Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med 2019;380:1726-37. DOI: 10.1056/NEJMoa1817226

This supplement contains the following items:

1. Original protocol, final protocol, and summary of changes
2. Original statistical analysis plan, final statistical analysis plan, and summary of changes

CLINICAL STUDY PROTOCOL CRB-401

A Phase 1 Study of bb2121 in BCMA-Expressing Multiple Myeloma

Study Sponsor: bluebird bio, Inc.
150 Second Street
Cambridge, MA 02141

Protocol Version: Version 1.0

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1 STUDY OBJECTIVES AND ENDPOINTS

1.1 Study Objectives

There are two parts to this study.

The primary objective of the dose escalation part of the study (Part A) is to:

- Determine the maximally tolerated dose (MTD) of bb2121 in subjects with MM whose tumors express BCMA and a recommended phase 2 dose (RP2D) for future studies.

The primary objective of the cohort expansion part of the study (Part B) is to:

- Confirm the safety of the dose chosen in Part A

The secondary objective of the study is to:

- Provide preliminary efficacy data on the anti-tumor effects of treatment with bb2121 in subjects with MM whose tumors express BCMA

The exploratory objectives of the study are:

- Evaluate the overall survival and progression-free survival of subjects treated with bb2121
- Evaluate the persistence, immune phenotype, and function of bb2121 in the blood, bone marrow and/or tumor tissue
- Evaluate cytokine/chemokine induction in the blood of subjects after infusion of bb2121
- Evaluate the level of BCMA+ cells in blood and bone marrow, and the level of circulating soluble BCMA
- Evaluate measures of tumor sensitivity/resistance to bb2121
- Evaluate minimal residual disease (MRD) in subjects achieving a complete response
- Evaluate the development of an anti-CAR immune response
- Evaluate the utility of the IHC BCMA expression assay

1.2 Study Endpoints

The primary endpoints of the study are:

- Incidence of adverse events (AEs) and abnormal laboratory test results, including dose-limiting toxicities (DLTs).

The secondary endpoints of the study are:

- Disease-specific response criteria including, but not limited to: complete response (CR), very good partial response (VGPR), and partial response (PR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma.

The exploratory endpoints of the study are:

- Overall survival
- Progression-free survival
- Detection and quantification of bb2121 in blood, bone marrow and/or tumor tissue over time
- Detection and quantification of circulating soluble BCMA over time
- Assessment of BCMA expression in plasma cells and tumor cells over time
- Measurement of serum and urine immunoglobulin levels (e.g., IgG, IgA, IgM) and kappa and lambda free light chains
- Evaluation of minimal residual disease in subjects achieving a complete response
- Assessment of baseline IHC BCMA expression as it correlates to clinical response

2 STUDY DESIGN

This is a 2-part, non-randomized, open label, multi-site Phase 1 study.

2.1 Part A: Dose Escalation, Overview

Up to approximately 30 adults with BCMA+ MM will be enrolled using a 3+3 dose escalation approach:

- Three subjects are entered per dose level.
    - If none of the 3 subjects enrolled at the first dose level experience a DLT, then dose escalation will proceed to the next dose level.

  - If 1 of these 3 subjects experiences a DLT, up to 3 more evaluable subjects will be enrolled at this dose level. If that 1 subject remains the only one to experience a DLT out of 6 subjects, then dose escalation will proceed to the next dose level.
  - If 2 or more of the subjects at this dose level experience a DLT, then dose escalation will be halted and the previous lower dose level will be declared the MTD. If the MTD cohort included only 3 subjects, up to an additional 3 subjects will be enrolled at that dose level to confirm that < 2 of 6 subjects experience a DLT at that dose.
- Dose escalation will not proceed until the appropriate number of subjects at that dose level have met the requirements for MTD determination, which includes a minimum of 21 days of follow-up post bb2121 infusion for DLT determination.

Subjects during the dose escalation portion of the study will be enrolled sequentially, and bb2121 infusions will be staggered with a minimum of 14 days between each subject. The start of lymphodepletion of each new subject may begin no fewer than 9 days after the preceding subject's bb2121 infusion. In addition, there will be a minimum of 28 days between escalating dose levels from the time of the last subject's bb2121 infusion on the lower dose level to the first subject's bb2121 infusion on the higher dose level. This will allow for review of the full 21-day DLT assessment period to determine the appropriate 3+3 dose escalation procedure.

A subject is evaluable for DLT if the subject received at least the minimum planned bb2121 dose, and either completed 21-days of follow-up on this study after drug product infusion, or experienced a DLT. Enrolled subjects who are not evaluable for DLT during dose escalation (Part A) will be replaced.

At the discretion of the Safety Review Committee (SRC), the dose escalation cohorts may be divided into independent groups based upon tumor burden (e.g., low versus high tumor burden), and the distinct groups would continue independent dose escalation in the described standard 3+3 manner. The decision to divide dose cohorts into groups may occur during an ongoing cohort or at the start of the next dose level. If subjects of only 1 of the divided groups have been included in dose escalation and the decision is made to divide into 2 groups, whichever group has not been included in dose escalation must start at least 1 dose level lower than the most recently successfully completed combined cohorts. Any alteration to the cohorts based on tumor burden will be agreed upon by the study SRC and included in an amendment to the study protocol.

2.2 Dose Escalation Levels

The dose escalation scheme is described in Table 2-1. Intermediate dose levels may be explored based upon pharmacokinetics, pharmacodynamics, clinical observations, and/or drug product manufacturing data. Any alteration to the dose levels in Table 2-1 will be agreed upon by the study SRC. Regular teleconferences will occur between the Sponsor, SRC, and study staff prior to dose escalations to discuss the ongoing safety of bb2121.

Table 2-1 Dose Escalation Cohorts

Dose Level	Target Total Fixed Dose[a] CAR+ T Cells (± 20%)
-1	2.5×10^7
1 (Starting Dose)	5.0×10^7
2	15×10^7
3	45×10^7
4	80×10^7
5	120×10^7

[a] bb2121 dose is expressed as the number of anti-BCMA CAR+ T cells per subject; the total number of T cells in the dose will be greater.

Note: Subjects may receive more than one cycle of treatment, but subsequent treatments may not occur until at least 8 weeks after the first treatment, and will not be considered in determining the DLT.

2.3 Maximally Tolerated Dose (MTD) Definition

The MTD is the highest dose that causes DLTs in < 2 of 6 subjects. For a dose level to be declared the MTD, at least 5 evaluable subjects must be enrolled with no DLTs reported, or 6 evaluable subjects if 1 subject experiences a DLT.

A MTD may not be determined in this study. A decision to move to expansion cohorts may be made in the absence of a MTD provided the dose is at or below the maximum dose studied in Part A of the study.

2.4 Dose-Limiting Toxicity (DLT) Definition

DLTs are defined as any bb2121-related Grade 3 to 5 toxicity occurring within the 21 days immediately after infusion of the drug product, with the following exceptions:

- Grade 3 Cytokine Release Syndrome (CRS) that responds to appropriate medical intervention within 3 days (see Table 2-3) (recovers to ≤ Grade 2)
- Grade 3 to 4 Tumor Lysis Syndrome (TLS) lasting < 7 days
- Hematologic toxicities:
  - Grade 3 neutropenia of any duration or Grade 4 neutropenia lasting < 14 days
  - Grade 3 anemia of any duration or Grade 4 anemia lasting < 14 days
  - Grade 3 thrombocytopenia of any duration or Grade 4 thrombocytopenia lasting < 21 days
  - All cytopenias except neutropenia, anemia, and thrombocytopenia as described above
- Non-hematologic toxicities:
  - Fever of any grade, including febrile neutropenia
  - Grade 3 diarrhea lasting < 72 hours
  - Grade 3 nausea and/or vomiting lasting < 72 hours
  - Grade 3 fatigue lasting < 7 days
  - Grade 3 to 4 transaminase, bilirubin, creatinine kinase, blood urea nitrogen (BUN), or creatinine elevation lasting < 7 days

- Asymptomatic lipase elevation in the absence of any clinical signs or symptoms of pancreatitis
- Any non-hematologic Grade 3 clinical laboratory AE that is asymptomatic and rapidly reversible (returns to baseline or to ≤ Grade 2 within 7 days).

bb2121-related Grade 3 or 4 toxicities occurring after the first 21 days after infusion of bb2121 will be discussed during the regular SRC meetings and will be considered in decisions regarding the MTD and recommended dose for Part B. Dosing of another subject or escalation to a higher dose level will be delayed if qualification of an ongoing toxicity as a DLT is pending.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) will be used to grade toxicities during the trial unless specified above.

2.5 Cytokine Release Syndrome (CRS) Definition and Management

The primary acute toxicity observed to date with B cell malignancy-targeted CAR T cells has been CRS, and this protocol will follow the recommendations and management for CRS as defined by Lee et al. (2014) (see Table 2-2, Table 2-3, Table 2-4, and Table 2-5). For this protocol, a CRS is defined as a constellation of symptoms which may include (but are not limited to) fever, chills, hypotension, dyspnea, hypoxia, confusion, mental status changes, seizures, myalgias, nausea and vomiting, and laboratory abnormalities including elevated AST, ALT, bilirubin, D-dimers, ferritin, urea and/or creatinine (see Table 2-2). Cytokine panels are also typically markedly abnormal, but are considered exploratory in nature. The work-up of a CRS should include hospitalization and evaluation for an infectious etiology (e.g., blood cultures, urine culture, chest X-ray, as required). Treatment of a CRS will follow the recommendations as per Lee et al. (Lee et al., 2014) and may be modified in the future as more published guidelines become available.

In addition, any subject hospitalized for a fever or work up of CRS should have blood drawn for CAR+ T cells and cytokine assessments along with study-outlined chemistries and hematology including ferritin, fibrinogen, lactate dehydrogenase (LDH), and C-reactive Protein.

Because of the risk of CRS, subjects treated on this protocol must remain within a 30-mile radius of the participating institution for 21 days after infusion with bb2121.

Table 2-2 Clinical Signs and Symptoms Associated with CRS

Organ System	Symptoms
Constitutional	Fever +/- rigors, malaise fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-Dimer, hypofibrinogenemia +/- bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetira, altered gait, seizures

Table 2-3 CRS Revised Grading System

Grade	Toxicity
Grade 1	Symptoms not life-threatening and require symptomatic treatment only e.g., fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement < 40% or Hypotension responsive to fluids or low dose[a] of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40%, or Hypotension requiring high dose[a] or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

[a] Refer to Table 2-4
Grades 2 to 3 refer to CTCAE v4.0 grading

Table 2-4 High Dose Vasopressors (all doses are required for ≥ 3 hours)

Pressor	Dose
Norepinephrine monotherapy	≥ 20 μg/min
Dopamine monotherapy	≥ 10 μg/kg/min
Phenylephrine monotherapy	≥ 200 μg/min
Epinephrine monotherapy	≥ 10 μg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥ 10 μg/min[a]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 ug/min[a]

[a] VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (μg/min)] + [dopamine (μg/kg/min) / 2] + [epinephrine (μg/min)] + [phenylephrine (μg/min) / 10]

Table 2-5 Treating Algorithm for Management of CRS Based on the Revised CRS Grading System

Grading Assessment	Excessive Co-morbidities	Treatment
Grade 1 CRS	Yes or No	• Vigilant supportive care • Assess for infection (Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed)
Grade 2 CRS	No	• Vigilant supportive care as above (In addition, monitor cardiac and other organ function closely)
Grade 2 CRS	Yes	• Vigilant supportive care as above • Tocilizumab +/- corticosteroids
Grade 3 CRS	Yes or No	
Grade 4 CRS	Yes or No	

It is recommended that norepinephrine at a standard dose of 10 μg/minute be used as the initial vasopressor.

Guidelines for the management of toxicities related to bb2121 infusion have been provided, to be used in concert with Table 2-2 through Table 2-5. These guidelines are based on available literature for the management of CRS and may need to be adjusted based on the individual clinical circumstances of each subject. The guidelines are not protocol required therapy as they may need to be adjusted, but serve to provide a single consistent framework for the evaluation and management of CRS and bb2121 related toxicity to mitigate risk to subject.

2.6 Neurologic Toxicity

Neurologic toxicities have been reported in anti-CD19 CAR T cell studies, including confusion, obtundation, aphasia, and myoclonus. The reported neurologic toxicities in these anti-CD19 CAR T cells studies have been often been transient; however there is evidence that persistent neurologic toxicity may also occur (Kochenderfer et al., 2012; Kochenderfer et al., 2015). The mechanism of action of these neurologic toxicities remains unclear and under investigation.

Because these syndromes are only now being characterized in the setting of CAR T cell therapy, in the event of neurologic toxicity it is recommended investigators thoroughly assess subjects including the use of MRI and lumbar punctures to investigate possible mechanisms of action.

2.7 Dose for Subjects for Whom the Minimal Dose Cannot be Manufactured

bb2121 is made on a per-subject basis and there is expected to be heterogeneity in the number of CAR+ T cells that are manufactured for each subject. For a particular dose level, if the number of CAR+ T cells that are manufactured is above this range, only a portion of the manufactured dose will be given with the remainder cryopreserved (where cryopreserved material may either be used for retreatment or research purposes).

If the number of CAR+ T cells manufactured is below the number required at that dose level, the subject may be treated at a dose level previously studied. The subject will be included in

safety and efficacy analyses based on the dose received. The subject will not be included in analyses for DLTs or determining the MTD unless it is necessary to expand the size of a lower dose cohort in order to determine the MTD in accordance with Section 2.1.

2.8 Safety Review Committee

The SRC will be made up of at least one investigator from each active clinical site as well as the Medical Monitor from the Sponsor and other ad hoc members as appropriate. The SRC will meet at least monthly (typically by teleconference), prior to dose escalation and to discuss any protocol-related death or occurrence of Grade 4 CRS. The SRC will also review accumulated safety data. The SRC will assist in determining whether any particular AE qualifies as a CRS event retrospectively. At the appropriate time (typically once the MTD is defined) the SRC will meet to determine the dose to be used in Part B (Expansion Cohort). This dose must be at or below the MTD. Notably, the SRC may allow several doses to be evaluated in Part B as long as they are at or below the MTD. Any disagreements that occur in the SRC will be adjudicated by the Sponsor.

2.9 Part B: Expansion Cohorts

Part B encompasses an expansion cohort of patients with BCMA+ MM.

The SRC will decide when to open the cohort, the cohort size, and the dose to be used (must be at or below the MTD). The expansion cohort will include 20 evaluable subjects. This decision will be based on a review of the preliminary safety and efficacy data generated in Part A of the study and in discussion with Regulatory Authorities.

2.10 Retreatment

Subjects who experience a DLT will not be eligible for retreatment. Subjects who are retreated will be treated at their original dose during study participation unless it exceeds an established MTD, in which case the MTD will be administered. Subjects may only undergo retreatment once. Subjects may undergo retreatment with bb2121 only if the following criteria are met:

- At least 8 weeks since their last bb2121 infusion.
- Best response to bb2121 was no change/stable disease, partial response (PR), or complete response (CR) based on standard response criteria according to the IMWG Uniform Response Criteria for Multiple Myeloma. For those subjects whose best response was CR, the subject must be positive for MRD or have demonstrated subsequent progression prior to retreatment.
- Eligibility criteria continue to be met (except for the exclusion of subjects who have received treatment with any gene therapy-based therapeutic for cancer).
- No evidence of persistent, high titer anti-CAR antibodies that may block bb2121 BCMA recognition.
- Continued evidence that the tumor is BCMA positive based on tissue biopsy.
- At least a 10-fold reduction in circulating anti-BCMA CAR+ T cells from peak.
- Additional manufacture of bb2121 is not required (i.e., retreatment is done using unused drug product from first drug product manufacture).

2.11 Longterm Follow-up

All subjects who complete the study, as well as those who withdraw from the study after receiving bb2121 for reasons other than death or meeting the early termination criteria, will be asked to continue to undergo longterm follow-up in a companion study for up to 15 years after their last bb2121 infusion, with a focus on longterm safety and efficacy.

2.12 Study Withdrawal

It is expected that the most common reason for withdrawal from the study will be disease progression. Subjects, however, may withdraw from this study at any time, for any reason. Other than progressive disease or death, other possible reasons for study withdrawal include:

- Toxicity
- Subject preference, including decision to undergo alternative treatment
- Physician preference
- Failure of transduced cells to be dispositioned for clinical use
- Closure of the study

It is strongly requested that subjects who respond, but then develop progressive disease, undergo a tumor biopsy prior to study discontinuation.

Subjects who withdraw from the study at any time after receiving bb2121 will be asked to continue to undergo longterm follow-up in a companion study for a total of 15 years after their last bb2121 infusion.

Subjects enrolled in the companion longterm follow-up study may be withdrawn from the longterm gene therapy safety follow up requirements (e.g., visits for clinical assessments and vector copy number [VCN] testing) provided the subject has undetectable VCN (< 0.0003 copies per diploid genome) in peripheral blood cells for 2 consecutive measurements at least 1 month apart at least 12 months after drug product infusion. These subjects will still be followed for progressive disease, relapse, and survival as appropriate.

Subjects withdrawn from the study prior to treatment with bb2121 may be replaced.

2.13 Study Pausing Criteria

Enrollment in this study may be paused at any time for safety reasons. In the event enrollment is suspended, the decision as to whether subjects who have already undergone lymphodepletion will receive bb2121 will be made on a case-by-case basis by the SRC. Subjects who have already been treated with bb2121 will continue in the study.

Enrollment and treatment with drug product may be temporarily suspended for any of the following reasons pending review and recommendations from the SRC:

- Death that is not related to disease progression within 30 days of the bb2121 infusion*
- Determination of unexpected, clinically significant, or unacceptable risk to subjects (e.g., development of drug product-related Grade 4 toxicities that have > 35% incidence at the expansion dose level once the MTD has been determined and at least 15 subjects have been treated as part of the expansion)
- Detection of vector-derived replication competent lentivirus (RCL) in any subject

*Any death that is not due to disease progression within 30 days after receiving bb2121 will result in a hold of further enrollment and treatment with drug product until an investigation into the cause of death is performed. If it is determined that the death was not related to the drug product, then enrollment/treatment with drug product may restart. If the relationship between the drug product and the death is not clear, or it appears that the death may be related to study drug, enrollment and treatment with drug product will be held until the SRC assessment and recommendations as described above.

3 STUDY POPULATION

This study will enroll subjects with BCMA+ MM.

3.1 Number of Subjects

Part A (Dose Escalation): Initially, up to approximately 30 evaluable subjects will be enrolled. Depending on the outcome of these cohorts and decisions made by the SRC, additional subjects may be enrolled as described in Section 3.1. Subjects not evaluable for DLT assessment will be replaced.

Part B (Expansion Cohort): 20 evaluable subjects will be enrolled. Replacement subjects may be added if subjects withdraw prior to completing one post-bb2121 infusion tumor staging evaluation.

3.2 Eligibility

3.2.1 Inclusion Criteria

1. ≥ 18 years of age at the time of signing informed consent
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
3. Diagnosis of MM with relapsed or refractory disease and have had at least 3 different prior lines of therapy including proteasome inhibitor (e.g., bortezomib or carfilzomib) and immunomodulatory therapy (e.g., lenalidomide or pomalidomide)
4. Subjects must have measurable disease, including at least one of the criteria below:
    - Serum M-protein greater or equal to 0.5 g/dL
    - 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
    - A biopsy-proven evaluable plasmacytoma
    - Bone marrow plasma cells > 30% of total bone marrow cells
5. Evidence of cell membrane BCMA expression, as determined by a validated immunohistochemistry (IHC) of formalin-fixed, paraffin-embedded (FFPE) tumor tissue (e.g., bone marrow biopsies or plasmacytoma)
6. Women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or tubal ligation or who has not been naturally postmenopausal for at least 24 consecutive months, must have a negative serum pregnancy test prior to treatment. All sexually active WCBP and all sexually active male subjects must agree to use effective methods of birth control throughout the study
7. Recovery to ≤ Grade 1 or baseline of any non-hematologic toxicities due to prior treatments, excluding alopecia and Grade 2 neuropathy

8. Ability and willingness to adhere to the study visit schedule and all protocol requirements
9. Voluntarily sign informed consent form(s)

3.2.2 Exclusion Criteria

1. Treatment with the following therapies within the specified time period:
    a. Any prior systemic therapy for MM within 14 days prior to schedule protocol required leukapheresis
    b. Any prior systemic therapy for MM within 14 days prior to the start of cyclophosphamide and fludarabine lymphodepletion
    c. Investigational cellular therapies within 8 weeks prior to the start of conditioning
2. Subjects with known central nervous system disease
3. Inadequate hepatic function defined by aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2.5 x upper limit of normal (ULN) and direct bilirubin > 1.5 x ULN
4. Inadequate renal function defined by serum creatinine > 1.6 mg/dL
5. International ratio (INR) or partial thromboplastin time (PTT) > 1.5 x ULN, unless on a stable dose of anticoagulant for a thromboembolic event consistent with exclusion criteria 15.
6. Inadequate bone marrow function defined by absolute neutrophil count (ANC) < 1000 cells/mm^3, platelet count < 50,000 mm^3, or hemoglobin < 9 g/dL.
7. Left ventricular ejection fraction < 50%
8. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine or systemic steroids at any dose)
9. Presence of active infection within 72 hours prior to lymphodepletion; subjects with ongoing use of prophylactic antibiotics, antifungals, or antivirals are eligible as long as there is no evidence of active infection and the antibiotic is not included on the list of prohibited medications
10. Previous history of an allogeneic bone marrow transplantation or treatment with any gene therapy-based therapeutic for cancer
11. Significant co-morbid condition or disease which in the judgment of the Investigator would place the subject at undue risk or interfere with the study; examples include, but are not limited to, cirrhotic liver disease, sepsis, recent significant traumatic injury, and other conditions
12. Known human immunodeficiency virus (HIV) positivity
13. Subjects with a history of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control
14. Subjects with second malignancies in addition to myeloma, if the second malignancy has required therapy in the last 3 years or is not in complete remission; exceptions to this

criterion include successfully treated non-metastatic basal cell or squamous cell skin carcinoma, or prostate cancer that does not require therapy

15. Subjects who have had a venous thromboembolic event (e.g., pulmonary embolism or deep vein thrombosis) requiring anticoagulation and who meet any of the following criteria:
    a. Have been on a stable dose of anticoagulation for < 1 month
    b. Have had a Grade 2, 3, or 4 hemorrhage in the last 30 days
    c. Are experiencing continued symptoms from their venous thromboembolic event (e.g. continued dyspnea or oxygen requirement)

    NOTE: Subjects who have had a venous thromboembolic event but do not meet any of the above 3 criteria are eligible for participation
16. Pregnant or lactating women

3.3 Subject Screening and Registration

Subjects willing to participate in the study will provide written informed consent according to Good Clinical Practice (GCP). Written informed consent must be obtained before the conduct of any Screening tests.

