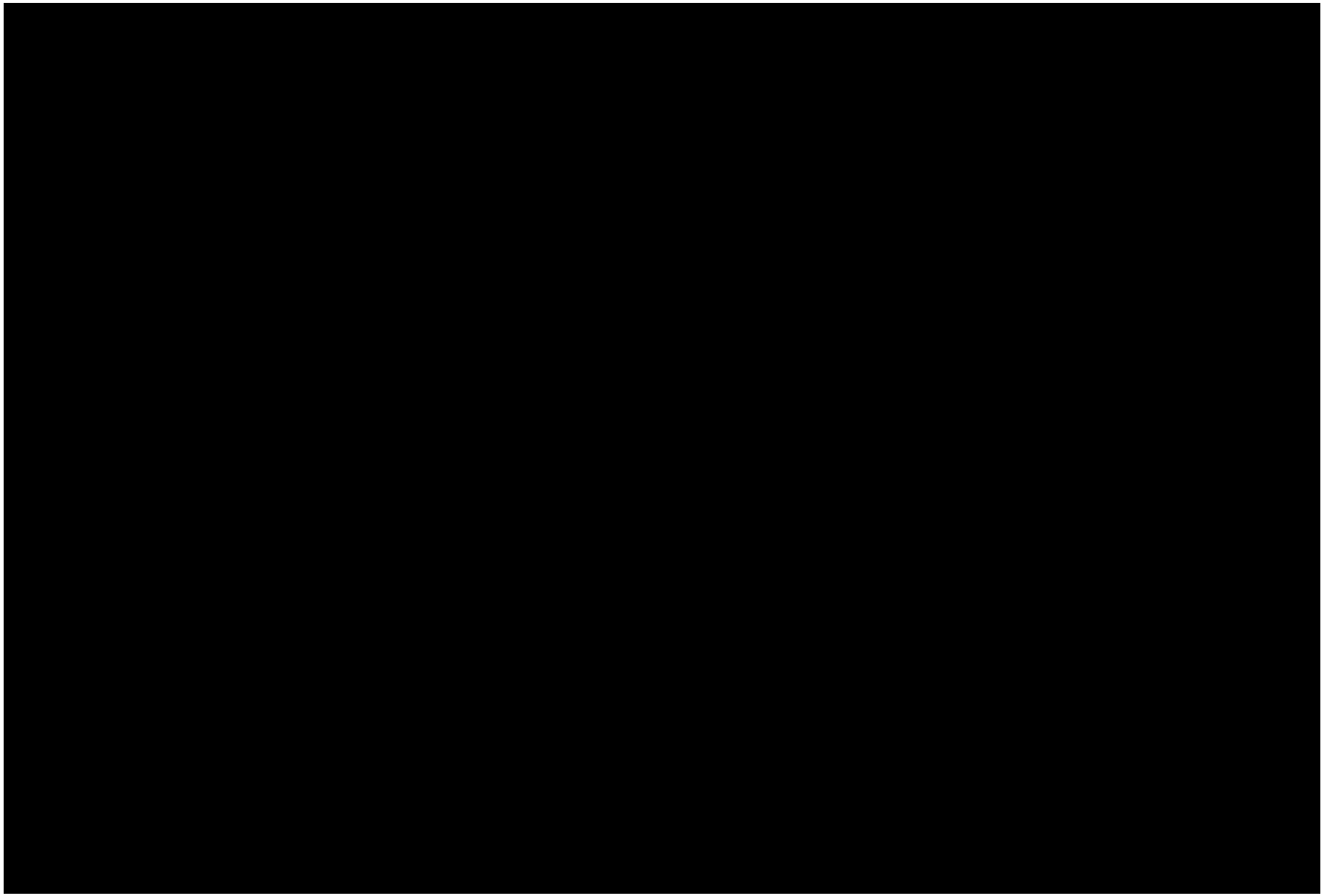
15.4. Retreatment with P-BCMA-101

If sufficient P-BCMA-101 cells remain from manufacturing when a subject's disease progresses, with Safety Committee approval additional cells may be administered up to the highest dose level that has successfully completed dose-limiting toxicity assessment.