Upon signing the informed consent, the subject will be registered and assigned a unique subject number. Once a subject number has been assigned, it cannot be reused, and the number stays with the subject even if the subject is subsequently determined to be ineligible for the study.

There will be two consent forms for this study. The first consent form is to allow BCMA pre-screening by immunohistochemistry. The BCMA IHC assay is an investigational laboratory screen that may eventually be developed for a Companion Diagnostic if efficacy and safety is observed with bb1221. BCMA pre-screening may be performed at any time following the site initiation visit. This screening will occur on archived FFPE tissue.

The second consent form will be for the participation in the general study and must be completed prior to any clinical screening or baseline evaluations. If subjects require a biopsy in order to obtain tissue for BCMA screening, the second consent form for the general study must be completed prior to the biopsy. Biopsies performed as part of standard of care and associated FFPE tissue may be submitted using the BCMA pre-screening consent form.

Screening evaluations must take place after informed consent is obtained.

4 STUDY TREATMENTS AND ASSESSMENTS

4.1 Description of bb2121

bb2121 is defined as autologous T cells transduced ex-vivo with anti-BCMA02 CAR lentiviral vector encoding the chimeric antigen receptor (CAR) targeted to human BCMA, suspended in cryopreservative solution.

Anti-BCMA02 CAR lentiviral vector is used to transduce autologous T cells. This vector uses the murine leukemia virus-derived MND promoter to drive expression of the chimeric receptor, a multi-domain protein consisting of the extracellular antigen recognition domain (V_L and V_H),

the CD8α hinge domain, a transmembrane domain (CD8 TM), and the intracellular CD137 co-stimulatory (4-1BB) and CD3zeta chain signaling domains.

A schematic of the anti-BCMA CAR is shown in Figure 4-1.

Figure 4-1 Anti-BCMA Chimeric Antigen Receptor

Abbrev.: V_L, light chain variable domain; V_H, heavy chain variable domain; TM, transmembrane

4.2 Transduction Process, Storage of Drug Product, Packaging and Labeling, and Traceability

All cell manipulation procedures will be performed in the Good Manufacturing Practice (GMP) manufacturing suite at Celgene Cellular Therapeutics (CCT) in accordance with Current GMPs following process-specific procedures and batch records.

The drug product, autologous T cells genetically modified to express the anti-BCMA CAR, is cryopreserved in a 5% final dimethyl sulfoxide (DMSO) solution (containing 50% Plasma-Lyte® A and 50% CryoStor® 10) and stored in the vapor phase of liquid nitrogen at CCT GMP facility until release testing and disposition for infusion.

bb2121 will be labeled by the manufacturing facility according to GMP, and detailed records will be maintained to allow for accurate traceability of the bb2121, to ensure that the drug product is administered to the original donor.

Refer to Section 4.4 and the Study Cell Product Handling and Administration Manual for details regarding traceability.

4.3 Blinding, Packaging and Labeling

4.3.1 Blinding and Breaking the Blind

This is an unblinded, open-label study.

4.3.2 Packaging and Labeling

bb2121 consists of autologous T cells transduced ex vivo with the anti-BCMA02 CAR lentiviral vector. bb2121 is suspended in cryopreservative solution.

bb2121 will be labeled by the transduction facility according to GMP.

4.4 Product Accountability

bb2121 accountability and traceability is ultimately the responsibility of the Investigator and Sponsor. However, this responsibility may be delegated to suitably qualified personnel listed on Food and Drug Administration (FDA) Form 1572 who has had appropriate study-specific training and whose name has been appropriately listed on the Delegation of Responsibility Log for this task.

Detailed records will be maintained to allow for accurate accountability of the bb2121 as per applicable sponsor and clinical site procedures. These records will include details of storage of

bb2121; transfer bb2121 from the transduction facility, administration to subjects, and disposal of remaining materials.

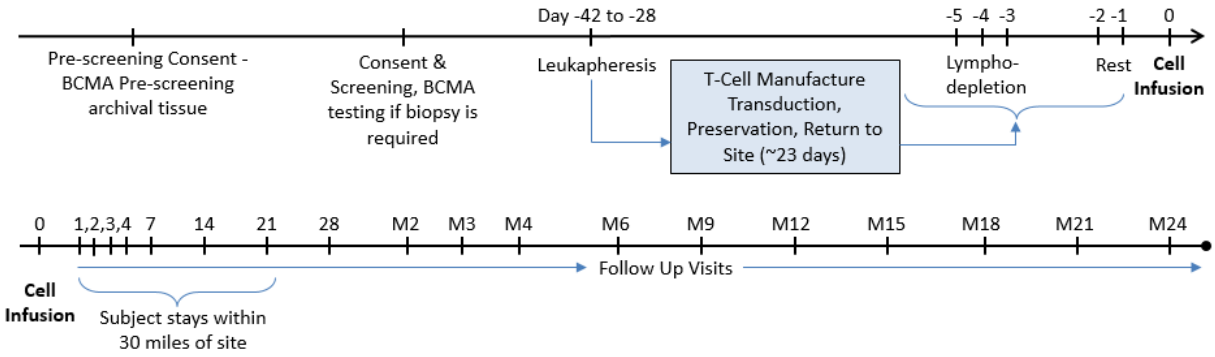
In the event that drug product cannot be administered due to triggering of stopping rules or other reasons, drug product will be kept cryopreserved in the vapor phase of liquid nitrogen until further instruction by the sponsor.

All material containing bb2121 will be treated and disposed of as hazardous waste in accordance with governing regulations and clinical site procedures.

4.5 Summary of Treatments to be Performed or Administered

Figure 4-2 describes the timeline of Study CRB-401, including pre-screening, cell infusion, and follow-up visits.

Figure 4-2 Schematic of Study CRB-401



Top row: BCMA Pre-screening through Day 0 cell infusion
Bottom row: Day 0 cell infusion, follow-up visits

4.5.1 Leukapheresis

In order to obtain a sufficient number of peripheral blood mononuclear cells for CAR T cell drug product manufacturing, enrolled subjects will undergo a leukapheresis procedure processing approximately two times the subject's total blood volume (the target is to collect at least 2.5 x10^9 mononuclear cells). The handling of subject cells will be in accordance with *FDA Draft Guidance for Industry (January 2009); Current Good Tissue Practices (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps).*

Peripheral blood mononuclear cells are procured by leukapheresis at designated Apheresis Collection Centers (ACC) qualified by the Sponsor. As part of the Sponsor ACC qualification process, institutional Standard Operating Procedures are collected and reviewed to confirm that procedures are in place to collect starting material for bb2121 manufacturing. If additional controls are necessary to support bb2121 manufacturing, information will be provided by the Sponsor in an apheresis collection manual. Once collected, the leukapheresis products are shipped to the bb2121 GMP manufacturing facility, CCT, where all cell manipulation procedures are performed according to their Standard Operating Procedures. Detailed records

will be maintained to allow for accurate accountability of leukapheresis products as per applicable Sponsor, ACC, and CCT procedures.

4.5.2 Lymphodepletion

4.5.2.1 Criteria for starting Lymphodepletion

Subjects must meet the following criteria prior to starting lymphodepletion:

1. No prior systemic therapy for MM within 14 days prior to the start of cyclophosphamide and fludarabine lymphodepletion
2. Echocardiogram with left ventricular ejection fraction ≥ 50% within 6 weeks of starting lymphodepletion
3. Adequate hepatic function defined by AST and/or ALT ≤ 2.5 x ULN and direct bilirubin ≤ 1.5 x ULN
4. Adequate renal function defined by serum creatinine ≤ 1.6 mg/dL
5. INR or PTT ≤ 1.5 x ULN, unless on a stable dose of anticoagulant for a thromboembolic event consistent with exclusion criteria 15.
6. Adequate bone marrow function defined by ANC ≥ 1000 cells/mm^3, platelet count ≥ 50,000 mm^3, or a hemoglobin ≥ 9 g/dL.
7. No Presence of active infection within 72 hours of lymphodepletion. Subjects with ongoing use of prophylactic antibiotics, antifungals, or antivirals are eligible as long as there is no evidence of active infection and the antibiotic is not included on the list of prohibited medication
8. Subjects should recover to baseline or ≤ Grade 2 of any non-hematologic toxicities due to prior treatments, excluding alopecia
9. Subjects should complete the following assessments within the 7 days prior to starting lymphodepletion consistent with Table 5-2:
    a. Physical Exam, ECOG performance status and vital signs
    b. Clinical laboratory tests (Table 5-4)
    c. Clinical Disease Staging including Imaging and Bone Marrow Biopsy and Aspirate
    d. Blood for Cytokine Panel, BCMA+ cells, CAR+ T cells, soluble BCMA, Anti-CAR Antibody, VCN (CD3 and Whole Blood), RCL and cellular immunology

4.5.2.2 Lymphodepletion Treatment Plan

Subjects will receive one 3-day cycle of lymphodepletion starting 5 days prior to bb2121 infusion on Day 0 (Table 4-1).

Table 4-1 Lymphodepletion treatment plan

Drug	Dose	Day
Cyclophosphamide	300 mg/m^2 IV infusion over 30 min	-5, -4, and -3
Fludarabine	30 mg/m^2 IV infusion over 30 minutes administered immediately after cyclophosphamide (fludarabine dose should be reduced based on renal function)[a]	-5, -4, and -3

[a] Adult subjects with moderate impairment of renal function (creatinine clearance 30 to 70 mL/min/1.73 m^2) should have a 20% dose reduction of Fludarabine Phosphate Injection, USP. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cf5255cc-91fd-4132-973b-764dba142eae

Chemotherapy should be administered according to institutional guidelines. The following details are recommendations unless otherwise noted.

On Days -5, -4, and -3, it is suggested that subjects receive pre-hydration with 1000 mL 0.9% sodium chloride IV over 1 to 3 hours.

Anti-emetics may be administered according to local institutional guidelines, **but dexamethasone or other steroids are not to be administered.** The use of ondansetron, oral or IV, or similar serotonin inhibitor, on days -5, -4 and -3 prior to chemotherapy is suggested. Subjects may receive education and prescriptions for anti-emetics such as ondansetron, lorazepam, or prochlorperazine for use when not in clinic.

After the administration of fludarabine on Days -5, -4 and -3, subjects should receive 1000 mL 0.9% sodium chloride IV over 1 to 2 hours. Diuretics may be used as needed based on clinical assessment.

On Days -2 and -1, there are no required clinical interventions except those for supportive care including continued anti-emetics for nausea. Subjects should be encouraged to increase fluid intake to minimize bladder toxicity or be supplemented with IV hydration.

4.5.3 bb2121 Infusion Procedures and Administration

bb2121 is to be given on Day 0, after lymphodepletion on Days -5, -4 and -3. There are no interventions other than supportive care on Days -2 and -1.

On Day 0, bb2121 will be administered IV through non-filtered tubing (**IMPORTANT—AN IN-LINE LEUKOCYTE FILTER MUST NOT BE USED**). A central venous access device, such as a Hickman line or peripherally inserted central catheter (PICC) line, may be utilized and is encouraged in subjects with poor peripheral access. Pre-medication should occur approximately 30 minutes prior to the infusion and should include acetaminophen 650 mg orally and diphenhydramine 12.5 mg IV or 25 to 50 mg orally. Subjects should not receive corticosteroids as pre-medication.

bb2121 must be delivered to the subject care unit, thawed at the infusion site in a 37°C water bath and infused immediately within 1 hour; alternately, bb2121 may be thawed in the appropriate cell manipulation facility and administered as soon as possible within a maximum of 1 hour after thawing. If multiple drug product bags are to be administered to meet the protocol assigned dose, each bag will be thawed and administered 1 bag at a time within a maximum of 1 hour for each bag until the appropriate volume and corresponding CAR+ T cell dose has been administered.

All procedures involving bb2121 must be performed using aseptic techniques by trained personnel. See bb2121 Infusion Procedures and Administration Manual for more detail.

Vitals signs are to be monitored prior to bb2121 infusion, upon completion of the infusion, and every hour for the next 4 hours. Infusion reactions, including anaphylaxis, will be managed according to the medical judgment of the physician overseeing the infusion.

4.5.4 Temperature Self-Monitoring

Once discharged from clinic after cell infusion, subjects must take their temperature every 6 to 8 hours post bb2121 infusion and contact their treating investigator for any fever ≥ 100.0°F from Day 0 through Day 21. Subjects should not take any nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen (Motrin, Advil), Naproxen Sodium (Aleve), aspirin or acetaminophen (Tylenol) because these can mask fevers. Fevers are a critically important sign that requires subjects to report to the treating institution as soon as possible for mandatory inpatient admission. Fevers might possibly be the only warning of life-threatening toxicity that can quickly arise in patients receiving CAR T cells. If subjects are in clinic for a visit when a self-monitoring temperature is to be done the temperature may be taken in the clinic by clinic staff. At the discretion of individual investigators, subjects may remain hospitalized for AE monitoring if preferred.

If a subject has a temperature ≥ 100.0°F, they should be hospitalized until afebrile for at least 18 hours and evaluated for symptoms of CRS and managed accordingly (see Section 2.5for detailed guidelines). The work-up of a CRS should include hospitalization and evaluation for an infectious etiology (e.g., blood cultures, urine culture, chest X-ray, as required). During the 21 day period after infusion it is recommended that subjects not be alone because of the risk of the onset of cytokine release syndrome; subjects without an accompanying caregiver may be hospitalized at the discretion of their investigator. Subjects are required to stay within a 30 mile radius of the treating institution; subjects should be evaluated and or admitted to the treating institution due to the institutions familiarity with the treatment protocol and appropriate management of CRS.

4.6 Duration of Subject Participation

Subjects will be followed for AEs, clinical status, and laboratory parameters for up to 24 months, unless they terminate early due to disease progression, or due to meeting one of the withdrawal criteria.

All subjects who complete the study, as well as those who withdraw from the study for reasons other than death or meeting the early termination criteria, will be asked to continue to undergo longterm follow-up in a companion study for a total of 15 years after their last bb2121 infusion.

5 STUDY ASSESSMENTS

5.1 Schedule of Events

Evaluations and procedures identified in the Schedule of Events may be performed at unscheduled visits, as clinically indicated, at the Investigator’s discretion in consultation with the Sponsor.

Table 5-1 Schedule of Events: BCMA Screening, Screening Period 1 and Leukapheresis

Procedure	IHC Pre-Screening (Any time prior to general Consent)	Screening Period 1	Leukapheresis (Day -42 to -28)
BCMA IHC pre-screening consent	X		
BCMA IHC screening assay (FFPE) [1]	X		
General Informed Consent		X	
Demographics		X	
Medical History		X	
Disease History		X	
Physical Examination, Vital Signs		X	
ECOG Performance Status		X	
Blood for Clinical Laboratory Tests		X[2]	X[3]
Bone Marrow Aspirate and Biopsy[4]		X	
Blood for Serum Pregnancy Test (women of child-bearing potential)		X	
Blood for Serology Testing[5]		X	
Echocardiogram		X	
Adverse Event Collection (from General Consent)		X	
Concomitant Medication Collection (from General Consent)		X	
Eligibility Confirmation[6]		X	
Leukapheresis			X
T, B, NK, CD14+ cell counts[2]			X[7]

[1] A positive central BCMA IHC assay is required to be eligible for leukapheresis; 14-20 unstained slides, or blocks will be collected.
[2] Central laboratory (See Section 5.2.6.1 for details)
[3] Local laboratory (See Section 5.2.6.1 for details)
[4] If BCMA pre-screening did not occur due to lack of archival tissue, a new biopsy is required; a positive BCMA IHC assay is required to be eligible for leukapheresis; if a biopsy is performed in this screening period it does not need to be repeated within the 7 days prior to lymphodepletion but requires the submission of unstained slides and aspirate per the study lab manual consistent with bone marrow biopsy and aspirate in screening period 2
[5] See Section 5.2.6.2; serology should be performed within 7 days prior to leukapheresis;
[6] Subjects must meet eligibility criteria prior to leukapheresis; subjects withdrawn from the study prior to treatment with bb2121 may be replaced.
[7] T, B, NK and CD14+ cell counts to be performed on leukapheresis product

Table 5-2 Schedule of Events Screening Period 2, bb2121 infusion, Follow-up

Procedure	Day (D), Month (M), (± window)																			
	D (-12 to -6)[8]	D (-5 to -3)	D 0	D (+1 to +4)	D +7	D +9	D +11	D +14	D +21	M +1	M +2	M +3	M +4	M +6	M +9	M +12	M +15	M +18	M +21	M +24 /LSV
				±1	±1	±1	±1	±2	±2	±2d	±7d	±7d	±7d	±14d	±14d	±14d	±14d	±14d	±14d	±14d
ECOG, physical examination, vital signs	X	X	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for serum pregnancy test (WCP)	X																			
Blood for clinical laboratory tests[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Disease Staging/Response Assessment[11]	X									X	X	X	X	X	X	X	X	X	X	X
Bone Marrow Biopsy/Aspirate													As clinically indicated for response assessment; if performed, tissue should be sent to the central lab for analysis							
Morphology/Cytogenetics[12]	X							X		X		X								
BCMA+ cells, CAR+ T cells[2]	X							X		X		X								
Minimal Residual Disease[13]	X							X		X		X								
Blood Cytokine Panel[2]	X		X[14]	X	X	X	X	X	X	X										
Blood BCMA + Cells[2]	X			X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood CAR+ T cells[2]	X			X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Soluble BCMA[2]	X			X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood anti-CAR antibody[2]	X				X			X		X		X		X	X	X	X	X	X	X
Blood VCN (CD3)[2]	X			X[15]	X	X	X	X	X	X	X	X		X		X		X		X
Blood VCN (whole blood)[2]	X									X		X		X		X		X		X
Blood RCL test[2]	X											X		X		X				X
Blood for Cellular Immunology[2]	X							X		X		X		X		X		X		X
Lymphodepletion		X																		
bb2121 Infusion			X																	
Temperature self-monitoring[16]			Daily, every 6-8 hours																	
Adverse Event collection	Continuous from General Consent																			
Concomitant medication collection	Continuous from General Consent																			

Note: If subject discontinues early, reason for early discontinuation must be documented on CRF and subjects should have last study visit (LSV) assessments performed

[8] Assessments should be performed within 7 days prior to lymphodepletion
[9] Vital signs should be taken prior to bb2121 infusion, once during the infusion, once at the end of infusion, and then hourly for 4 hours
[10] Local laboratory (See Section 5.2.6.1 for details)
[11] See Section 5.2.5 for details
[12] Cytogenetics only to be performed at baseline
[13] Minimal Residual Disease aspirate for assessment will be provided for assessment only at suspected CR
[14] Prior to bb2121 infusion
[15] Assessment should be performed at D +2 and D +4
[16] Subjects must take temperature every 6-8 hrs daily post bb2121 infusion through D +21 visit and contact their treating investigator for any fever ≥ 100.0° F

Table 5-3 Assessments to be Performed Daily if a Subject is Hospitalized for Adverse Events Following Day 0 Through Month 1 Visit

Procedure	Daily During Hospitalization, in addition to scheduled timepoints in Table 5-2
Blood for clinical laboratory tests	X
Blood for cytokine panel[a]	X
Blood for CAR+ T cells[a]	X

[a] Central laboratory; site study teams may be unable to collect blood for cytokines and CAR+ T cells on certain days (e.g., if event occurs on weekend or evening) or situations where they are unable to provide collection mechanisms to the ER or inpatient setting during unscheduled visits

5.2 Study Assessments

5.2.1 Tumor BCMA Expression

Evidence of cell membrane BCMA expression by (IHC) of formalin-fixed, paraffin-embedded tumor tissue may be performed in the local lab of a participating clinical CRB-401 trial site or the central lab for the clinical study. BCMA expression must be detected on ≥ 50% of malignant plasma cells from either a bone marrow biopsy or a plasmacytoma. The tumor samples evaluated locally for BCMA expression must have the remainder of the block or at least 10 unstained slides from the same sample sent to the central lab for retrospective confirmatory testing.