In order to receive an additional P-BCMA-101 cell infusion, subjects will be assigned a new subject identification number, they will have to meet all eligibility criteria as outlined in Section 4, and will undergo the same screening, enrollment, conditioning chemotherapy, and follow-up procedures except for leukapheresis, as outlined in Table 9 and Table 10.







15.5. Cycle Administration

During Phase 1 – Cycle Administration, multiple doses of P-BCMA-101 will be administered intravenously in 2 cycles (Cohort A and Cohort C) or 3 cycles (Cohort B) of 2 weeks. The total dose administered may start at ≤ the MTD as determined during Phase 1 single dose escalation.

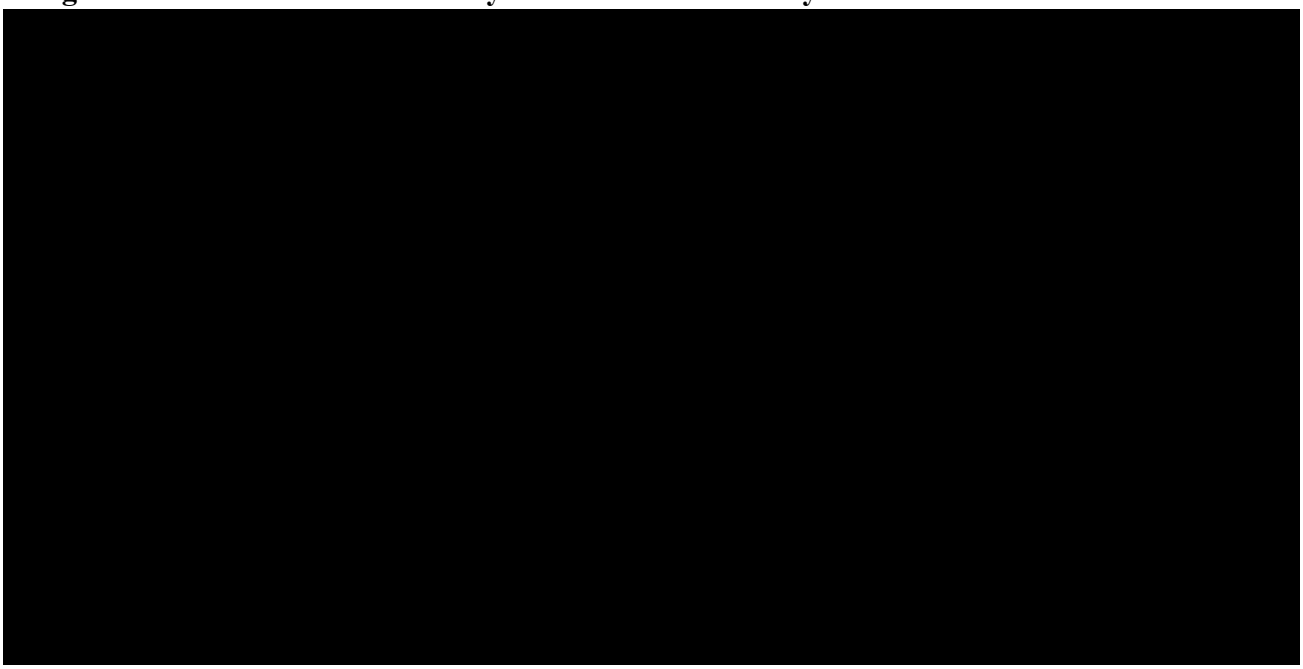
In the first cycle for both cohorts A and B, 1/3 the total dose will be administered. In Cohort A up to 2/3 the total dose will be administered in the 2nd cycle. In Cohort B up to 1/3 the total dose will be administered in each of the 2nd and 3rd cycles. In Cohort C up to 2/3 the total dose will be administered in the 1st cycle and up to 1/3 the total dose will be administered in the 2nd cycle. Schematics of the study design are shown in Figure 5 for Cohort A and Cohort C, and Figure 6 for Cohort B.