5.2.2 Demographics and Medical History

Demographic data includes gender, age, race, and ethnicity.

A complete medical history should include all relevant prior and current medical history, and should also include anti-cancer therapies.

5.2.3 Physical Examination and Vital Signs

A physical examination includes general appearance; head eyes, ears, nose, and throat; cardiovascular; dermatologic, abdominal; genitourinary; lymph nodes; hepatic; musculoskeletal; respiratory; and neurological, and weight. Height is also to be measured at Screening.

Vital signs include systolic/diastolic blood pressure, pulse, respiration rate, and temperature. On the day of infusion, vital signs should be taken prior to bb2121 infusion, once during the infusion, once at the end of infusion, and then hourly for 4 hours.

Echocardiogram will also be performed.

5.2.4 Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status assessment is to be assessed during screening and at visits according to the Schedule of Events.

5.2.5 MM Response Assessments

MM response assessments include the following:

- Skeletal Survey: At baseline and at any time post cell infusion if the treating investigator believes there are signs or symptoms of increased or new skeletal lesions. At the discretion of the investigator, magnetic resonance imaging (MRI), positron emission

tomography (PET) scan, computerized axial tomography (CAT) scan, or PET/CAT scan may be done at screening in place of a skeletal survey provided the same modality will be used for future assessments

- Radiographic Disease Assessment: Should be performed for any subjects with documented extramedullary disease according to the schedule of assessments. The same imaging modality used at screening (MRI, PET, CAT, or PET/CAT) should be used throughout the study. Imaging should be performed at Month 1, 2, 4, 6 and then every 3 months until Month 24.
- Serum beta-2-microglobulin
- Serum (SPEP) and urine (24 hour collection) (UPEP) electrophoresis for M-protein measurement. Serum only subjects will have urine collected at baseline and in the setting of CR or progressive disease and at the end of study.
- Serum and urine immunofixation
- Serum Free Light Chain (FLC, kappa and lambda)
- Quantification of Ig (IgG, IgM, IgA)
- Bone Marrow Biopsy and Aspirate: Will be performed at baseline, Day +14, Month 1, and Month 3, and as clinically indicated to accurately assess response according to the IMWG Uniform Response Criteria for Multiple Myeloma. If the subject is considered to possibly have resolution of serum and urine M-protein consistent with CR, the biopsy will be used to confirm CR. The biopsy may also be used in suspected progressive disease as applicable. Bone marrow assessments should include flow cytometry, fluorescence in situ hybridization (FISH), cytogenetics, and morphology. Bone marrow aspirate will also be used for evaluation of MRD at appropriate timepoints.

  If a bone marrow biopsy or aspirate is performed at any time during the study, biopsy and/or aspirate samples should be collected for the clinical response assessments and for potential research if available (optional; see Section 5.2.7.1).

If a subject has partial response (PR) or better and then becomes resistant via relapse or progression, a tumor biopsy is strongly encouraged. In addition, if a subject meets the criteria for retreatment, a new biopsy is required to evaluate tumor for BCMA via IHC.

Additional assessments may be performed as part of standard of care as needed for response assessment.

Response assessments will be made according to the IMWG Uniform Response Criteria for Multiple Myeloma.

5.2.6 Laboratory Tests

5.2.6.1 Clinical Laboratory Tests

Clinical laboratory tests (Table 5-4) are to be performed by the local laboratory, and reviewed by the Investigator or qualified designee (e.g., physician’s assistant, nurse practitioner).

Table 5-4 Clinical Laboratory Tests

Hematology	Serum Chemistry	Coagulation	Enzymes & Liver Studies
CBC with differential ferritin fibrinogen	sodium potassium, chloride bicarbonate creatinine glucose blood urea nitrogen calcium uric acid phosphate magnesium C-reactive protein	prothrombin time (PT)/ partial thromboplastin time (PTT), international normalized ratio (INR)	AST ALT alkaline phosphatase total and direct bilirubin albumin LDH

Abbrev.: CBC, complete blood count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase

CBC includes hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

Additional clinical laboratory tests may be performed at the Investigator's discretion.

5.2.6.2 Additional Eligibility-Determining Laboratory Tests

During Screening, blood samples will be collected for additional eligibility-determining laboratory tests, as follows:

- **Serology for eligibility**

  Screening serology will be evaluated using standard methods. The serology panel should include the following:

  - HIV-1 and HIV-2
  - hepatitis B virus core antibody (HBcAb)
  - hepatitis B virus surface antibody (HBsAb)
  - hepatitis B virus surface antigen (HBsAg)
  - hepatitis C virus (HCV) antibody
  - HCV RNA
  - HTLV-1 and HTLV-2
  - Rapid plasma reagin for syphilis
  - CMV Antibody
  - West Nile Virus individual donor testing (IDT) of a nucleic acid test (NAT)
  - Chagas Antibody

  Blood may also be drawn for additional serology testing if subject has risk factors or clinical evidence of infection with other communicable disease agents or disease.

  Serology should be performed within 7 days prior to leukapheresis. Additional serology may be performed if required according to country-specific and institutional guidelines.

- **Serum β-human chorionic gonadotropin pregnancy test**

  Required for women of child-bearing potential.

5.2.6.3 Replication Competent Lentivirus (RCL)

The p24 enzyme-linked immunoabsorbent assay (ELISA) will be performed, and, if positive, a test to assess the presence of RCL in peripheral blood leukocytes will be performed. Pre-bb2121 RCL samples will be collected, but will only be tested if samples after bb2121 infusion are positive.

5.2.6.4 Vector Copy Number (VCN)

Polymerase chain reaction to determine VCN will be performed in DNA from whole blood and T cells to monitor for persistence of vector sequences.

5.2.6.5 Blood and Bone Marrow Analysis for CAR and BCMA

CAR+ T cells and BCMA+ cells will be measured in peripheral blood and bone marrow by flow cytometry. Soluble BCMA will be measured in serum by ELISA.

5.2.6.6 Anti-CAR Antibodies

To examine immunogenicity to CAR, anti-CAR antibody testing will be performed by ELISA.

5.2.6.7 Cytokines

Cytokine analysis will be performed in serum.

Examples of inflammatory cytokines that may be measured include IFNg, the IFNg–responsive chemokines CXCL9 and CXCL10, interleukin-6, soluble interleukin-2 receptor, TNFa.

5.3 Adverse Events

5.3.1 Definitions, Documentation, and Reporting

5.3.1.1 Adverse Events

An AE is any change in physical signs, symptoms, and/or clinically significant laboratory change occurring in any phase of a clinical study regardless of its relationship to study drug. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This definition includes intercurrent illnesses or injuries, and exacerbation of pre-existing conditions. A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the informed consent form and is documented as part of the subject's medical history.

5.3.1.2 Unexpected Adverse Events

An AE is considered unexpected with bb2121 if it is not consistent in nature or severity with information contained in the written information or current Investigator's Brochure provided to the Investigator by the Sponsor.

5.3.1.3 Serious Adverse Events

A serious adverse event (SAE) is any AE occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death

from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

- Requires in subject hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned). Planned hospitalizations for bb2121 infusion and inpatient monitoring required by institutional guidelines are also not considered SAEs.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a subject's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event.
    - An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs.
    - For the purposes of this study, any new malignancy or new diagnosis of a neurologic, rheumatologic, or hematologic disorder that, in the Investigator's opinion, is clinically significant and requires medical intervention will be considered medically important and therefore serious.

5.3.2 Medical Events of Special Interest (ESIs)

Grade 3 or greater CRS events are medical ESIs, and therefore immediately reportable to the Sponsor, even if the events do not meet SAE criteria.

All Grade 3 or greater CRS events will be reported to the sponsor within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to bb2121. All Grade 3 CRS events should be communicated to the Sponsor on the SAE report form as described in the SAE reporting section.

5.3.3 Adverse Event Assessment

For both serious and non-serious AEs, the Investigator must determine both the intensity of the event and the relationship of the event to bb2121 administration.

Intensity will be assessed by the Investigator using the NCI CTCAE, version 4.0. If the AE is not included in the CTCAE, then the Investigator is to determine the intensity of the AE according to the criteria in Table 5-5.

Table 5-5 Grades of Adverse Events

Grade	Definition
Mild (Grade 1)	The AE is noticeable to the subject, but does not interfere with routine activity.
Moderate (Grade 2)	The AE interferes with routine activity, but responds to symptomatic therapy or rest.
Severe (Grade 3)	The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy.

Life-Threatening (Grade 4)	The subject is at immediate risk of death.
Death (Grade 5)	Death

If the intensity (grade) changes within a day, the maximum intensity (grade) should be recorded.

Relationship will be determined by the Investigator according to the criteria below. Relationship of AEs to bb2121 will be determined after the start of bb2121 infusion on Day 0; prior to that time, relationship to study treatment other than bb2121 will be assessed according to Table 5-6.

Table 5-6 Relationship of Adverse Events to Drug Product

Investigator Assessment	Definition	Classification for Reporting Purposes
Not Related	Exposure to the drug product did not occur, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to the drug product.	Not Related
Possibly Related	The study treatment and the AE were not closely related in time, there is an association between the event and the administration of study treatment, and there is a plausible mechanism for the event to be related to the study product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.	Related
Probably Related	The study treatment and the AE were reasonably related in time, there is an association between the event and the administration of bb2121, there is a plausible mechanism for the event to be related to the study product, and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.	Related
Related	The study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the drug product than by other causes, or the drug product was the most likely cause of the AE.	Related

5.4 Pregnancy and Contraception

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (e.g., spontaneous abortion, which may qualify as an SAE). However, all pregnancies occurring during this study (in subjects or female partners of subjects) are to be reported in the same time frame as SAEs using the Pregnancy Form. The course of all pregnancies, including perinatal and neonatal outcome, regardless of whether the subject has discontinued participation in the study, will be followed until resolution, including follow-up of the health status of the newborn to 6 weeks of age.

Cyclophosphamide and fludarabine have been shown in animal studies to be teratogenic. The effects of administration of bb2121 on the pregnant female or the developing fetus are unknown. Female subjects of child-bearing potential are required to use effective contraception from Screening through at least 6 months after drug product infusion. Male subjects are required to use effective contraception (including condoms) from Screening through at least 6 months after drug product infusion.

5.5 Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or to follow-up on AEs or as deemed necessary by the Investigator. Evaluations and procedures to be performed at unscheduled visits, as clinically indicated at the Investigator's discretion in consultation with the Sponsor, and may be based on those listed in the Schedule of Events.

6 STATISTICAL PROCEDURES

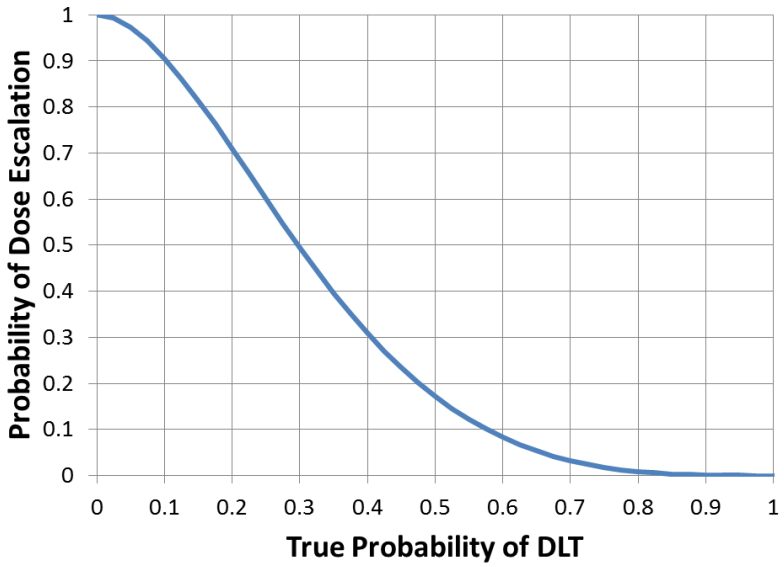
6.1 Sample Size Estimation

The sample size for this study was not determined by formal statistical methods, but will be sufficient to provide preliminary information on safety, as well as efficacy and pharmacodynamic parameters. This sample size would provide 95% assurance for the detection of at least one safety event with a true rate of occurrence of approximately 10%.

Based on the planned dose escalation scheme (Section 2.1), up to approximately 30 evaluable subjects will be enrolled in part A of the study. An additional 20 subjects will be enrolled in part B of the study.

Figure 6-1 presents the probability of escalation from a lower dose to the next higher dose for a range of true rates of DLT in the standard 3+3 dose-escalation design. For example, if the true DLT rate were 20%, then the chance of dose escalation would be approximately 70%.

Figure 6-1 Probability of Dose Escalation for the 3+3 Design



In part B, a minimum sample size of 25 subjects (the 20 additional subjects from Part B plus at least 5 subjects treated at the MTD from Part A) would allow the detection of at least 1 AE with a true incidence of 11.3% with 95% confidence. With this sample size and a true incidence of 11.3% for a specific AE, there is a 95% chance of observing at least one occurrence of that AE.

With at least 5 subjects treated at the MTD in Part A and 20 additional subjects in the expansion study, there are potentially 25 subjects who are evaluable for efficacy. The study would have at least 80% power to reject the null hypothesis that bb2121 therapy has a ≤ 10% objective response rate (ORR) assuming a one-sided test with alpha = 0.05 and a minimum efficacy of 30%. A 30% ORR would justify further studies of bb2121 therapy in subjects with relapsed or refractory MM.

6.2 Populations for Analysis

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: All subjects who initiate any study procedures beginning with leukapheresis. This is the primary set for the analysis of safety data with the exception of determining the MTD and for the analysis of efficacy data. Safety will be evaluated based on specific study periods as noted below.
- The MTD Population: All subjects in Part A of the study who were infused with bb2121 and either completed 21-days of follow-up on this study after drug product infusion or who experienced a DLT. Subjects for whom the minimal dose could not be manufactured (Section 3.6) will not be included in the MTD population unless it was necessary to expand the size of a lower dose cohort in order to determine the MTD in accordance with Section 2.1. This is the primary data set for the analysis of safety data for determining the MTD.
- The Efficacy Population (EP): All subjects in Part A of the study treated at the MTD and all subjects enrolled in Part B of the study. This is the primary set for analysis of efficacy data.

- CAR T Population (CP): All subjects who undergo bb2121 infusion, should the number of subjects included in this population be different than that in the ITT population. It is anticipated that the ITT Population and CP will be identical, in which case, analyses performed using the ITT Population will not be repeated for the CP. This is the primary data set for evaluation of exploratory CAR T parameters.

6.3 Interim Analyses

There will be no formal interim analyses of the data. Interim safety reviews will be conducted by the SRC following completion of each dosing cohort prior to dose escalation and enrollment in the next cohort. The SRC will also evaluate all safety data prior to determining the dose(s) to be used in Part B of the study.

6.4 Statistical Methods

6.4.1 General Methods

Statistical analyses will be primarily descriptive in nature.

Tabulations will be produced separately for each part of the study for appropriate disposition, demographic, baseline, safety, and efficacy parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of observations, mean, median, standard deviation, minimum and maximum values will be presented.

Descriptive summary statistics as well as 2-sided, 90% confidence intervals will be presented on selected parameters.

For change from baseline analyses, baseline will be defined as the value closest to, but prior to infusion of bb2121. Longitudinal data (collected serially over time on study and follow-up) will be presented by appropriate time intervals, such as monthly, quarterly and so forth, depending on the nature of the data.

All data will be provided in by-subject listings.

6.4.2 Demographic, Baseline Characteristics and Disposition of Subjects

Demographic and baseline characteristics (e.g., disease, medical history, prior treatment) will be summarized.

Baseline values of all clinical efficacy parameters will be included in tables of baseline, post-baseline and change from baseline, with all individual data included in the summary statistics included in by-subject, by-time data listings.

A tabulation of the disposition of subjects will be presented, including the number enrolled, the number treated with bb2121, and the reasons for study discontinuation. Tables and listings will be provided for subjects in each analysis data set. Subject data will also be displayed by site. Deviations from protocol treatment and assessment specifications will be tabulated and listed.

6.4.3 Efficacy, Pharmacokinetic, and Pharmacodynamic Analyses

The proportion of subjects who meet disease-specific response criteria after treatment with bb2121 will be tabulated along with a 90% exact binomial confidence interval. A one-sided, alpha = 0.05, Fisher's exact test will be performed to test the null hypothesis that the ORR is 10% or less. This information will be provided by cohort and overall for subjects. Disease-specific response includes, but is not limited to:

- complete response (CR), very good partial response (VGPR), and partial response (PR) according to the IMWG Uniform Response Criteria for Multiple Myeloma.

Subjects who are lost to follow up or who die prior to meeting the above criteria will be considered non-responders for the purpose of this analysis.

Estimates of overall survival and progression-free survival will be presented using Kaplan-Meier curves.

These analyses will be provided for the efficacy population.

Details on the evaluation of the remaining exploratory analyses, including pharmacokinetic and pharmacodynamic analyses, will be described in the statistical analysis plan.

6.4.4 Safety Analysis

A summary of study drug exposure, including retreatment, will be produced.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All treated subjects will be included in the assessment of safety. Safety summaries will use the bb2121 dose group as classifications. For Part A, the primary safety summaries will be by dose level (originally assigned level) and overall. For Part B, the primary safety summaries will be by cohort and overall. For Part A, a summary of the number and type of DLTs experienced by subjects will be produced per dose group, accompanied by a detailed subject listing of DLT events, with the description, severity and relationship of the event. A summary of the number and severity of CRS AEs will also be produced by dose level and overall for Part A and by cohort and overall for Part B.

Adverse events will be summarized by MedDRA system organ class and preferred terms, and separate tabulations also will be produced for related adverse events (those considered by the Investigator as at least possibly drug related), SAEs, ESIs, discontinuations due to adverse events, and events of at least Grade 3 severity.

AEs will be summarized for those events that occur during the following periods:

1) After initiating any study procedure (not including pre-screening for BCMA by archival tissue), through leukapheresis, and up to but not including the day of the first dose of lymphodepletion
2) From the day of the first dose of lymphodepletion up to but not including Day 0 (the day of bb2121 infusion)
3) From the day of bb2121 infusion (Day 0) through 24 months after drug product infusion (all AEs)

All AEs will be listed in by-subjects, by-time data listings, including any events that may have occurred after signing informed consent but prior to leukapheresis.

Vital signs data and laboratory data will be tabulated for changes over time on study.

Laboratory parameters will be summarized for changes across study by using descriptive statistics including shifts relative to CTCAE criteria for laboratory abnormalities. Laboratory measures will also be compared with their corresponding normal ranges and the incidence of abnormally high and abnormally low laboratory values will be calculated for each relevant protocol-specified laboratory test. Laboratory values that are of Grade 3 severity or greater will be tabulated by dose and listed on an individual subject basis.

Additional tabulations of safety data may be produced, as warranted by the data.

All safety data will be provided in subject-level listings.

7 REFERENCES

Kochenderfer, J.N., Dudley, M.E., Feldman, S.A., Wilson, W.H., Spaner, D.E., Maric, I., Stetler-Stevenson, M., Phan, G.Q., Hughes, M.S., Sherry, R.M.*, et al.* (2012). B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood *119*, 2709-2720.

Kochenderfer, J.N., Dudley, M.E., Kassim, S.H., Somerville, R.P., Carpenter, R.O., Stetler-Stevenson, M., Yang, J.C., Phan, G.Q., Hughes, M.S., Sherry, R.M.*, et al.* (2015). Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor. J Clin Oncol *33*, 540-549.

Lee, D.W., Gardner, R., Porter, D.L., Louis, C.U., Ahmed, N., Jensen, M., Grupp, S.A., and Mackall, C.L. (2014). Current concepts in the diagnosis and management of cytokine release syndrome. Blood *124*, 188-195.

8.1 Guidelines for management of common toxicities that occur after CAR T cell infusions

Infusions of CAR T cells are often complicated by significant acute toxicities in the first 2 to 3 weeks after the infusion. In many cases the toxicities correlate with serum inflammatory cytokine levels (Kochenderfer et al., 2012).

The toxicities most often experienced by patients receiving infusions of CAR T cells include, but are not limited to, TLS, fever, fatigue, hypotension, tachycardia, acute renal failure, and neurological toxicities such as aphasia, ataxia, headache, and obtundation (Kochenderfer et al., 2012; Kochenderfer et al., 2015; Lee et al., 2014) Fever is usually the first toxicity to occur.

Note these are guidelines that might require modification based on clinical circumstances of each patient, and failure to exactly follow these guidelines is not a protocol deviation or violation.

Administration of corticosteroids should be avoided if at all possible to avoid killing or impairing the function of the CAR T cells.

1. All patients with significant malignancy burdens and without a contradiction such as allergy should be started on allopurinol at the time of the start of the chemotherapy conditioning regimen or 1 day before the CAR T cell infusion. The suggested allopurinol dose is 200 to 300 mg/day with a possible loading dose of 300 to 400 mg.
2. Vital signs should be checked a minimum of every 4 hours during hospitalization. Increasing the time interval between vital sign checks for patient convenience or other reasons should be avoided.
3. Strict ins and outs should be recorded on all patients.
4. As a minimum, keep hemoglobin greater than 8.0 g/dL and platelets greater than 20K/microliter.
5. Fevers should be treated with acetaminophen and comfort measures. NSAIDs and corticosteroids should be avoided.
6. Patients with a heart rate persistently higher than 115 beats/minute and fever should have vital signs checked every 2 hours.
7. Patients who are neutropenic and febrile should be receiving broad-spectrum antibiotics.
8. A CBC will be obtained twice daily while the patient is inpatient. If the ANC becomes < 500 cells/mm^3, Filgrastim will be initiated at a dose of 300 μg daily for patients under 70 kg in weight and a dose of 480 μg daily for patients over 70 kg in weight only in patients with ANCs less than 500 cells/mm^3. Filgrastim will be discontinued as soon as the ANC recovers to 1500 cells/mm^3.
9. Hypotension is a common toxicity requiring intensive care unit (ICU) admission. In general patients should be kept well-hydrated. Maintenance IV fluids (normal saline [NS]) should be started on most patients with high fevers especially if oral intake is poor or the patient has tachycardia. IV fluids are not necessary for patients with good oral intake and mild fevers. For patients who are not having hypotension or TLS, a generally even fluid balance should be strived for after allowing for insensible fluid losses in patients with high fevers. The baseline systolic blood pressure is defined for this protocol as the average of all systolic

blood pressure readings obtained during the 24 hours prior to the CAR T-cell infusion. The first treatment for hypotension is administration of IV NS boluses.

- **Patients with a systolic blood pressure that is < 80% of their baseline blood pressure and < 100 mm Hg should receive a 1 L NS bolus.**
- **Patients with a systolic blood pressure < 85 mm Hg should receive a 1 L NS bolus regardless of baseline blood pressure.**
- **Patients with a systolic blood pressure that is < 80% of their baseline blood pressure and > 100 mm Hg on 2 occasions separated by at least 2 hours should receive a 500 mL to 1 L NS bolus.**

These IV fluid management suggestions may need to be modified based on the clinical characteristics of individual patients such as pulmonary status, cardiac function, edema, and other factors.

10. Patients receiving > 1 fluid bolus for hypotension should have a stat electrocardiogram (ECG) and troponin, and a cardiac echocardiogram within 24 hours of the second fluid bolus.
11. Patients should be transferred to the ICU under these circumstances. Patients not meeting these criteria could also require ICU admission at the discretion of the clinical team caring for the patient.
    - Systolic blood pressure < 75% the patient's baseline blood pressure and l< 100 mm Hg after administration of a 1L NS bolus.
    - Anytime the systolic blood pressure is < 90 mm Hg after a 1L NS bolus if 90 mm Hg is less than the patient's baseline systolic blood pressure.
    - Continuous tachycardia with a heart rate higher than 125 beats/minute on at least 2 occasions separated by 4 hours.
    - Oxygen requirement of more than a 4L standard nasal cannula
    - > Grade 2 neurological toxicity
12. All patients transferred to the ICU for hypotension or tachycardia should have a stat ECG and a cardiac echocardiogram within 24 hours of the time of transfer.
13. Patients with hypotension not responding to IV fluid resuscitation should be started on norepinephrine at doses called for by standard ICU guidelines.
14. Patients should have a cardiac echocardiogram and an ECG within 12 hours of starting norepinephrine.
15. Patients in the ICU should get twice-daily labs (CBC with differential, acute care panel, mineral panel, hepatic panel, uric acid, LDH. Patients in the ICU should also get a daily troponin level).
16. Anecdotal evidence suggests that the IL-6 receptor blocker tocilizumab can be an effective treatment for CRS toxicities after CAR T cell infusions. Tocilizumab should be administered under the following circumstances if the listed disorders are thought to be due

to cytokine release from CAR T cells. Tocilizumab is administered at a dose of 4 mg/kg infused IV over 1 hour (dose should not exceed 800 mg).

- Left ventricular ejection fraction less than 40% by echocardiogram
- Creatinine greater than 3-fold higher than the most recent level prior to CAR T-cell infusion
- Norepinephrine requirement for 48 hours since the first administration of norepinephrine even if norepinephrine administration was not continuous.
- Systolic blood pressure of 90 mm Hg cannot be maintained with norepinephrine.

17. THERE IS NO EVIDENCE THAT TOCILIZUMAB HELPS NEUROLOGICAL TOXICITY, SO IT SHOULD NOT BE ADMINISTERED FOR THIS PURPOSE.
18. If no improvement in hypotension or tachycardia occurs within 6 hours of tocilizumab infusion, consider other agents such as methylprednisolone 1 mg/kg every 12 hours or etanercept.
19. Avoid meperidine due to seizure risk.
20. All patients with Grade 2 or greater neurological toxicities should get a neurology consult. It is recommended investigators thoroughly assess subjects with neurologic toxicities including the use of MRI and lumbar punctures to assess for possible mechanisms of action.
21. The following patients should receive dexamethasone 10 mg IV every 6 hours until the toxicities improve to Grade 1 or resolve or until at least 8 doses of dexamethasone have been given.
    - Patients with Grade 3 neurological toxicities suspected to be related to the CAR T cell infusion that lasts continuously for 24 hours or longer. This does not apply to headaches. Dexamethasone is not recommended for isolated Grade 3 headaches.
    - Patients with Grade 4 neurological toxicity of any duration that is suspected to be related to the CAR T-cell infusion.
    - Patients with any generalized seizure

Note: for seizures, administer standard seizure therapies in addition to dexamethasone.

A Phase 1 Study of bb2121 in BCMA-Expressing Multiple Myeloma

PROTOCOL NUMBER:	**CRB-401**
DATE FINAL:	**09 May 2018**
EudraCT NUMBER:	**Not applicable**
IND NUMBER:	**16664**
SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

CRB-401 Protocol Amendments

Protocol Version 1.0, dated 28 August 2015 - ORIGINAL

SUMMARY OF KEY CHANGES:

Protocol Version 1.1, dated 14 September 2015 (prior to 1st patient infused)

- CRS monitoring: added 10-day mandatory hospitalization and subsequent readmission/ discharge criteria (fever >100.0F before D21/afebrile for at least 18 hr)
- Added creatinine phosphokinase to Clinical Laboratory Tests

Protocol Version 2.0, dated 19 July 2016

- Opened eligibility to include "double-refractory" population (myeloma patients refractory to both a proteasome inhibitor and an immunomodulatory drug)
- Introduced option to divide dose escalation cohort into independent groups based on high versus low tumor burden (>= 50% vs < 50% CD138+ bone marrow plasma cells)
- Eliminated stagger between infusions during dose expansion
- Revised DLT definition (Grade 4 neutropenia/thrombocytopenia duration extended from 14 to 28 days)
- Specified equal representation of BCMA high versus low subjects (>= 50% vs < 50% tumor BCMA expression) in dose expansion
- Removed requirement for tumor BCMA expression in dose expansion
- Allowed use of archival samples to determine tumor BCMA expression
- Allowed option to explore 2 RP2D groups in dose expansion based on tumor burden
- Added Grade >= 3 neurotoxicity as Event of Special Interest

Protocol Version 3.0, dated 03 March 2017

- Added exploratory endpoint to study mechanisms of response/resistance
- Revised DLT definition (added Grade >=3 neurotoxicity lasting < 3 days as an exception)
- Revised criteria for bb2121 retreatment (removed specific requirements around BCMA expression, CAR T cell persistence, anti-CAR antibody titers and manufacturing)
- Clarified that lymphodepletion would be required for retreatment
- Revised criteria for starting lymphodepletion to allow treatment of subjects with inadequate bone marrow function due to plasma cell involvement

- Introduced MRD assessment at specified time points (independent of response) and at suspected VGPR or better response
- Introduced analysis of bb2121 persistence (VCN) in the bone marrow
- Introduced confirmatory central testing for tumor burden

Protocol Version 4.0, dated 26 September 2017

(Protocol went to the FDA but was never released to sites)

Protocol Version 4.1, dated 01 November 2017 (under Celgene)

- Changed Sponsor from bluebird bio, Inc to Celgene Corporation
- Excluded subjects with history of CNS pathology, ongoing therapeutic anticoagulation, plasma cell leukemia or clinically significant amyloidosis
- Updated bone marrow function eligibility and treatment criteria to mitigate risk of serious adverse events
- Extended mandatory hospitalization to 14 days
- Modified hospitalization discharge criteria (afebrile for 24 hr, CRS/neurotoxicity resolved, declining CRP) and readmission criteria (fever > 100.0F, CRP > 20 mg/dL or rapidly rising before D30) criteria
- Increased outpatient visits (added D17 and D24) and oversight
- Allowed patients with CNS involvement to be retreated
- Allowed for change in manufacturing process during dose expansion
- Extended time of follow-up from 24 to 60 months
- Introduced fludarabine dose reduction in case of renal dysfunction

Protocol Version 5.0, dated 09 May 2018 (under Celgene)

- Added Expansion Cohort 3 to evaluate an expanded dose range of 150 to 450 x 10^6 CAR+ T cells using the commercial manufacturing process
- Excluded retreatment if repeat leukapheresis required
- Removed plasmacytomas and bone marrow plasma cell involvement as acceptable independent criteria for measurable disease
- Added minimum time required for subject follow-up (6 months) independent of tumor progression
- Added minor response (MR) as IMWG Response Category

TABLE OF CONTENTS

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Study Objectives

There are two parts to this study.

The primary objective of the dose escalation part of the study (Part A) is to:

- Determine the maximally tolerated dose (MTD) of bb2121 in subjects with MM whose tumors express BCMA and a recommended phase 2 dose (RP2D) for future studies

The primary objective of the cohort expansion part of the study (Part B) is to:

- Confirm the safety of the dose chosen in Part A

The secondary objective of the study is to:

- Provide preliminary efficacy data on the anti-tumor effects of treatment with bb2121 in subjects with MM whose tumors express BCMA

The exploratory objectives of the study include:

- Evaluate the progression-free survival of subjects treated with bb2121
- Evaluate the persistence, immune phenotype, and function of bb2121 in the blood, bone marrow and/or tumor tissue
- Evaluate cytokine/chemokine, and soluble factor induction in the blood of subjects after infusion of bb2121
- Evaluate the level of BCMA+ cells in blood and bone marrow, and the level of circulating soluble BCMA
- Evaluate minimal residual disease (MRD)

1.2. Study Endpoints

The primary endpoints of the study are:

- Incidence of adverse events (AEs) and abnormal laboratory test results, including dose-limiting toxicities (DLTs).

The secondary endpoints of the study are:

- Disease-specific response criteria including, but not limited to: complete response (CR), very good partial response (VGPR), and partial response (PR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma.

The exploratory endpoints of the study include:

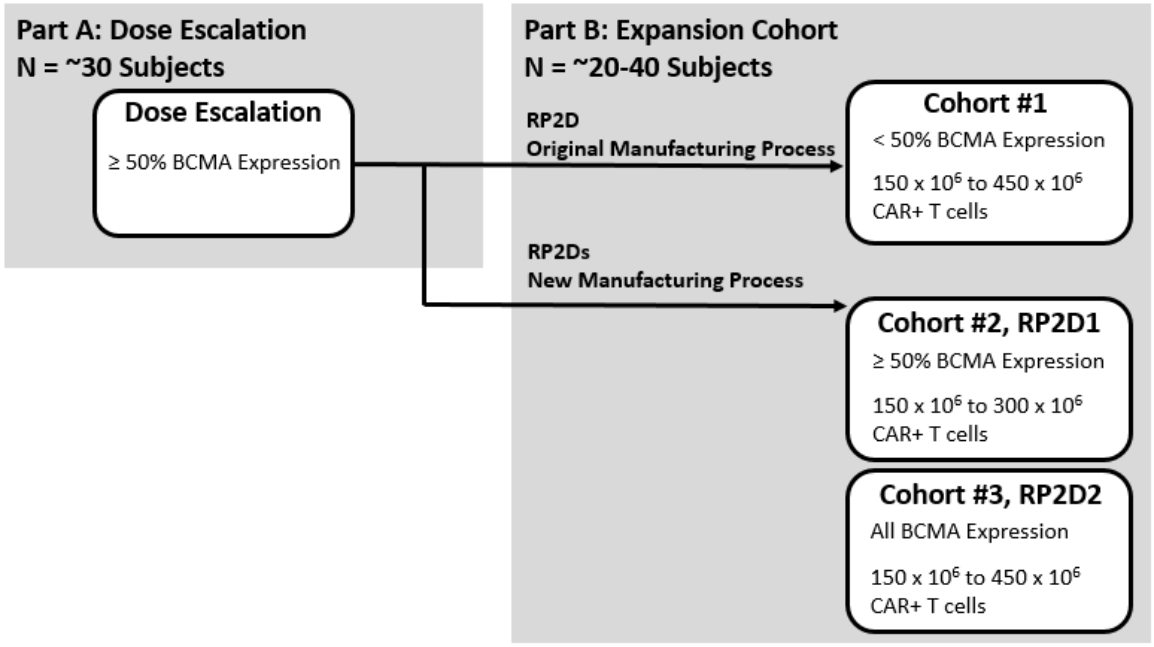
- Overall survival
- Progression-free survival
- Detection and quantification of bb2121 in blood, bone marrow and/or tumor tissue over time

- Detection and quantification of circulating soluble BCMA over time
- Assessment of BCMA expression in plasma cells and tumor cells over time
- Measurement of serum and urine immunoglobulin levels (e.g., IgG, IgA, IgM) and kappa and lambda free light chains
- Evaluation of minimal residual disease
- Assessment of baseline IHC BCMA expression as it correlates to clinical response

2. STUDY DESIGN

This is a 2-part, non-randomized, open label, multi-site Phase 1 study. A schematic of the study design depicts 2 parts: Part A (Dose Escalation), in which the RP2D is determined, and Part B (Expansion Cohorts), in which subjects are treated with the determined RP2D (Figure 2-1).

Figure 2-1 Schematic of Study Design



Abbrev: RP2D, recommended phase 2 dose

2.1. Part A: Dose Escalation, Overview

Up to approximately 30 adults with BCMA+ MM will be enrolled using a 3+3 dose escalation approach:

- Initially, 3 subjects are entered at Dose Level 1.
  - If none of the 3 subjects enrolled at the first dose level experience a DLT, then dose escalation will proceed to the next dose level.
  - If 1 of these 3 subjects experiences a DLT, up to 3 more evaluable subjects will be enrolled at this dose level. If that 1 subject remains the only one to experience a DLT out of 6 subjects, then dose escalation will proceed to the next dose level.
  - If 2 or more of the subjects at this dose level experience a DLT, then dose escalation will be halted and the previous lower dose level will be declared the MTD. If the MTD cohort included only 3 subjects, up to an additional 3 subjects will be enrolled at that dose level to confirm that <2 of 6 subjects experience a DLT at that dose.
- Dose escalation will not proceed until the appropriate number of subjects at that dose level have met the requirements for MTD determination, which includes a minimum

of 21 days of follow-up post bb2121 infusion for DLT determination. An RP2D may be determined without determining an MTD (see Section 2.3).

Subjects during the dose escalation portion of the study will be enrolled sequentially, and bb2121 infusions will be staggered with a minimum of 14 days between each subject. The start of lymphodepletion for each new subject may begin no fewer than 9 days after the preceding subject's bb2121 infusion. In addition, there will be a minimum of 28 days between escalating dose levels from the time of the last subject's bb2121 infusion on the lower dose level to the first subject's bb2121 infusion on the higher dose level. This will allow for review of the full 21-day DLT assessment period to determine the appropriate 3+3 dose escalation procedure.

A subject is evaluable for DLT if the subject received at least the minimum planned bb2121 dose, and either completed 21-days of follow-up on this study after drug product infusion, or experienced a DLT. Enrolled subjects who are not evaluable for DLT during dose escalation (Part A) will be replaced.

At the discretion of the Safety Review Committee (SRC), the dose escalation cohorts may be divided into independent groups based upon tumor burden (e.g., low versus high tumor burden), and the distinct groups would continue independent dose escalation in the described standard 3+3 manner. The decision to divide dose cohorts into groups may occur during an ongoing cohort or at the start of the next dose level. If subjects of only 1 of the divided groups have been included in dose escalation and the decision is made to divide into 2 groups, whichever group has not been included in dose escalation must start at least 1 dose level lower than the most recently successfully completed combined cohorts. Any alteration to the cohorts based on tumor burden will be agreed upon by the study SRC. Independent dose escalation groups will be investigated in parallel and the applicable stagger between infusions will be implemented within the independent groups (low versus high tumor burden), but not between groups. Separate MTDs or RP2Ds may be identified for low and high tumor burden groups. In order to declare RP2D(s), 6 subjects will be treated at that dose; if the RP2D(s) is not dependent on tumor burden, the 6 subjects may consist of low and high tumor burden patients.

2.2. Dose Escalation Levels

The dose escalation scheme is described in Table 2-1. Intermediate dose levels may be explored based upon pharmacokinetics, pharmacodynamics, clinical observations, and/or drug product manufacturing data. Any alteration to the dose levels in Table 2-1 will be agreed upon by the study SRC. Regular teleconferences will occur between the Sponsor, SRC, and study staff prior to dose escalations to discuss the ongoing safety of bb2121.

Table 2-1 Dose Escalation Cohorts

Dose Level	Target Total Fixed Dose[a] CAR+ T Cells (± 20%)
-1	25×10^6
1 (Starting Dose)	50×10^6
2	150×10^6
3	450×10^6
4	800×10^6
5	1200×10^6

[a] bb2121 dose is expressed as the number of anti-BCMA CAR+ T cells per subject; the total number of T cells in the dose will be greater.

Note: Subjects may receive more than one cycle of treatment, but subsequent treatments may not occur until at least 8 weeks after the first treatment, and will not be considered in determining the DLT.

2.3. Maximally Tolerated Dose (MTD) Definition

The MTD is the highest dose that causes DLTs in <2 of 6 subjects. For a dose level to be declared the MTD, at least 5 evaluable subjects must be enrolled with no DLTs reported, or 6 evaluable subjects if 1 subject experiences a DLT.

A MTD may not be determined in this study. A decision to move to expansion cohorts using the RP2D may be made in the absence of a MTD provided the dose is at or below the maximum dose studied in Part A of the study.

2.4. Dose-Limiting Toxicity (DLT) Definition

DLTs are defined as any bb2121-related Grade 3 to 5 toxicity occurring within the 21 days immediately after infusion of the drug product, with the following exceptions:

- ≤Grade 3 Cytokine Release Syndrome (CRS) that responds to appropriate medical intervention within 3 days (see Table 2-3) (recovers to ≤Grade 2)
- ≤Grade 3 neurotoxicity lasting <3 days (recovers to ≤Grade 2)
- ≤Grade 3 to 4 Tumor Lysis Syndrome (TLS) lasting <7 days
- Hematologic toxicities:
  - ≤Grade 3 neutropenia of any duration or Grade 4 neutropenia lasting <28 days
  - ≤Grade 3 anemia of any duration or Grade 4 anemia lasting <28 days

  - ≤Grade 3 thrombocytopenia of any duration or Grade 4 thrombocytopenia lasting <28 days
  - All cytopenias except neutropenia, anemia, and thrombocytopenia as described above
- Non-hematologic toxicities:
  - Fever of any grade, including febrile neutropenia
  - ≤Grade 3 diarrhea lasting <72 hours
  - ≤Grade 3 nausea and/or vomiting lasting <72 hours
  - ≤Grade 3 fatigue lasting <7 days
  - ≤Grade 4 transaminase, bilirubin, creatinine kinase, blood urea nitrogen (BUN), or creatinine elevation lasting <7 days
  - Asymptomatic lipase elevation in the absence of any clinical signs or symptoms of pancreatitis
  - Any non-hematologic Grade 3 clinical laboratory AE that is asymptomatic and rapidly reversible (returns to baseline or to ≤Grade 2 within 7 days).

bb2121-related Grade 3 or 4 toxicities occurring after the first 21 days after infusion of bb2121 will be discussed during the regular SRC meetings and will be considered in decisions regarding the MTD and RP2D for Part B. Dosing of another subject or escalation to a higher dose level will be delayed if qualification of an ongoing toxicity as a DLT is pending.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) will be used to grade toxicities during the trial unless specified above.