The same 3+3 dose escalation and/or de-escalation rules described for single administration will be utilized. [redacted]

Figure 5: Schematic for Study P-BCMA-101-001 –Cycle Administration– Cohort A and Cohort C

[redacted]

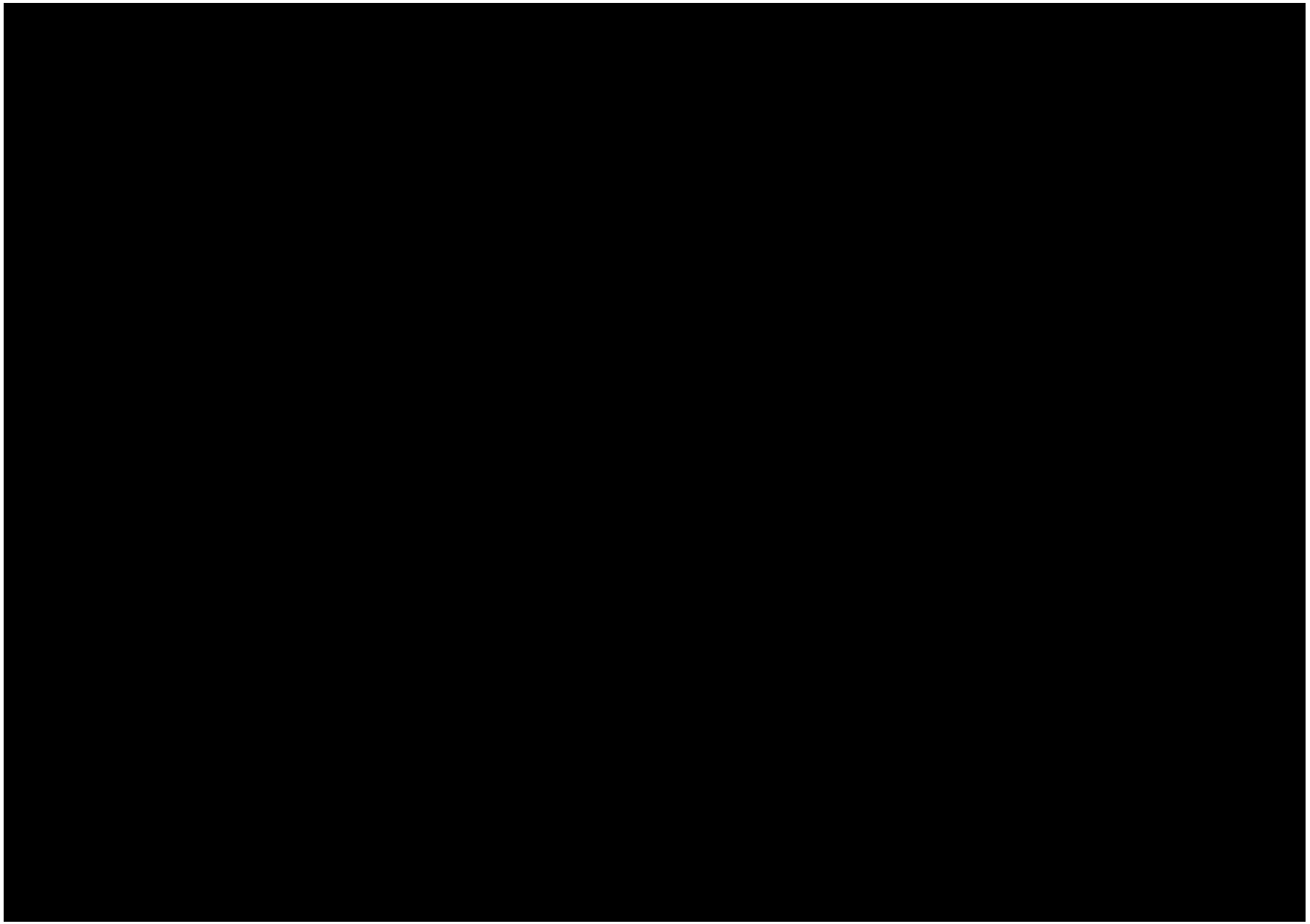
Figure 6: Schematic for Study P-BCMA-101-001 –Cycle Administration – Cohort B