2.5. Cytokine Release Syndrome (CRS) and Inpatient Monitoring

The primary acute toxicity observed to date with B cell malignancy-targeted and BCMA-targeted CAR T cells has been CRS, and this protocol will follow the recommendations and management for CRS as defined by Lee et al. (2014a) (see Table 2-2, Table 2-3, and Table 2-4, Table 2-5). For this protocol, a CRS is defined as a constellation of symptoms which may include (but are not limited to) fever, chills, hypotension, dyspnea, hypoxia, confusion, mental status changes, seizures, myalgias, nausea and vomiting, and laboratory abnormalities including elevated AST, ALT, bilirubin, D-dimers, ferritin, urea and/or creatinine (see Table 2-2). Cytokine panels are also typically markedly abnormal, but are considered exploratory in nature.

Treatment of a CRS will follow the recommendations as per Lee et al. (2014a), and may be modified in the future as more published guidelines become available. Any subject with a fever ≥100.0°F should have a work up for CRS. The work-up of a CRS should include hospitalization, evaluation for an infectious etiology (e.g., blood cultures, urine culture, chest X-ray, as required), and have blood drawn for CAR+ T cells and cytokine assessments along with study-outlined clinical laboratory tests (Table 5-5).

Because of the risk of CRS, subjects treated on this protocol must be admitted for inpatient monitoring from Day 0 through Day 14 post bb2121 infusion; subjects may receive bb2121 as an outpatient, and then be hospitalized following the infusion. Inpatient monitoring should include a daily physical exam and vital signs every 4 hours unless otherwise clinically indicated. In addition, the schedule of assessments (Table 5-2) should be followed unless otherwise clinically indicated, in which case additional clinical assessments or interventions should be performed. Prior to discharge, subjects should be afebrile for 24 hours, signs or symptoms of CRS or neurotoxicity should be resolved except for cytopenias, C-Reactive Protein (CRP) should be declining, if elevated from baseline, or stable and not rising.

After discharge from inpatient mandatory hospitalization, subjects experiencing a fever > 100.0°F, CRP > 20 mg/dL (200mg/L), or rapidly rising CRP at any point before Day 30 should be hospitalized and evaluated for symptoms of CRS and neurotoxicity and managed accordingly. Prior to discharge, subjects should be afebrile for 24 hours, signs or symptoms of CRS or neurotoxicity should be resolved, except for cytopenias, C-Reactive Protein (CRP) should be declining if elevated from baseline, or stable and not rising.

Subjects with impaired renal function may be at increased risk from CRS and TLS. They may experience worsening renal function, greater difficulty in management of fluid and electrolyte shifts, and have increased risk of severe, life threatening or even fatal CRS/TLS. Such subjects may require dialysis for management of worsening renal function associated with CRS/TLS.

Table 2-2 Clinical Signs and Symptoms Associated with CRS

Organ System	Symptoms
Constitutional	Fever +/- rigors, malaise fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-Dimer, hypofibrinogenemia +/- bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

Table 2-3 CRS Revised Grading System

Grade	Toxicity
Grade 1	Symptoms not life-threatening and require symptomatic treatment only e.g., fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose[a] of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40%, or Hypotension requiring high dose[a] or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

[a] Refer to Table 2-4
Grades 2 to 3 refer to CTCAE v4.0 grading

Table 2-4 High Dose Vasopressors (all doses are required for ≥ 3 hours)

Pressor	Dose
Norepinephrine monotherapy	≥20 µg/min
Dopamine monotherapy	≥10 µg/kg/min
Phenylephrine monotherapy	≥200 µg/min
Epinephrine monotherapy	≥10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥10 µg/min[a]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 ug/min[a]

[a] VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) / 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) / 10]

Table 2-5 Treating Algorithm for Management of CRS Based on the Revised CRS Grading System

Grading Assessment	Excessive Co-morbidities	Treatment
Grade 1 CRS	Yes or No	• Vigilant supportive care • Assess for infection (Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed)
Grade 2 CRS	No	• Vigilant supportive care as above (In addition, monitor cardiac and other organ function closely)
Grade 2 CRS	Yes	• Vigilant supportive care as above • Tocilizumab +/- corticosteroids
Grade 3 CRS	Yes or No	
Grade 4 CRS	Yes or No	

It is recommended that norepinephrine at a standard dose of 10 μg/minute be used as the initial vasopressor.

Guidelines for the management of toxicities related to bb2121 infusion have been provided, to be used in concert with Table 2-2 through Table 2-5. These guidelines are based on available literature for the management of CRS and may need to be adjusted based on the individual clinical circumstances of each subject. The guidelines are not protocol required therapy as they may need to be adjusted, but serve to provide a single consistent framework for the evaluation and management of CRS and bb2121 related toxicity to mitigate risk to the subject.

2.6. Temperature Self-Monitoring

Once discharged after inpatient monitoring from Day 0 through Day 14 post bb2121 infusion, subjects must take their temperature every 6 to 8 hours and contact their treating investigator for any fever ≥100.0°F through Day 30 post-bb2121 infusion. Subjects should not take any nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin, Advil), Naproxen Sodium (Aleve), aspirin or acetaminophen (Tylenol) because these can mask fevers. Fevers are a critically important sign that requires subjects to report to the treating institution as soon as possible for mandatory inpatient admission. Fevers might possibly be the only warning of life-threatening toxicity that can quickly arise in subjects receiving CAR T cells. If subjects are in clinic for a visit when a self-monitoring temperature is to be done, the temperature may be taken in the clinic by clinic staff. At the discretion of individual investigators, subjects may remain hospitalized for AE monitoring if preferred.

If a subject has a temperature ≥100.0°F , or CRP > 20 mg/dL (200mg/L) or rapidly rising CRP at any point before Day 30, they should be hospitalized until afebrile for at least 24 hours and evaluated for symptoms of CRS and neurotoxicity and managed accordingly (see Section 2.5 for detailed guidelines). The work-up of a CRS should include hospitalization and evaluation for an infectious etiology (e.g., blood cultures, urine culture, chest X-ray, as required). After discharge and through Day 30 after infusion, subjects are required to have a caregiver with them in the event of sudden onset of developing symptoms of CRS and/or neurotoxicity. Documentation of subject awareness of the requirement for a mandatory caregiver should be made during the informed consent process. Subjects are also required to stay within a 30 minute radius of the treating institution. The 30 minute radius should be determined by the Principal Investigator based on local knowledge of traffic and travel patterns. Subjects should be evaluated and or admitted to the treating institution due to the institutions familiarity with the treatment protocol and appropriate management of CRS.

2.7. Neurologic Toxicity

Neurologic toxicities have been reported in anti-CD19 CAR T cell studies, including confusion, obtundation, aphasia, and myoclonus. Life threatening neurotoxicity has also been reported in anti-BCMA CAR T trials, including with bb2121 (Cohen et al., 2016). The reported neurologic toxicities in the anti-CD19 and BCMA CAR T cell studies have often been transient; however there is evidence that persistent neurologic toxicity may also occur (Kochenderfer et al., 2012; Kochenderfer et al., 2015). The mechanism of action of these neurologic toxicities remains unclear and under investigation.

Because these syndromes are only now being characterized in the setting of CAR T cell therapy, in the event of neurologic toxicity it is recommended investigators thoroughly assess subjects including the use of MRI and lumbar punctures to investigate possible mechanisms of action.

2.8. Dose for Subjects for Whom the Minimal Dose Cannot be Manufactured

bb2121 is made on a per-subject basis and there is expected to be heterogeneity in the number of CAR+ T cells that are manufactured for each subject. For a particular dose level, if the number of CAR+ T cells that are manufactured is above this range, only a portion of the manufactured dose will be given with the remainder cryopreserved (where cryopreserved material may either be used for retreatment or research purposes).

If the number of CAR+ T cells manufactured is below the number required at that dose level, the subject may be treated at a dose level previously studied. The subject will be included in safety and efficacy analyses based on the dose received. The subject will not be included in analyses for DLTs or determining the MTD unless it is necessary to expand the size of a lower dose cohort in order to determine the MTD in accordance with Section 2.1.

2.9. Safety Review Committee

The SRC will be made up of at least one investigator from each active clinical site as well as the Medical Monitor from the Sponsor and other ad hoc members as appropriate. The SRC will meet at least monthly (typically by teleconference), prior to dose escalation and to discuss any protocol-related death or occurrence of Grade 4 CRS. The SRC will also review accumulated safety data. The SRC will assist in determining whether any particular AE qualifies as a CRS event retrospectively. In the event that tumor burden cannot be determined by a bone marrow biopsy, the determination for high or low tumor burden will be discussed at the SRC. At the appropriate time (typically once the MTD is defined) the SRC will meet to determine the dose to be used in Part B (Expansion Cohort). This dose must be at or below the MTD. Notably, the SRC may allow several doses to be evaluated in Part B as long as they are at or below the MTD. Any disagreements that occur in the SRC will be adjudicated by the Sponsor.

2.10. Part B: Expansion Cohorts

Part B encompasses expansion cohorts of subjects with MM.

The SRC will decide when to initiate Part B and the RP2Ds (at or below the MTD) to be implemented in 3 cohorts. As depicted in Figure 2-1, the expansion cohorts will include approximately 20 to 40 evaluable subjects.

In Cohort 1, the original manufacturing process will be used, and the dose range will be 150 x 10^6 to 450 x 10^6 CAR+ T cells. BCMA expression is targeted at < 50% in at least 10 subjects.

After 18 October 18, 2017, the current manufacturing process will be implemented for subjects in Cohort 2 and Cohort 3.

- The dose range for Cohort 2 will be 150 x 10^6 to 300 x 10^6 CAR+ T cells. Treatment of the initial 3 subjects will be staggered by 2 weeks between infusions.
- The dose range for Cohort 3 will be 150 x 10^6 to 450 x 10^6 CAR+ T cells.

For all expansion cohorts, a specified dose range assumes an allowance of ± 20%.

2.11. Retreatment

Subjects who experience a DLT will not be eligible for retreatment. Eligible subjects will only receive a second infusion of bb2121 if the following criteria are met:

- At least 8 weeks since their last bb2121 infusion.
- Best response to bb2121 was stable disease or better based on standard response criteria according to the IMWG Uniform Response Criteria for Multiple Myeloma.
- Evidence of disease progression according to IMWG criteria.
- No history of Grade 4 CRS or neurotoxicity with prior bb2121 treatment
- Available cryopreserved bb2121 drug product or PBMC to initiate re-manufacture of bb2121 (eg, repeat leukapheresis is not allowed)
- Eligibility criteria for enrollment continue to be met, except for the following criteria:
  - Exclusion of subjects who have myeloma CNS involvement
  - Exclusion of subjects who received treatment with any gene therapy-based therapeutic for cancer
  - For bone marrow function, follow criteria for starting lymphodepletion (Section 4.5.2.1)
- Eligibility criteria for starting LD chemotherapy needs to be met (refer to Section 4.5.2.1)

Subjects who are retreated:

- Will be administered a dose within the protocol specified dose range, not to exceed the MTD.
- Will receive a course of lymphodepletion before the second infusion of bb2121.
- Blood should be analyzed for CD4+/CD8+ cell analysis at retreatment Baseline.

2.12. Study Discontinuation

Possible reasons for study discontinuation include:

- Adverse event
- Withdrawal by subject
- Lost to follow-up
- Physician decision
- Progressive disease, with at least 6 months of follow up post bb2121 infusion(s)
- Study terminated by sponsor
- Death

- Adequate cells are not collected during harvests, or failure of transduced cells to be dispositioned for clinical use

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by Celgene. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

2.13. Length of Study

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

2.14. Long-term Follow-up

All subjects who complete the study, as well as those who discontinue from the study after receiving bb2121 for reasons other than death, will be asked to participate in a long-term follow-up study. Long-term bb2121-related toxicity, and viral vector safety as well as survival status and subsequent anti-cancer therapies will continue to be monitored under the separate long-term follow-up study for up to 15 years after the last bb2121 infusion as per competent authority guidelines.

2.15. Study Pausing Criteria

Enrollment in this study may be paused at any time for safety reasons. In the event enrollment is suspended, the decision as to whether subjects who have already undergone lymphodepletion will receive bb2121 will be made on a case-by-case basis by the SRC. Subjects who have already been treated with bb2121 will continue in the study.

Enrollment and treatment with drug product may be temporarily suspended for any of the following reasons pending review and recommendations from the SRC:

- Death that is not related to disease progression within 30 days of the bb2121 infusion*
- Determination of unexpected, clinically significant, or unacceptable risk to subjects (e.g., development of drug product-related Grade 4 toxicities that have > 35% incidence at the expansion dose level once the MTD has been determined and at least 15 subjects have been treated as part of the expansion)
- Detection of vector-derived replication competent lentivirus (RCL) in any subject

*Any death that is not due to disease progression within 30 days after receiving bb2121 will result in a hold of further enrollment and treatment with drug product until an investigation into the cause of death is performed. If it is determined that the death was not related to the drug product, then enrollment/treatment with drug product may restart. If the relationship between the drug product and the death is not clear, or it appears that the death may be related to study drug, enrollment and treatment with drug product will be held until the SRC assessment and recommendations as described above.

3. STUDY POPULATION

This study will enroll subjects with BCMA+ MM.

3.1. Number of Subjects

Part A (Dose Escalation): Initially, up to approximately 30 evaluable subjects will be enrolled. Depending on the outcome of these cohorts and decisions made by the SRC, additional subjects may be enrolled as described in Section 2.1. Subjects not evaluable for DLT assessment will be replaced.

Part B (Expansion Cohorts): approximately 20 to 40 evaluable subjects will be enrolled. Replacement subjects may be added if subjects discontinue prior to completing one post-bb2121 infusion tumor staging evaluation.

3.2. Eligibility

3.2.1. Inclusion Criteria

1. ≥18 years of age at the time of signing informed consent
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
3. a) For Part A: Diagnosis of MM with relapsed or refractory disease and have had at least 3 different prior lines of therapy including proteasome inhibitor (PI; e.g., bortezomib or carfilzomib) and immunomodulatory therapy (IMiD; e.g., lenalidomide or pomalidomide), or have "double refractory" disease to a PI and IMiD, defined as progression on or within 60 days of treatment with these agents.

   b) For Part B: Diagnosis of MM with relapsed or refractory disease with previous exposure to PI (e.g., bortezomib or carfilzomib), IMiDs (e.g., lenalidomide or pomalidomide), and daratumumab, and refractory (based on IMWG criteria) to their last line of therapy
4. Subjects must have measurable disease, including at least one of the criteria below:
   - Serum M-protein greater or equal to 0.5 g/dL
   - 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
5. For Part A (Dose Escalation) only: Evidence of cell membrane BCMA expression, as determined by a validated immunohistochemistry (IHC) of formalin-fixed, paraffin-embedded (FFPE) tumor tissue (e.g., bone marrow biopsies or plasmacytoma)
6. Women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or tubal ligation or who has not been naturally postmenopausal for at least 24 consecutive months, must have a negative serum pregnancy test prior to treatment. All sexually active WCBP and all sexually active male subjects must agree to use highly effective methods of birth control through one year

post bb2121 infusion and until CAR T cells are absent by qPCR on two consecutive tests.

Women of childbearing potential (WCBP) must:

- Have a negative pregnancy test as verified by the Investigator, one negative serum beta human chorionic gonadotropin [β-hCG] pregnancy test result at screening, prior to LD chemotherapy. This applies even if the subject practices true abstinence* from heterosexual contact.
- Either commit to true abstinence* from heterosexual contact or agree to use, and be able to comply with, effective measures of contraception without interruption, from screening through at least 1 year following last bb2121 infusion. Contraception methods must include 1 highly effective and 1 additional effective (barrier) method of contraception from screening until at least 12 months following bb2121 infusion and until CAR T cells are no longer present by qPCR on two consecutive tests, whichever occurs last.
- Agree to abstain from breastfeeding during study participation and for at least 1-year post-bb2121 infusion and until CAR T cells are no longer present by qPCR on two consecutive tests, whichever occurs last.

Male subjects must:

- Practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential for at least one year post BB2121 infusion, even if he has undergone a successful vasectomy. Subjects will be followed from screening until at least 1 year following last bb2121 infusion and until CAR T cells are no longer present by qPCR on two consecutive tests, whichever occurs last.

Note: Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective and additional effective methods of contraception:

- Intrauterine device (IUD)
- Hormonal (birth control pill, injections, implants)
- Tubal ligation
- Partner's vasectomy
- Male condom (additional effective method)
- Diaphragm (additional effective method)
- Cervical cap (additional effective method)

7. Recovery to ≤Grade 1 or baseline of any non-hematologic toxicities due to prior treatments, excluding alopecia and Grade 2 neuropathy

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

8. Ability and willingness to adhere to the study visit schedule and all protocol requirements
9. Voluntarily sign informed consent form(s) (ICFs)

3.2.2. Exclusion Criteria

1. Treatment with the following therapies within the specified time period:
    a. Any prior systemic therapy for MM within 14 days prior to scheduled protocol-required leukapheresis
    b. Investigational cellular therapies within 8 weeks prior to the start of lymphodepletion (Note: Criterion 1c does not apply to subjects undergoing retreatment)
2. Subjects with known central nervous system (CNS) disease. History or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, subarachnoid hemorrhage or CNS bleed, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis (Note: this criterion does not apply to subjects undergoing retreatment unless Grade 4 neurotoxicity was observed following prior treatment with bb2121)
3. Inadequate hepatic function defined by aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >2.5 × upper limit of normal (ULN) and direct bilirubin >1.5 × ULN
4. Inadequate renal function defined by creatinine clearance ≤45 ml/min using the Cockcroft-Gault formula
5. International ratio (INR) or partial thromboplastin time (PTT) >1.5 × ULN
6. Inadequate bone marrow function defined by absolute neutrophil count (ANC) <1000 cells/mm^3 in the absence of growth factor support (Neupogen within 7 days or Neulasta within 14 days) and platelet count <50,000 cells/mm^3, in the absence of transfusion support (platelet transfusion within 7 days)
7. Left ventricular ejection fraction <50%
8. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine or systemic steroids at any dose). Intermittent topical, inhaled, or intranasal corticosteroids are allowed
9. Presence of active infection within 72 hours prior to leukapheresis or lymphodepletion; subjects with ongoing use of prophylactic antibiotics, antifungals, or antivirals are eligible as long as there is no evidence of active infection
10. Previous history of an allogeneic bone marrow transplantation or treatment with any gene therapy-based therapeutic for cancer
11. Significant co-morbid condition or disease which in the judgment of the Investigator would place the subject at undue risk or interfere with the study; examples include, but are not limited to, cirrhotic liver disease, sepsis, recent significant traumatic injury, and other conditions

12. Known human immunodeficiency virus (HIV) positivity
13. Subjects with a history of class III or IV congestive heart failure or non-ischemic cardiomyopathy, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the previous 6 months
14. Subjects with second malignancies in addition to myeloma, if the second malignancy has required therapy in the last 3 years or is not in complete remission; exceptions to this criterion include successfully treated non-metastatic basal cell or squamous cell skin carcinoma, or prostate cancer that does not require therapy
15. Subjects who have had a venous thromboembolic event (e.g., pulmonary embolism or deep vein thrombosis) requiring anticoagulation and who meet any of the following criteria:
    a. Requires ongoing therapeutic anticoagulation
    b. Have had a Grade 2, 3, or 4 hemorrhage in the last 30 days
    c. Are experiencing continued symptoms from their venous thromboembolic event (e.g. continued dyspnea or oxygen requirement)
    d. NOTE: Subjects who have had a venous thromboembolic event but do not meet any of the above 3 criteria are eligible for participation
16. Subjects who have plasma cell leukemia or clinically significant amyloidosis
17. Pregnant or lactating women

3.3. Subject Screening and Registration

Subjects willing to participate in the study will provide written informed consent according to Good Clinical Practice (GCP). Written informed consent must be obtained before the conduct of any Pre-Screening or Screening tests. Pre-Screening for BCMA expression will not be required for Cohort 3.

Upon signing the informed consent, the subject will be registered and assigned a unique subject number. Once a subject number has been assigned, it cannot be reused, and the number stays with the subject even if the subject is subsequently determined to be ineligible for the study.