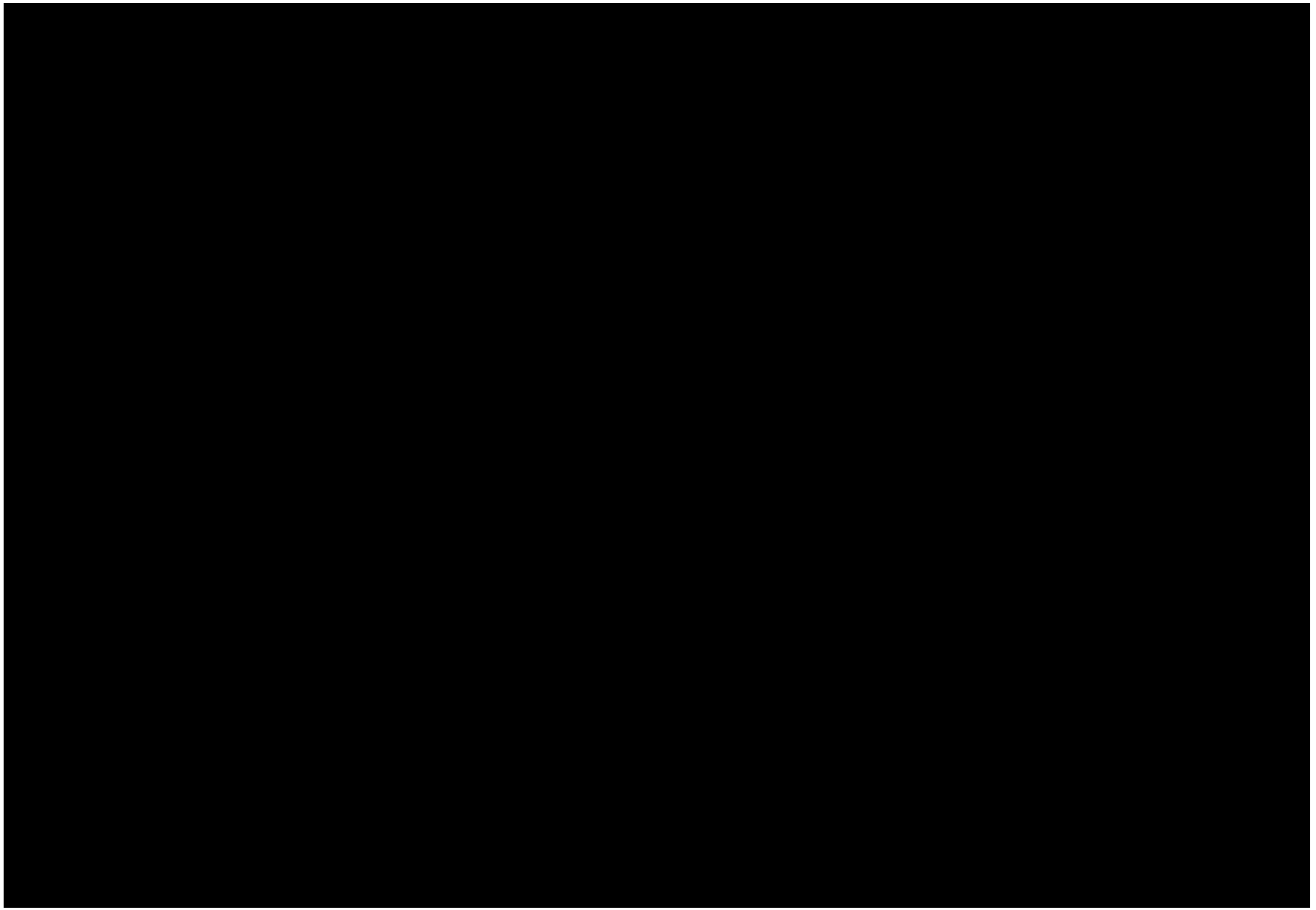


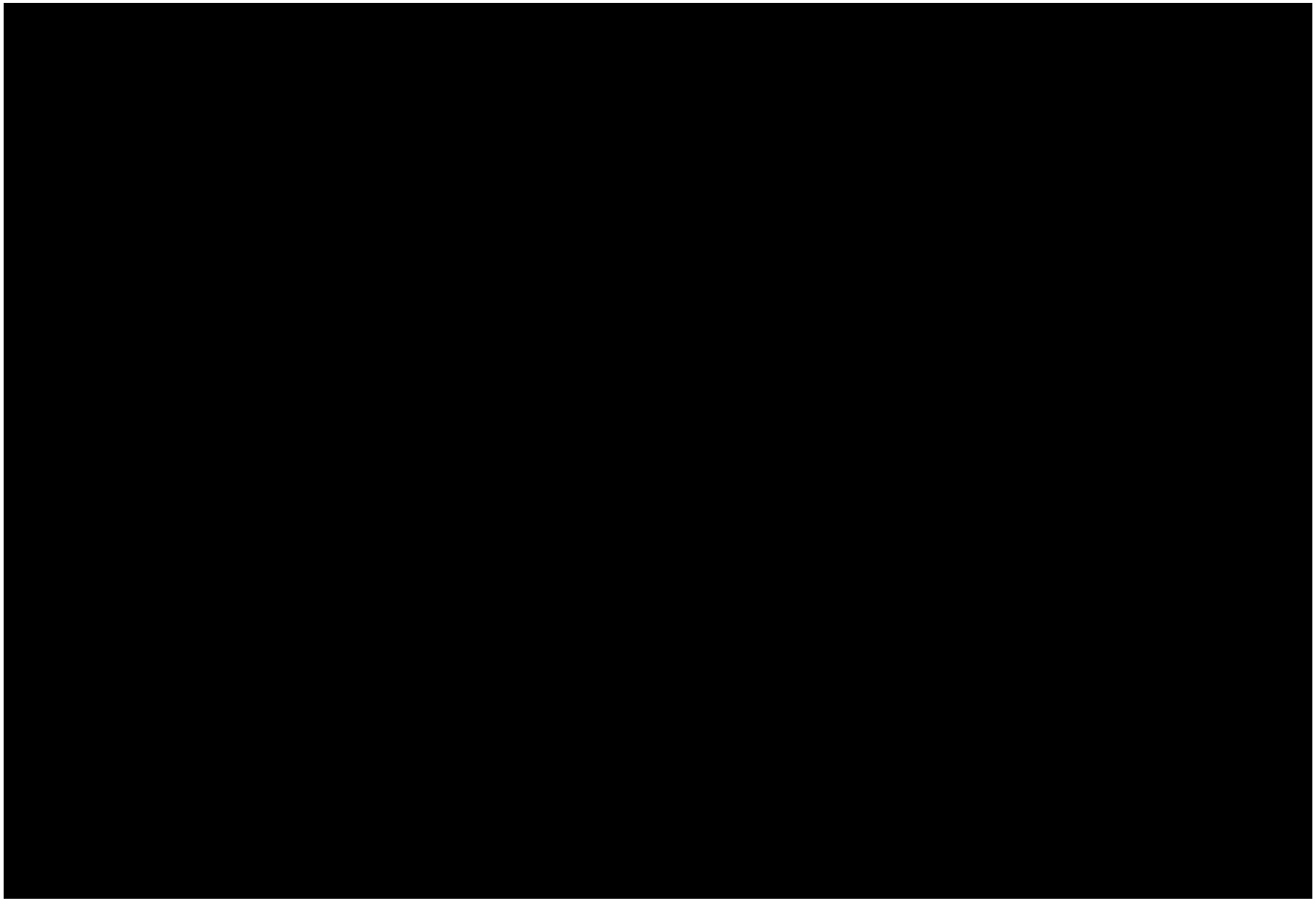
The Schedule of Events for Screening through conditioning chemotherapy for Cohorts A, B, and C is shown in Table 11.

The Schedule of Events for P-BCMA-101 administration for cycle dosing is shown in Table 12 for Cohort A and Cohort C, and Table 13 for Cohort B.

The Schedule of Events for post-treatment follow-up for Cohorts A, B, and C is shown in Table 14.







15.6. Phase 1 – Combination Administration

In Phase 1 – Combination Administration, P-BCMA-101 will be administered in combination with approved therapies:

Lenalidomide

Cohort R: lenalidomide [redacted] before P-BCMA-101 infusion; and

Cohort RP: lenalidomide [redacted] before apheresis [redacted] before P-BCMA-101 infusion.

Dosing with lenalidomide will continue for Cohort R and Cohort RP unless disease progresses. Refer to the lenalidomide package insert for prescribing information (Lenalidomide, 2019) (note particularly that lenalidomide is a presumed teratogen, pregnancy avoidance and monitoring is necessary). The following are additional recommendations specific to this protocol. If no DLTs are reported and platelets are ≥50,000/µL and neutrophils ≥1000/µL 28 days after P-BCMA-101 administration the dose may be [redacted] If <2 DLTs are reported in the first 6 patients treated at this dose, the starting dose in all patients may be [redacted] at the determination of the Safety Committee. During treatment if neutrophils decrease to <1000/µL hold lenalidomide until they are ≥1000/µL, [redacted] During treatment if platelets decrease to <30,000/µL hold lenalidomide until they are ≥30,000/µL, [redacted] If creatinine clearance is 30-60 mL/min the maximum lenalidomide dose [redacted] If creatinine clearance is <30 mL/min hold lenalidomide. Lenalidomide should be discontinued in case of DLT. The lowest dose allowed on this study [redacted] The investigator and Safety Committee may decide to discontinue lenalidomide at time based on other safety findings. Patients should receive concomitant anticoagulation as indicated (eg. aspirin 325 mg orally daily). Do not administer glucocorticoids with lenalidomide.

Rituximab

Cohort RIT: [redacted] Refer to the rituximab package insert for prescribing information (Rituximab, 2019). The following are additional recommendations specific to this protocol. Rituximab should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur. [redacted] Administer only as an intravenous infusion. Do not administer as an intravenous push or bolus. Premedicate before each infusion with acetaminophen, an antihistamine, and 100 mg intravenous methylprednisolone to be completed 30 minutes prior to each infusion. Rituximab should be discontinued in case of infusion reaction or DLT. The investigator and Safety Committee may decide to discontinue rituximab at any time based on other safety findings. *Pneumocystis* pneumonia (PCP) prophylaxis should be considered for patients during and following treatment.

The dose of P-BCMA-101 administered will escalate or de-escalate following the 3+3 design starting at ≤ the MTD as determined during dose escalation.

Figure 7: Schematic for Study P-BCMA-101-001 – Phase 1 Combination Administration

The Schedule of Events for Screening through conditioning chemotherapy for combination administration is shown in Table 15. The Schedule of Events for P-BCMA-101 administration and follow-up for combination administration is shown in Table 16.