There will be two consent forms for this study. The first consent form is to allow BCMA pre-screening by immunohistochemistry. The BCMA IHC assay is an investigational laboratory screen that may eventually be developed for a Companion Diagnostic if efficacy and safety is observed with bb2121. BCMA pre-screening may be performed at any time following the site initiation visit. This screening will occur on archived FFPE tissue or if unavailable, a biopsy may be performed and the tissue sample submitted for BCMA screening. If a biopsy was previously analyzed by the Sponsor designated central lab, then the central lab pre-screening report may be submitted for pre-screening. Biopsies performed as part of standard of care and associated FFPE tissue may be submitted to a Sponsor designated central lab using the BCMA pre-screening consent form.

The second consent form (Main ICF) will be for the participation in the general study and must be completed prior to any clinical screening or baseline evaluations.

Screening evaluations must take place after main informed consent is obtained.

Leukapheresis must occur ≤ 28 days after the start of assessments in Screening. Thus, if re-screening is necessary:

- Main Informed Consent and Demographics need not be repeated
- Only new Medical History and Disease History since previous screening will be collected
- All other assessments in Table 5-1 under Screening must be repeated.
- The subject will maintain their originally assigned unique subject number.

Re-screening of assessments during Baseline may be performed at the discretion of the Investigator and Sponsor.

3.4. Screen Failures

Subjects are screen failures if:

- They sign the Main ICF, but cannot finish assessments for Screening or are ineligible based on those assessments
- They sign the Main ICF and meet eligibility criteria during Screening, but do not undergo leukapheresis

Data collected on Screen Failure subjects will only include:

- Pre-screening ICF information, including IHC data
- Demography
- Eligibility

If a subject does ***not*** sign the Main ICF, they are considered a pre-screen failure and their data will not be collected.

Note: Subjects who discontinue from the study after leukapheresis but prior to infusion with bb2121 will be considered discontinuations. All study data collected through the point of discontinuation will be captured for subjects who discontinue early.

4. STUDY TREATMENTS AND ASSESSMENTS

4.1. Description of bb2121

bb2121 is defined as an autologous T lymphocyte-enriched population that contains cells transduced with an anti-BCMA02 CAR lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen, suspended in cryopreservative solution.

Anti-BCMA02 CAR lentiviral vector is used to transduce an autologous T cell-enriched population. This vector uses the murine leukemia virus-derived MND promoter to drive expression of the chimeric receptor, a multi-domain protein consisting of the extracellular antigen recognition domain (V_L and V_H), the CD8α hinge domain, a transmembrane domain (CD8 TM), and the intracellular 4-1BB (CD137) co-stimulatory and CD3zeta chain signaling domains.

A schematic of the anti-BCMA CAR is shown in Figure 4-1.

Figure 4-1 Anti-BCMA Chimeric Antigen Receptor

Abbrev.: V_L, light chain variable domain; V_H, heavy chain variable domain; TM, transmembrane

4.2. Transduction Process, Storage of Drug Product, Packaging and Labeling, and Traceability

All cell manipulation procedures will be performed in the Good Manufacturing Practice (GMP) manufacturing suite at Celgene Cellular Therapeutics (CCT) in accordance with Current GMPs following process-specific procedures and batch records.

The drug product, which contains autologous T cells genetically modified to express the anti-BCMA CAR, is cryopreserved in a 5% final dimethyl sulfoxide (DMSO) solution (containing 50% Plasma-Lyte® A and 50% CryoStor® 10) and stored in the vapor phase of liquid nitrogen at CCT GMP facility until release testing and disposition for infusion.

bb2121 will be labeled by the manufacturing facility according to GMP, and detailed records will be maintained to allow for accurate traceability of the bb2121, to ensure that the drug product is administered to the original donor.

Refer to Section 4.4 and the Study Cell Product Handling and Administration Manual for details regarding traceability.

4.3. Blinding, Packaging and Labeling

4.3.1. Blinding and Breaking the Blind

This is an unblinded, open-label study.

4.3.2. Packaging and Labeling

bb2121 contains autologous T cells transduced ex vivo with the anti-BCMA02 CAR lentiviral vector. bb2121 is suspended in cryopreservative solution.

bb2121 will be labeled by the transduction facility according to GMP.

4.4. Product Accountability and Disposal

bb2121 accountability and traceability is ultimately the responsibility of the Investigator and Sponsor. However, this responsibility may be delegated to suitably qualified personnel listed on Food and Drug Administration (FDA) Form 1572 who has had appropriate study-specific training and whose name has been appropriately listed on the Delegation of Responsibility Log for this task.

Detailed records will be maintained to allow for accurate accountability of the bb2121 as per applicable sponsor and clinical site procedures. These records will include details of storage of bb2121; transfer bb2121 from the transduction facility, administration to subjects, and disposal of remaining materials.

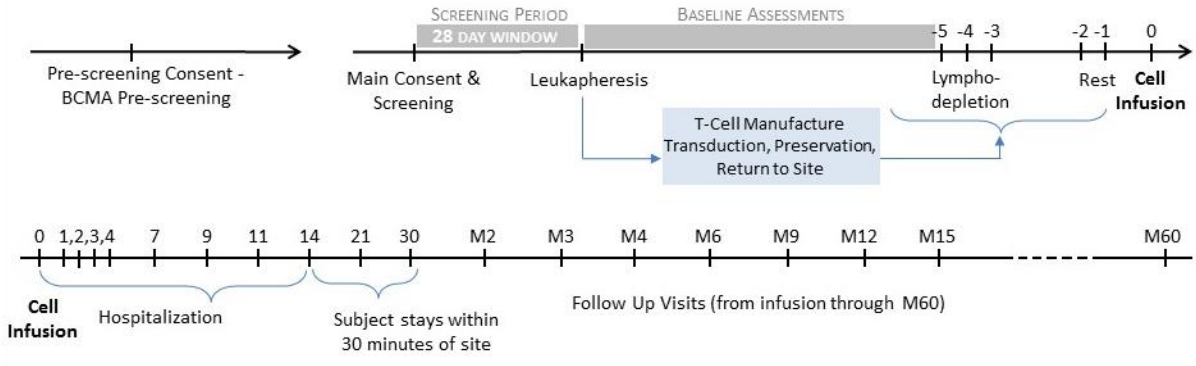
In the event that drug product cannot be administered due to triggering of stopping rules or other reasons, drug product will be kept cryopreserved in the vapor phase of liquid nitrogen until further instruction by the sponsor.

All material containing bb2121 will be treated and disposed of as hazardous waste in accordance with governing regulations and clinical site procedures.

4.5. Summary of Treatments to be Performed or Administered

Figure 4-2 describes the timeline of Study CRB-401, including pre-screening, cell infusion, and follow-up visits.

Figure 4-2 Schematic of Study CRB-401



Top row: BCMA Pre-screening through Day 0 cell infusion
Bottom row: Day 0 cell infusion, follow-up visits

4.5.1. Leukapheresis

In order to obtain a sufficient number of peripheral blood mononuclear cells for CAR T cell drug product manufacturing, enrolled subjects will undergo a leukapheresis procedure processing approximately two times the subject's total blood volume (the target is to collect at least 2.5×10^9 mononuclear cells). The handling of subject cells will be in accordance with *FDA Draft Guidance for Industry (January 2009); Current Good Tissue Practices (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps).*

Peripheral blood mononuclear cells are procured by leukapheresis at designated Apheresis Collection Centers (ACC) qualified by the Sponsor. As part of the Sponsor ACC qualification process, institutional Standard Operating Procedures are collected and reviewed to confirm that procedures are in place to collect starting material for bb2121 manufacturing. If additional controls are necessary to support bb2121 manufacturing, information will be provided by the Sponsor in an apheresis collection manual. Once collected, the leukapheresis products are shipped to the bb2121 GMP manufacturing facility, CCT, where all cell manipulation procedures are performed according to their Standard Operating Procedures. Detailed records will be maintained to allow for accurate accountability of leukapheresis products as per applicable Sponsor, ACC, and CCT procedures.

4.5.2. Lymphodepletion

4.5.2.1. Criteria for Starting Lymphodepletion

Subjects must meet the following criteria prior to starting lymphodepletion:

1. No prior systemic therapy for MM within 14 days prior to the start of cyclophosphamide and fludarabine lymphodepletion
2. Echocardiogram with left ventricular ejection fraction ≥50% within 8 weeks of starting lymphodepletion
3. Adequate hepatic function defined by AST and/or ALT ≤2.5 × ULN and direct bilirubin ≤1.5 × ULN within the 7 days prior to starting lymphodepletion
4. Renal Function:
   - Subjects with moderate impairment of renal function should have a dose reduction of each daily Fludarabine dose (Table 4-1).
   - Subjects with creatinine clearance < 30 mL/min should not receive fludarabine. In addition, their eligibility will be reviewed and decided upon by the Safety Review Committee based on an overall risk/benefit assessment.
5. INR or PTT ≤1.5 × ULN
6. Adequate bone marrow function defined by ANC ≥500 cells/mm^3 and platelet count ≥50,000 cells/mm^3, within the 7 days prior to starting lymphodepletion (unless inadequate bone marrow function is thought to be related to bone marrow plasma cell involvement, and should be discussed with Medical Monitor)

7. No presence of active infection within 72 hours of lymphodepletion. Subjects with ongoing use of prophylactic antibiotics, antifungals, or antivirals are eligible as long as there is no evidence of active infection
8. No intercurrent illness or toxicity that would place the subject at undue risk of proceeding to lymphodepleting chemotherapy and bb2121 infusion (should be discussed with the Medical Monitor)
9. No therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 72 hours prior to lymphodepletion chemotherapy. Physiologic replacement, topical, intranasal and inhaled steroids are permitted.
10. No active urinary outflow obstruction
11. Subjects should complete the following assessments within the 7 days prior to starting lymphodepletion consistent with Table 5-2:
    a. Physical Exam, ECOG performance status and vital signs
    b. Clinical laboratory tests (Table 5-5)
    c. Clinical Disease Staging including Imaging and Bone Marrow Biopsy and Aspirate
    d. Blood for Cytokine Panel, BCMA+ cells, CAR+ T cells, soluble BCMA, Anti-CAR Antibody, VCN (CD3 and Whole Blood), RCL, cellular immunology, and CAR T cell phenotyping

4.5.2.2. Lymphodepletion Treatment Plan

Subjects will receive one 3-day cycle of lymphodepletion starting 5 days prior to bb2121 infusion on Day 0 (Table 4-1).

Table 4-1 Lymphodepletion treatment plan

Drug	Dose	Day
Cyclophosphamide	300 mg/m^2 IV infusion over 30 min	-5, -4, and -3
Fludarabine	30 mg/m^2 IV infusion over 30 minutes administered immediately after cyclophosphamide (fludarabine dose should be reduced based on renal function)[a]	-5, -4, and -3

[a] Subjects with creatinine clearance 50 to 70 mL/min should have a 20% dose reduction of each daily Fludarabine dose; subjects with creatinine clearance of 30 to 49 mL/min should have a 40% dose reduction of each daily Fludarabine dose. Fludarabine should not be administered to subjects with CrCl <30mL/min. The Cockcroft Gault formula should be used to calculate renal function.
http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cf5255cc-91fd-4132-973b-764dba142eae

Chemotherapy should be administered according to institutional guidelines. The following details are recommendations unless otherwise noted.

On Days -5, -4, and -3, it is suggested that subjects receive pre-hydration with 1000 mL 0.9% sodium chloride IV over 1 to 3 hours.

Anti-emetics may be administered according to local institutional guidelines, **but dexamethasone or other steroids are not to be administered.** The use of ondansetron, oral or IV, or similar serotonin inhibitor, on days -5, -4 and -3 prior to chemotherapy is suggested.

Subjects may receive education and prescriptions for anti-emetics such as ondansetron, lorazepam, or prochlorperazine for use when not in clinic.

After the administration of fludarabine on Days -5, -4 and -3, subjects should receive 1000 mL 0.9% sodium chloride IV over 1 to 2 hours. Diuretics may be used as needed based on clinical assessment.

On Days -2 and -1, there are no required clinical interventions except those for supportive care including continued anti-emetics for nausea. Subjects should be encouraged to increase fluid intake to minimize bladder toxicity or be supplemented with IV hydration.

4.5.3. bb2121 Infusion Procedures and Administration

bb2121 is to be given on Day 0, after lymphodepletion on Days -5, -4 and -3. There are no interventions other than supportive care on Days -2 and -1.

On Day 0, bb2121 will be administered IV through non-filtered tubing (**IMPORTANT—AN IN-LINE LEUKOCYTE FILTER MUST NOT BE USED**). A central venous access device, such as a Hickman line or peripherally inserted central catheter (PICC) line, may be utilized and is encouraged in subjects with poor peripheral access. Pre-medication should occur approximately 30 minutes prior to the infusion and should include acetaminophen 650 mg orally and diphenhydramine 12.5 mg IV or 25 to 50 mg orally (or equivalent). Subjects should not receive corticosteroids as pre-medication.

bb2121 must be delivered to the subject care unit, thawed at the infusion site in a ~37°C water bath and infused immediately within 1 hour; alternately, bb2121 may be thawed in the appropriate cell manipulation facility and administered as soon as possible within a maximum of 1 hour after thawing. If multiple drug product bags are to be administered to meet the protocol assigned dose, each bag will be thawed and administered 1 bag at a time within a maximum of 1 hour for each bag until the appropriate volume and corresponding CAR+ T cell dose has been administered.

All procedures involving bb2121 must be performed using aseptic techniques by trained personnel. See bb2121 Infusion Procedures and Administration Manual for more detail.

Vital signs are to be monitored prior to bb2121 infusion, upon completion of the infusion, and every hour for up to 4 hours post bb2121 infusion. Infusion reactions, including anaphylaxis, will be managed according to the medical judgment of the physician overseeing the infusion.

4.6. Duration of Subject Participation

Subjects will be followed for AEs, clinical status, and laboratory parameters up until disease progression or for a maximum of 60 months, whichever is earlier. Subjects who progress prior to Month 6 and are not eligible for retreatment will be followed up through Month 6 (see Table 4-2 for assessments). For subjects who are retreated and progress prior to 6 months post retreatment, they will be followed up through 6 months post retreatment. All subjects who receive bb2121 will be asked to continue to undergo long-term follow-up in a companion study for a total of 15 years after their last bb2121 infusion.

Table 4-2 Assessments for Subjects with PD Prior to Month 6

Procedure
Blood VCN (CD3)
Blood VCN (whole blood)
Blood RCL test
Adverse Event Collection[1]
AE Associated Concomitant Medication Collection
AE Associated Concomitant Procedures Collection
Subsequent Anti-Cancer Therapy Collection
Tumor Biopsy (new or recurrent neoplasm)

[1] All AEs are to be collected through Month 6.

5. STUDY ASSESSMENTS

5.1. Schedule of Events

Evaluations and procedures identified in the Schedule of Events may be performed at unscheduled visits, as clinically indicated, at the Investigator's discretion in consultation with the Sponsor.

Table 5-1 Schedule of Events: BCMA Pre-Screening, Screening, and Leukapheresis

Procedure	Pre-Screening (Any time prior to Main Consent)	Screening (after Main Consent)	Leukapheresis
BCMA IHC pre-screening consent[1]	X		
BCMA IHC screening assay (FFPE)[2]	X		
Main Informed Consent		X	
Demographics		X	
Medical History		X[3]	
Disease History		X[3]	
Physical Examination, Vital Signs		X[4]	
ECOG Performance Status		X[4]	
Blood for Clinical Laboratory Tests[5]		X[4]	X[6]
Blood for CD19+/CD4+/CD8+ Cell Analysis[5]			X[6]
Bone Marrow Aspirate and Biopsy[7]	(X)[8]	X[4,9,10]	
Blood for Serum Pregnancy Test (women of child-bearing potential)[5]		X[4]	
Blood for Serology Testing[5]		X[4]	
Echocardiogram		X[4,11]	
Adverse Event Collection (from Main Consent)		X[3]	
Concomitant Medication Collection (from Main Consent)		X[3]	
Eligibility Confirmation[12]		X	
Leukapheresis			X[13]

[1] Pre-screening will not be performed for Expansion Cohort 3.
[2] A BCMA IHC assay is required to be eligible for leukapheresis. Either archival or newly-obtained biopsy sample may be used.
[3] If performed >28 days before leukapheresis, must be re-confirmed within the 28 days prior to leukapheresis
[4] Assessment must be performed within the 28 days prior to leukapheresis.
[5] Local laboratory (See Section 5.2.6 for details)
[6] Assessment must be performed within the 3 days prior to leukapheresis.
[7] A tumor biopsy of plasmacytoma should also be collected, if medically safe and feasible.
[8] Will serve as Screening assessment if completed within Screening window of 28 days before leukapheresis. If performed outside Screening window, will need to be recollected.
[9] To be performed only if archival tissue was unavailable for Pre-Screening; must occur ≥14 days before leukapheresis; see Table 5-2 for assessment details.
[10] The SRC may choose to evaluate 2 RP2Ds based on tumor burden. In this case, this assessment will be performed on all subjects at Screening, and not at Baseline.
[11] Assessment must be performed within 8 weeks of starting lymphodepletion.
[12] Subjects must meet eligibility criteria prior to leukapheresis.
[13] If local lab routinely performs CBC on collected material if feasible, results will be provided.

Table 5-2 Schedule of Events for Baseline, bb2121 infusion, Follow-up through Month 24

Procedure	Day (D), Month (M), Window (±days)																						
	Baseline[1]	D -5, -4, -3	D 0	D +1, +2, +3, +4	D +7	D +9	D +11	D +14	D + 17	D +21	D + 24	M +1	M +2	M +3	M +4	M +6	M +9	M +12	M +15	M +18	M +21	M +24	PD[2]
				-1	-1	-1	-1	-1	±1	±1	±1	±2	±7	±7	±7	±14	±14	±14	±14	±14	±14	±14	+28
ECOG, physical examination, vital signs	X	X[3]	X[4]	X[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for serum pregnancy test (WCP)[5]	X													X				X					
Blood for clinical laboratory tests[6]	X	X[7]	X[8]	X[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]
Blood for CD19+/CD4+/CD8+ Cell Analysis[6]														X		X		X		X		X	X
Clinical Disease Staging/Response Assessment[10]	X											X	X	X	X	X	X	X	X	X	X	X	X
Bone Marrow Biopsy/Aspirate																							
Morphology/Cytogenetics	X[11]							X[12]				X[12]		X[12]		X[12]	X[12]	X[12]		X[12]		X[12]	X[12]
BCMA+ cells, CAR+ T cells[13]	X[11]							X[12]				X[12]		X[12]		X[12]	X[12]	X[12]		X[12]		X[12]	X[12]
Bone Marrow VCN[13]	X[11]							X[12]				X[12]		X[12]		X[12]	X[12]	X[12]		X[12]		X[12]	X[12]
Minimal Residual Disease[13,14]	X[11]							X[12]				X[12]		X[12]		X[12]	X[12]	X[12]		X[12]		X[12]	X[12]
Gene Expression[13]	X[11]							X[12]				X[12]		X[12]		X[12]	X[12]	X[12]		X[12]		X[12]	X[12]
Blood Cytokine Panel[13]	X		X[15]	X[8]	X	X	X	X		X		X											
Blood BCMA + Cells[13]	X			X[16]	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Blood CAR+ T cells[13]	X			X[16]	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Blood Soluble BCMA[13]	X			X[16]	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Blood anti-CAR antibody[13]	X				X			X				X		X		X	X	X	X	X	X	X	X
Blood VCN (CD3) [13]	X			X[16]	X	X	X	X		X		X	X	X		X		X		X		X	X
Blood VCN (whole blood)[13]	X				X	X	X	X		X		X		X		X		X		X		X	X
Blood RCL test[13,17]	X													X		X		X				X[18]	X
Blood for Cellular Immunology[13]	X				X			X				X		X		X		X		X		X	X

Blood for CAR T Cell Phenotyping[13]	X				X			X				X	X	X		X		X		X		X
Lymphodepletion		X[8]																				
bb2121 Infusion			X																			
Inpatient monitoring			Daily, every 4 hours[19]																			
Temperature self-monitoring									Daily, every 6-8 hrs[20]													
All Adverse Events (including ESIs) collection[21]	Continuous from Main Consent																					
Concomitant medication collection	Continuous from Main Consent																					

[1] Assessment should be performed ≤7 days before lymphodepletion
[2] Per IMWG Uniform Response Criteria all response categories require two consecutive assessments (except radiographic and bone marrow assessments) made at any time prior to start of new therapy. If a subject has PD within 24-months and it is determined during a scheduled visit according to the Schedule of Events, only missing assessments from the PD visit should be performed within 28 days of the last visit.
[3] Only to be performed on Day -5.
[4] Vital signs should be taken prior to bb2121 infusion, once during the infusion, once at the end of infusion, and then hourly for up to 4 hours post infusion
[5] Pregnancy testing must be performed at Screening (serum), 90 days post bb2121 infusion (urine, and serum if urine test positive), and one year post lymphodepleting chemotherapy (urine, and serum if urine test positive).
[6] Local laboratory (See Section 5.2.6 for details)
[7] Assessments should be performed daily.
[8] Assessment may be performed ≤3 days before bb2121 infusion
[9] Hematology and Serum Chemistry panel only (See Table 5-5)
[10] See Section 5.2.5 for details
[11] If the SRC decides to evaluate 2 RP2Ds, this assessment will be performed on all subjects at Screening (Table 5-1), and not at Baseline
[12] If disease is determined to be extramedullary at Screening or Baseline, a tumor biopsy of plasmacytoma should be collected in addition to bone marrow biopsy and aspirate. If subject has a radiologically measurable extramedullary plasmacytoma at progression, a tumor biopsy of plasmacytoma should be collected.
[13] Central laboratory (See Section 5.2.6 for details)
[14] Minimal Residual Disease aspirate for assessment will be collected at specified time points.
[15] Prior to bb2121 infusion
[16] Assessment should be performed at D +2 and D +4
[17] Two samples are required, one for RCL screening test, another for potential co-culture of PBLs if RCL screening test is positive
[18] If a subject's previous RCL tests were all negative, only the co-culture sample will be collected and archived
[19] Inpatient monitoring will occur from Day 0 through Day 14 post-bb2121 infusion, and should include a daily physical exam and vital signs every 4 hours unless otherwise clinically indicated.
[20] Subjects must take temperature every 6-8 hrs daily from discharge through Day +30, and contact their treating investigator for any fever ≥100.0° F which will require mandatory hospitalization until the subject has been afebrile for 24 hours; Subjects must remain within 30 minutes of site.
[21] All AEs on all subjects (excluding screen failures) will be collected through Month 24 (see Section 5.3 for details).

Table 5-3 Schedule of Events for Follow-up after Month 24

Procedure	Month (M), Window (±days)
	M+24 to M+60[1, 2] / LSV
	±14
ECOG, physical examination, vital signs	X[3]
Blood for serum pregnancy test (WCP)	
Blood for clinical laboratory tests[4]	X[2]
Blood for CD4+/CD8+ Cell Analysis[3]	X[5]
Clinical Disease Staging/Response Assessment[6]	X[7]
Bone Marrow Biopsy/Aspirate	
Morphology/Cytogenetics	X[4, 8]
BCMA+ cells, CAR+ T cells[9]	X[4, 8]
Bone Marrow VCN[9]	X[4, 8]
Minimal Residual Disease[9,10]	X[4, 8]
Gene Expression[9]	X[4, 8]
Blood Cytokine Panel[9]	
Blood BCMA + Cells[9]	X[2]
Blood CAR+ T cells[9]	X[2]
Blood Soluble BCMA[9]	X[2]
Blood anti-CAR antibody[9]	X[2]
Blood VCN (CD3) [9]	X[4]
Blood VCN (whole blood) [9]	X[4]
Blood RCL test[9]	X [11]
Blood for Cellular Immunology[9]	X[4]
Blood for CAR T Cell Phenotyping[9]	X[4]
Concomitant Medication Collection	Continuous from Main Consent
Adverse Event Collection[12]	Continuous from Main Consent

[1] Schedule starts after Month 24 follow up visit covered in Table 5-2
[2] Visits will occur every 3 months
[3] These assessments are performed every 3 months
[4] Local laboratory (See Section 5.2.6 for details)
[5] These assessments are performed every 6 months
[6] See section Section 5.2.5 for details
[7] These assessments are performed every 3 months, with the exception of Radiographic Disease Assessment, which is every 6 months
[8] If disease is determined to be extramedullary at Screening or Baseline, a tumor biopsy of plasmacytoma should be collected in addition to bone marrow biopsy and aspirate
[9] Central laboratory (See Section 5.2.6 for details)
[10] Minimal Residual Disease aspirate for assessment will be collected at specified time points, and analyzed at suspected or evidenced VGPR or better response.
[11] Samples will be collected annually after Month 12. If screening tests through the M12 Visit post bb2121 are negative, only the co-culture samples are collected and archived for subsequent visits.

Table 5-4 Assessments to be Performed Daily if a Subject Experiences Suspected CRS From Day 0 Through Day 30

Procedure	Daily During Hospitalization, in addition to scheduled timepoints in Tables 6-2 and 6-3
Blood for clinical laboratory tests	X
Blood for cytokine panel[a]	X
Blood for CAR+ T cells[a]	X[b]

[a] Central laboratory; site study teams may be unable to collect blood for cytokines and CAR+ T cells on certain days (e.g., if event occurs on weekend or evening) or situations where they are unable to provide collection mechanisms to the ER or inpatient setting during unscheduled visits

[b] Blood should be collected Monday through Friday only

5.2. Study Assessments

5.2.1. Tumor BCMA Expression and Tumor Burden

5.2.1.1. Tumor BCMA Expression

Assessment of cell membrane BCMA expression by IHC of formalin-fixed, paraffin-embedded tumor tissue may be performed in the local lab of a participating clinical CRB-401 trial site or the Sponsor-designated lab for the clinical study.

For subjects participating in Part A (Dose Escalation), BCMA expression must be detected on ≥50% of malignant plasma cells from either a bone marrow biopsy or a plasmacytoma. For subjects participating in Part B (Expansion Cohorts) BCMA expression may be analyzed.

The tumor samples evaluated locally for BCMA expression must have the remainder of the block or at least 10 unstained slides from the same sample sent to the central lab for retrospective confirmatory testing.

5.2.1.2. Tumor Burden

Tumor burden will be determined based on percent of bone marrow plasma cells or CD138+ cells using a bone marrow biopsy sample, as determined by either the sponsor-designated central lab or performed locally at the study site and/or other SRC determined markers of myeloma disease burden.

The tumor samples evaluated locally for tumor burden must have the remainder of the block or unstained slides from the same sample sent to the central lab for retrospective confirmatory testing. In the event that tumor burden cannot be determined by a bone marrow biopsy, the determination for high or low tumor burden will be discussed at the SRC.

5.2.2. Demographics and Medical History

Demographic data include gender, age, race, and ethnicity.

[12] Only SAEs of all Grades, Grade ≥3 AEs, and ESI (Section 5.3.2) regardless relationship to drug product will be collected after Month 24.

A complete medical history should include all relevant prior and current medical history, and should also include anti-cancer therapies, including start and end dates of prior therapies, best response, date of progression or relapse, and reason for progression.

5.2.3. Physical Examination and Vital Signs

A physical examination includes general appearance; head eyes, ears, nose, and throat; cardiovascular; dermatologic, abdominal; genitourinary; lymph nodes; hepatic; musculoskeletal; respiratory; and neurological, and weight. Height is also to be measured at Screening.

Vital signs include systolic/diastolic blood pressure, pulse, respiration rate, and temperature. On the day of infusion, vital signs should be taken prior to bb2121 infusion, once during the infusion, once at the end of infusion, and then hourly for up to 4 hours post bb2121 infusion.

Echocardiogram will also be performed.

5.2.4. Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status assessment is to be assessed during screening and at visits according to the Schedule of Events.

5.2.5. MM Response Assessments

MM response assessments include the following:

- Skeletal Survey: At Baseline and at any time post cell infusion if the treating investigator believes there are signs or symptoms of increased or new skeletal lesions. At the discretion of the investigator, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, computerized axial tomography (CAT) scan, or PET/CAT scan may be done at screening in place of a skeletal survey provided the same modality will be used for future assessments
- Radiographic Disease Assessment: Should be performed for any subjects with documented extramedullary disease according to the schedule of assessments. The same imaging modality used at screening (MRI, PET, CAT, or PET/CAT) should be used throughout the study. Imaging should be performed at Month 1, 2, 4, 6 and then every 3 months through Month 24, and then every 6 months until disease progression for up to 5 years.
- Serum beta-2-microglobulin
- Serum (SPEP) and urine (24 hour collection) (UPEP) electrophoresis for M-protein measurement. Serum only subjects will have urine collected at baseline and in the setting of CR or progressive disease and at the end of study.
- Serum and urine immunofixation
- Serum Free Light Chain (FLC, kappa and lambda)
- Quantification of Ig (IgG, IgM, IgA)
- Percent of plasma cells or CD138+ cells and BCMA expression will be assessed on bone marrow biopsy and aspirate samples collected per Schedule of Events and as clinically indicated to accurately assess response according to the IMWG Uniform

Response Criteria for Multiple Myeloma. A tumor biopsy of plasmacytoma should also be collected at Screening or Baseline if medically safe and feasible, and in addition to bone marrow biopsy and aspirate at subsequent visits in cases of extramedullary disease.

If the subject is considered to possibly have resolution of serum and urine M-protein consistent with CR, the biopsy will be used to confirm CR. The biopsy may also be used in suspected progressive disease as applicable.

Bone marrow assessments should include flow cytometry, fluorescence in situ hybridization (FISH), cytogenetics, and morphology. Bone marrow aspirate will also be used for evaluation of MRD at appropriate timepoints.

If a bone marrow biopsy or aspirate is performed at any time during the study, biopsy and/or aspirate samples should be collected for the clinical response assessments and for potential research if available.

If a subject has partial response (PR) or better and then becomes resistant via relapse or progression, a tumor biopsy (bone marrow or plasmacytoma) is strongly encouraged prior to study discontinuation or retreatment. In addition, if a subject meets the criteria for retreatment, all Baseline bone marrow biopsy and aspirate assessments must be performed per Schedule of Events prior to retreatment.

Additional assessments may be performed as part of standard of care as needed for response assessment.

Response assessments will be made according to the IMWG Uniform Response Criteria for Multiple Myeloma.

5.2.6. Laboratory Tests

5.2.6.1. Clinical Laboratory Tests

Clinical laboratory tests (Table 5-5) are to be performed by the local laboratory, and reviewed by the Investigator or qualified designee (e.g., physician’s assistant, nurse practitioner).

Table 5-5 Clinical Laboratory Tests

Hematology	Serum Chemistry	Coagulation	Enzymes & Liver Studies
CBC with differential ferritin fibrinogen	Sodium potassium, chloride bicarbonate creatinine glucose blood urea nitrogen calcium uric acid phosphate magnesium C-reactive protein Creatinine phosphokinase	prothrombin time (PT)/ partial thromboplastin time (PTT), international normalized ratio (INR)	AST ALT alkaline phosphatase total and direct bilirubin albumin LDH

Abbrev.: CBC, complete blood count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase

CBC includes hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

Blood will also be collected for analysis of B and T cell subsets, including CD19+, CD4+ and CD8+ cells.

Additional clinical laboratory tests may be performed at the Investigator's discretion.

5.2.6.2. Additional Eligibility-Determining Laboratory Tests

During Screening, blood samples will be collected for additional eligibility-determining laboratory tests, as follows:

- **Serology**

  Screening serology will be evaluated using standard methods. The serology panel should include the following:

  - HIV-1 and HIV-2
  - hepatitis B virus core antibody (HBcAb)
  - hepatitis B virus surface antibody (HBsAb)
  - hepatitis B virus surface antigen (HBsAg)
  - hepatitis C virus (HCV) antibody
  - HCV RNA
  - HTLV-1 and HTLV-2
  - Rapid plasma reagin for syphilis
  - CMV Antibody
  - West Nile Virus individual donor testing (IDT) of a nucleic acid test (NAT)

– Chagas Antibody

Blood may also be drawn for additional serology testing if subject has risk factors or clinical evidence of infection with other communicable disease agents or disease.

Serology should be performed within 28 days prior to leukapheresis. Additional serology may be performed if required according to country-specific and institutional guidelines.

- **Serum β-human chorionic gonadotropin pregnancy test**

Required for women of child-bearing potential.

5.2.6.3. Replication Competent Lentivirus (RCL)

An RCL screening assay will be performed, and, if positive, a test to assess the presence of RCL in peripheral blood leukocytes will be performed.

5.2.6.4. Vector Copy Number (VCN)

VCN will be determined from DNA in whole blood, blood T cells, and bone marrow to monitor for persistence of vector sequences.

5.2.6.5. Blood and Bone Marrow Analysis for CAR and BCMA

CAR+ T cells, BCMA+ cells, and resident immune cells will be measured and characterized in peripheral blood and bone marrow by flow cytometry. Soluble BCMA will be measured in serum by ELISA or Luminex.

5.2.6.6. Anti-CAR Antibodies

To examine immunogenicity to CAR, serum will be collected and archived for anti-CAR antibody testing.

5.2.6.7. Cytokines

Cytokine analysis will be performed in serum.

Examples of inflammatory cytokines that may be measured include interferon (IFN) gamma, IL-2, IL-6, IL-12, tumor necrosis factor (TNF) alpha, IL-1beta, monocyte chemoattractant protein-1 (MCP-1) and granulocyte macrophage colony-stimulating factor (GM-CSF)) .

5.3. Adverse Events

Monitoring of AEs will be conducted from main informed consent through the duration of the study. All AEs and associated concomitant medications for all subjects (excluding screen failures), will be recorded in the CRFs from the time Main ICF is signed through Month 24 post-bb2121infusion. For subjects that have disease progression prior to Month 6, all AEs will be collected up through Month 6. Retreated subjects will be followed until documented disease progression or for 6 months after retreatment, whichever occurs later. All SAEs, Grade ≥3 AEs, and ESIs (Section 5.3.2) regardless of relationship to drug product, and associated concomitant medications will be collected starting post Month 24 visit until the end of the study.

Note: all serious adverse events (SAEs) for all subjects from the time of signing main informed consent, *including screen failures,* will be immediately reported to Sponsor.

For subjects who discontinue from the study after leukapheresis but before bb2121 infusion, ongoing AEs will be followed-up for 30 days post-discontinuation, and no new AEs will be recorded unless they are related to study procedure, as determined by the Investigator.

5.3.1. Definitions, Documentation, and Reporting

5.3.1.1. Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in subjects, whether or not considered drug related. An AE may include a change in physical signs, symptoms, and/or clinically significant laboratory change occurring in any phase of a clinical study. This definition includes intercurrent illnesses or injuries, and exacerbation of pre-existing conditions. A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the Main ICF and is documented as part of the subject's medical history.

5.3.1.2. Unexpected Adverse Events

An AE is considered unexpected with bb2121 if it is not consistent in nature or severity with the bb2121 reference safety information which is contained in the current bb2121 Investigator's Brochure.

5.3.1.3. Serious Adverse Events

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in death.
- Is *immediately* life-threatening; i.e. the subject was at immediate risk of death at the time of the event. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Requires in inpatient hospitalization or prolongation of existing inpatient hospitalization. Hospitalization admissions occurring during the study period that are for procedures *planned prior to study entry* do not meet this criteria, unless there is a complication resulting from procedure that prolongs hospitalization. Planned hospitalizations for bb2121 infusion and inpatient monitoring required by institutional guidelines also do not meet serious criteria of hospitalization.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a subject's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event.
  - An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based

upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above.

– For the purposes of this study, any new malignancy will be considered medically important and therefore serious.

5.3.2. Medical Events of Special Interest (ESIs)

For the purposes of this study, the following are defined ESIs for bb2121:

- ≥ Grade 3 adverse event of CRS
- ≥ Grade 3 adverse event of macrophage activation syndrome (MAS)
- ≥ Grade 3 adverse event of neurologic toxicity
- ≥ Grade 3 adverse event of infection
- New malignancy
- New diagnosis or exacerbation of autoimmune like or rheumatologic disorder
- New diagnosis of hematologic disorder

Each of these ESIs are to be marked as an “Important Medical Event,” even if no other serious criteria apply. An ESI is to be reported as and SAE to the Sponsor within 24 hours of the Investigator’s first knowledge of the event, even if the experience does not appear to be related to bb2121. All ESIs should be communicated to the Sponsor using the SAE report form as described in the SAE reporting section (Section 6.3.5). The ESIs must also be documented in the appropriate page(s) of the eCRF and the subject’s source documents.

5.3.3. Adverse Event Assessment

For all AEs, the Investigator must determine both the severity of the AE and the relationship of the AE to bb2121.

For immediate reporting of SAEs, the Investigator must provide their assessment of relationship and assessment of serious criteria at the time of SAE report submission to the Sponsor.

Severity (i.e. 'Grade') will be assessed by the Investigator using the current version of the NCI CTCAE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the table below. If the AE is not included in the CTCAE, then the Investigator is to determine the severity of the AE according to the criteria in Table 5-6.

Table 5-6 Grades of Adverse Events

Grade	Definition
Grade 1	Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

If the Grade changes within one day, only the maximum Grade should be recorded in the CRF.

Relationship (i.e. 'Causality assessment'): The Investigator is required to provide their assessment of the relationship of bb2121 to all AEs. Table 5-7 provides a guideline for determining the relationship of bb2121 to an AE.

Table 5-7 Relationship of Adverse Events to Drug Product

Investigator Assessment	Definition	Classification for Reporting Purposes
Not Related	Exposure to the drug product did not occur, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to the drug product.	Not Related
Possibly Related	The study treatment and the AE were not closely related in time, there is an association between the event and the administration of study treatment, and there is a plausible mechanism for the event to be related to the study product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.	Related
Probably Related	The study treatment and the AE were reasonably related in time, there is an association between the event and the administration of bb2121, there is a plausible mechanism for the event to be related to the study product, and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.	Related
Related	The study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the drug product than by other causes, or the drug product was the most likely cause of the AE.	Related

5.4. Pregnancy and Contraception

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (e.g., spontaneous abortion, which requires reporting as an SAE). However, all pregnancies occurring during at least 1 year post bb2121 infusion (in subjects or female partners of subjects) are to be reported in the same time frame as SAEs using the Pregnancy Form. SAEs experienced by subject or female partner of male subject during the course of the pregnancy are required to be immediately reported (i.e. within 24 hours) on the SAE report form.

The course of all pregnancies, including perinatal and neonatal outcome, regardless of whether the subject has discontinued participation in the study, will be followed until outcome, including follow-up of the health status of the newborn through 1 year of age. SAEs experienced by newborn through 1 year of age are required to be immediately reported (i.e. within 24 hours) on the SAE report form.

Cyclophosphamide and fludarabine have been shown in animal studies to be teratogenic. The effects of administration of bb2121 on the pregnant female or the developing fetus are unknown. Female subjects of child-bearing potential are required to use highly effective contraception from Screening through one year post bb2121 infusion and until CAR T cells are absent by qPCR on two consecutive tests. Male subjects are required to use effective contraception (including condoms) from Screening through one year post bb2121 infusion and until CAR T cells are absent by qPCR on two consecutive tests.

5.5. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or to follow-up on AEs or as deemed necessary by the Investigator. Evaluations and procedures to be performed at unscheduled visits, as clinically indicated at the Investigator's discretion in consultation with the Sponsor, and may be based on those listed in the Schedule of Events.

6. STATISTICAL PROCEDURES

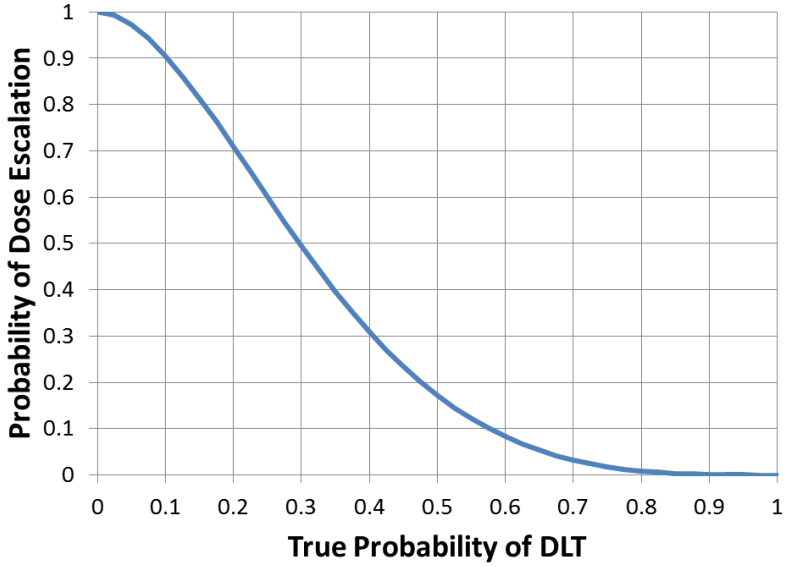
6.1. Sample Size and Power Estimation

The sample size for this study was not determined by formal statistical methods, but will be sufficient to provide preliminary information on safety, as well as efficacy and pharmacodynamic parameters.

Based on the planned dose escalation scheme (Section 2.1), up to approximately 30 evaluable subjects will be enrolled in Part A of the study. An additional approximately 20 to 40 subjects will be enrolled in Part B of the study.

Figure 6-1 presents the probability of escalation from a lower dose to the next higher dose for a range of true rates of DLT in the standard 3+3 dose-escalation design. For example, if the true DLT rate were 20%, then the chance of dose escalation would be approximately 70%.

Figure 6-1 Probability of Dose Escalation for the 3+3 Design



In Part B, a minimum sample size of 25 subjects (approximately 20 to 40 additional subjects from Part B plus at least 5 subjects treated at the MTD from Part A) for each of the RP2Ds would allow the detection of at least 1 AE with a true incidence of 11.3% with 95% confidence. With this sample size and a true incidence of 11.3% for a specific AE, there is a 95% chance of observing at least one occurrence of that AE.

With at least 5 subjects treated at the MTD in Part A and approximately 20 to 40 additional subjects in Part B, there are potentially 25 subjects who are evaluable for efficacy for each of the RP2Ds. The study would have at least 80% power to reject the null hypothesis that bb2121 therapy has a ≤10% objective response rate (ORR) assuming a one-sided test with alpha = 0.05 and a target efficacy of 30% ORR for each of the RP2Ds. A 30% ORR would justify further studies of bb2121 therapy in subjects with relapsed or refractory MM.

6.2. Populations for Analysis

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Screened Population: All subjects who have signed the main informed consent.
- Enrolled Population: All subjects in the Screened population who undergo leukapheresis.
- bb2121 Treated Population: All subjects who undergo bb2121 infusion. This is the primary population for safety and efficacy evaluation.
- Efficacy Evaluable (EE) Population: All subjects in the bb2121-treated population who have had a baseline and at least one post baseline (i.e., post bb2121 infusion) efficacy assessment.
- DLT Evaluable Population: All subjects in Part A of the study who were infused with at least the minimal planned bb2121 dose and either completed 21-days of follow-up on this study after drug product infusion or who experienced a DLT. Subjects for whom the minimal dose could not be manufactured (Section 2.8) will not be included in the DLT evaluable population unless it was necessary to expand the size of a lower dose cohort in order to determine the MTD in accordance with Section 2.1. This is the primary data set for the analysis of safety data for determining the MTD.
- Pharmacokinetic (PK) Analysis population: Subjects who received at least one bb2121 infusion and have evaluable PK data.

The primary analysis of safety and efficacy is planned when all subjects have had sufficient follow-up time for analysis. Ad hoc analysis will be performed as needed.

6.3. Interim Analyses

There will be no formal interim analyses of the data. Interim safety reviews will be conducted by the SRC following completion of each dosing cohort prior to dose escalation and enrollment in the next cohort. The SRC will also evaluate all safety data prior to determining the dose(s) to be used in Part B of the study.

6.4. Statistical Methods

6.4.1. General Methods

Statistical analyses will be primarily descriptive in nature.

Tabulations will be produced separately for each part of the study for appropriate disposition, demographic, baseline, safety, and efficacy parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of observations, mean, median, standard deviation, minimum and maximum values will be presented.

Descriptive summary statistics as well as 2-sided, 90% confidence intervals will be presented on selected parameters.

For change from baseline analyses, baseline for efficacy analyses will be defined as the value closest to, but prior to lymphodepletion; baseline for safety analyses will be defined as the value at screening. Longitudinal data (collected serially over time on study and follow-up) will be presented by appropriate time intervals, such as monthly, quarterly and so forth, depending on the nature of the data.

All data will be provided in by-subject listings.

6.4.2. Demographic, Baseline Characteristics and Disposition of Subjects

Demographic and baseline characteristics (e.g., disease, medical history, prior treatment) will be summarized.

Baseline values of all clinical efficacy parameters will be included in tables of baseline, post-baseline and change from baseline, with all individual data included in the summary statistics included in by-subject, by-time data listings.

A tabulation of the disposition of subjects will be presented, including the number enrolled, the number treated with bb2121, and the reasons for study discontinuation. Tables and listings will be provided for subjects in each analysis data set. Subject data will also be displayed by site. Deviations from protocol treatment and assessment specifications will be tabulated and listed.

6.4.3. Efficacy, Pharmacokinetic, and Pharmacodynamic Analyses

The proportion of subjects who meet disease-specific response criteria after treatment with bb2121 will be tabulated along with a 90% exact binomial confidence interval. This information will be provided by dose (Part A; Part B if >1 RP2D is evaluated) and overall for subjects. In Part B, this information may also be provided by BCMA expression. A one-sided exact binomial test will be performed to test the null hypothesis that the ORR is 10% or less at 0.05 level for the bb2121-treated population. This analysis will be performed by dose if >1 RP2D is evaluated. Disease-specific response includes, but is not limited to:

- complete response (CR), very good partial response (VGPR), and partial response (PR) according to the IMWG Uniform Response Criteria for Multiple Myeloma.

Subjects who are lost to follow up or who die prior to meeting the above criteria will be considered non-responders for the purpose of this analysis.

Estimates of overall survival and progression-free survival will be presented using Kaplan-Meier curves.

These analyses will be provided for the bb2121-treated population.

Details on the evaluation of the remaining exploratory analyses, including pharmacokinetic and pharmacodynamic analyses, will be described in the exploratory analysis plan.

6.4.4. Safety Analysis

All subjects in the bb2121-treated population will be included in the assessment of safety. Safety summaries will use the bb2121 dose group as classifications. For Part A, the primary safety summaries will be by dose level (originally assigned level) and overall. For Part B, the primary safety summaries may be provided by BCMA expression and overall. If >1 RP2Ds are evaluated, primary safety summaries will be by dose as well.

A summary of study drug exposure, including retreatment, will be produced.

For Part A, a summary of the number and type of DLTs experienced by subjects will be produced per dose group, accompanied by a detailed subject listing of DLT events, with the description, severity and relationship of the event.

For Part A and Part B, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized by MedDRA system organ class and preferred terms, and separate tabulations also will be produced for related adverse events (those considered by the Investigator as at least possibly drug related), SAEs, ESIs, discontinuations due to adverse events, and events of at least Grade 3 severity. A summary of the number and severity of CRS AEs will also be produced.

AEs will be summarized for those events that occur during the following periods:

2) From leukapheresis up to but not including the day of the first dose of lymphodepletion
3) From the day of the first dose of lymphodepletion up to but not including Day 0 (the day of bb2121 infusion)
4) From the day of bb2121 infusion (Day 0) through 24 months after drug product infusion (all AEs)
5) After the Month 24 visit through 60 months after drug product infusion (all SAEs, Grade ≥3 AEs, and ESIs regardless of relationship to drug product)

All AEs will be listed in by-subjects, by-time data listings, including any events that may have occurred after signing informed consent but prior to leukapheresis.

Vital signs data and laboratory data will be tabulated for changes over time on study.

Laboratory parameters will be summarized for changes across study using descriptive statistics including shifts relative to CTCAE criteria for laboratory abnormalities. Laboratory measures will also be compared with their corresponding normal ranges and the incidence of abnormally high and abnormally low laboratory values will be calculated for each relevant protocol-specified laboratory test. Laboratory values that are of Grade 3 severity or greater will be tabulated by dose and listed on an individual subject basis.

Additional tabulations of safety data may be produced, as warranted by the data.

All safety data will be provided in subject-level listings.

Analyses on the retreated subjects will be included and outlined in the statistical analysis plan.

7. REFERENCES

Cohen, A.D., Garfall, A.L., Stadtmauer, E.A., Lacey, S.F., Lancaster, E., Vogl, D.T., Dengel, K., Ambrose, D.E., Chen, F., Plesa, G., *et al.* (2016). B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T Cells (CART-BCMA) for Multiple Myeloma (MM): Initial Safety and Efficacy from a Phase I Study. Blood *128*, 1147.

Kochenderfer, J.N., Dudley, M.E., Feldman, S.A., Wilson, W.H., Spaner, D.E., Maric, I., Stetler-Stevenson, M., Phan, G.Q., Hughes, M.S., Sherry, R.M., *et al.* (2012). B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood *119*, 2709-2720.

Kochenderfer, J.N., Dudley, M.E., Kassim, S.H., Somerville, R.P., Carpenter, R.O., Stetler-Stevenson, M., Yang, J.C., Phan, G.Q., Hughes, M.S., Sherry, R.M., *et al.* (2015). Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor. J Clin Oncol *33*, 540-549.

Lee, D.W., Gardner, R., Porter, D.L., Louis, C.U., Ahmed, N., Jensen, M., Grupp, S.A., and Mackall, C.L. (2014a). Current concepts in the diagnosis and management of cytokine release syndrome. Blood *124*, 188-195.

8. APPENDICES

8. BB2121 MANAGEMENT GUIDELINES FOR CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

8.1.1. Cytokine Release Syndrome

Administration of cellular products such as chimeric antigen receptor (CAR)-expressing T cells can be associated with cytokine-associated toxicity due to systemic production and release of various cytokines into the circulation. Cytokine-associated toxicity, also known as cytokine release syndrome (CRS), is a toxicity that occurs as a result of immune activation (Lee, 2014; Gardner 2017).

8.1.1.1. Pathophysiology of CRS

The hallmark of CRS is immune activation resulting in elevated inflammatory cytokines. Cytokine release syndrome clinically manifests when large numbers of lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines. Cytokine release syndrome has classically been associated with therapeutic monoclonal antibody (mAb) infusions, most notably anti-CD3 (OKT3), anti-CD52 (alemtuzumab), anti-CD20 (rituximab), and the CD28 super-agonist, TGN1412. Cytokine release syndrome is also frequently observed following administration of bi-specific T cell engaging antibodies for leukemia, and adoptive cellular immunotherapies for cancer, most notably CAR T cells. Incidence, time to onset and severity of CRS due to CAR T cells is at least partially dependent on the infused cell dose and tumor burden/antigen density, presumably due to more rapid and higher levels of CAR T cell activation. Onset of CRS symptoms typically occurs days to occasionally weeks after the CAR T cell infusion, usually preceding maximal in vivo T cell expansion. Cytokine release syndrome is associated with elevated interferon gamma (IFNγ), interleukin (IL)-6, and tumor necrosis alpha (TNFα) levels, and increases in IL-2, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-10, IL-8, IL-5, and fracktalkine although the pattern of elevated cytokines varies among subjects (Davila, 2014; Hay, 2017). IL-6 has been identified as a central mediator of toxicity in CRS. IL-6 is a pleiotropic cytokine with anti-inflammatory and proinflammatory properties. High levels of IL-6, present in the context of CRS, likely initiates a proinflammatory IL-6-mediated signaling cascade.

8.1.1.2. Clinical Presentation of CRS

Cytokine release syndrome is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable (Table 10-1) (Lee, 2014), and management can be complicated by concurrent conditions. Cytokine release syndrome usually occurs within two weeks after infusion (Abramson, 2017; Berdeja, 2017; Schuster, 2017).

- Fever, especially high fever (≥ 38.5 °C or ≥ 101.3 °F), is a commonly-observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms, and appropriate cultures must be obtained and empiric antibiotic therapy initiated per institution standard of care.

- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurologic toxicity has been observed concurrently with CRS; refer to Section 8.1.2.
- With other CAR T cell products, CRS has been reported in a few cases to be associated with findings of macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), and the physiology of the syndromes may overlap.

Table 8-1 Clinical Signs and Symptoms Associated with CRS

Organ System	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, headache
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Acute kidney injury, azotemia
Gastrointestinal	Nausea, vomiting, diarrhea
Skin	Rash
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic*	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

Adapted from (Lee, 2014); *Neurologic symptoms are typically reversible, and can occur independent of CRS. Neurologic symptoms should be graded and treated independently even if overlapping with CRS (Refer to Section 8.1.2).

8.1.1.3. Clinical Management of CRS

Across various CAR T cell products, early manifestations of CRS can predict more severe toxicity for both CRS and neurotoxicity (NT).

Subjects with B-cell acute lymphoblastic leukemia (ALL) and high burden of disease are at high risk of developing CRS (Frey, 2017). Subjects with non-Hodgkin lymphoma (NHL) who have high baseline tumor burden (measured by the sum of product of the perpendicular diameters [SPD] or high serum lactate dehydrogenase [LDH; ≥ 500 U/L] prior to the start of lymphodepletion) also have a higher risk for developing CRS and/or neurotoxicity (Siddiqi, 2017).

High baseline levels of other commonly measured inflammatory markers, such as ferritin and C-reactive protein (CRP), were also associated with CRS.

It should be noted that, although useful for identifying subjects at higher risk for developing CRS, CRP, ferritin, and serum cytokine levels should not be used for CRS clinical management/treatment decisions in the absence of other clinical signs and symptoms of CRS; for example, a subject with an elevated CRP but no concomitant symptoms may not require intervention (Park, 2017). Thus, close observation of these subjects is strongly recommended.

A modification of the Common Toxicity Criteria for Adverse Events (CTCAE) CRS grading scale has been established to better reflect CAR T cell-associated CRS, as detailed in Table 10-2 (Lee, 2014).

Table 8-2 Grading Criteria for Cytokine Release Syndrome

	Symptoms/Signs	Cytokine Release Syndrome (CRS) Grade 1 (mild)	CRS Grade 2 (moderate)	CRS Grade 3 (severe)	CRS Grade 4 (life-threatening)
			CRS grade is defined by the most severe symptom (excluding fever)		
Vital Signs	Temperature ≥ 38.5 °C/101.3 °F	Yes	Any	Any	Any
	Systolic blood pressure (SBP) ≤ 90 mmHg	N/A	Responds to intravenous (IV) fluids or single low-dose vasopressor	Needs high-dose[a] or multiple vasopressors	Life-threatening
	Need for oxygen to reach oxygen saturation (SaO_2) > 90%	N/A	Fraction of inspired oxygen (FiO_2) < 40%	$FiO_2 \geq 40\%$	Needs ventilator support
Organ Toxicity		N/A	Grade 2	Grade 3 or transaminitis Grade 4	Grade 4 (excluding transaminitis)

[a] Definition of high-dose vasopressors in Table 8-3

Table 8-3 High Dose Vasopressors (all doses required for > 3 hours)

Vasopressor	Dose
Norepinephrine monotherapy	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min
Phenylephrine monotherapy	≥ 200 µg/min
Epinephrine monotherapy	≥ 10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 10 µg/min[a]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 µg/min[a]

[a] VASST Trial Vasopressor Equivalent Equation: Norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10]

Adapted from (Lee, 2014).

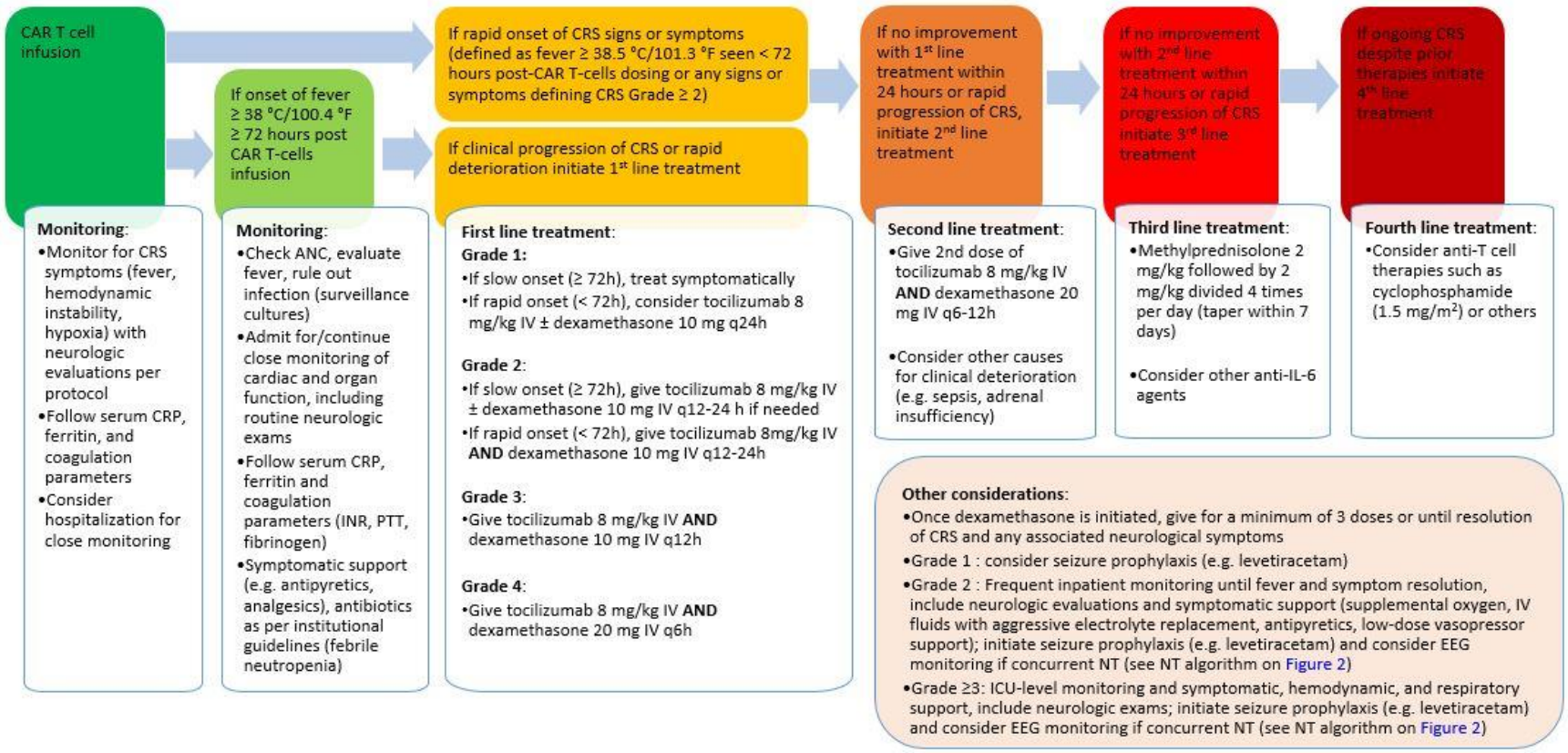
Detailed CRS management guidelines are shown in Figure 8-1. Treatment should be individualized for each subject's clinical needs. This guidance emphasizes the importance of early intervention for Grade 2 CRS, or in the setting of a rapid onset or rapid progression of CRS symptoms, to prevent the development of severe (Grade 3 or greater) CRS and neurotoxicity.

In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe CRS. Please refer to the currently approved Actemra® prescribing information (US) or RoActemra® Summary of Product Characteristics (EU). Actemra® has been approved by the Food and Drug Administration (FDA) for the treatment of CAR T cell-induced severe or life-threatening CRS in adults. The preferred dose to intervene in adult subjects with CRS is 8 mg/kg (maximum 800 mg) IV. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, additional doses of tocilizumab may be administered (please see Figure 8-1, Actemra® prescribing information (US) and Summary of Product Characteristics (EU).

Other anti-IL-6 agents, if available in the country, should be considered in the event of severe CRS not responding to tocilizumab and corticosteroids. Dosing of any other anti-IL-6 agent should be per prescribing information.

In the most unresponsive severe cases additional treatments with T cell depleting therapies such as cyclophosphamide should be considered (Brudno, 2016).

Figure 8-1 Cytokine Release Syndrome Treatment Algorithm



Abbreviations: ANC = absolute neutrophil count; CAR = chimeric antigen receptor; CRP = C-reactive protein; CRS = cytokine release syndrome; EEG = electroencephalogram; ICU = intensive care unit; IL-6 = interleukin 6; INR = international normalized ratio; IV = intravenous; NT = neurotoxicity; PTT = partial thromboplastin time; q = every.

8.1.2. Neurologic Toxicities

CAR T cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. The start of neurologic symptoms has been noted between 3 to 23 days (median 10 days) (Abramson, 2017) after CAR T cell infusion and in severe cases may require admission to the intensive care unit (ICU) for frequent monitoring, respiratory support, or intubation for airway protection. The symptoms are variable and generally occur as CRS is resolving or after CRS resolution.

8.1.2.1. Pathophysiology of Neurological Toxicities

The pathogenesis of neurotoxicity is poorly defined. Subjects with NHL who have high baseline tumor burden (measured by the sum of product of the perpendicular diameters or high serum LDH (≥ 500 U/L) prior to the start of lymphodepletion) also have a higher risk for developing neurotoxicity (Siddiqi, 2017). In addition, severe neurotoxicity has also been reported in subjects with B-cell ALL and higher disease burden at the time of CD19 directed CAR T cell infusion (Park, 2017; Gust, 2017).

Peak levels of IL-6, IFN-γ, ferritin, and CRP are significantly higher in subjects who develop any grade or Grade 3 or higher neurotoxicity (Turtle, 2016; Heipel, 2017). In a study treating NHL subjects with a CD19-directed CAR using a CD28 costimulatory domain, development of Grade ≥ 3 neurologic events and CRS correlated with elevation of various cytokines, including IL-6, IL-15, and IL-2Rα. Subjects with CRS-independent Grade ≥ 3 neurologic events had higher CAR T cell levels and specific cytokines, including interleukin-2, GM-CSF, and ferritin (Neelapu, 2017). Protein levels in the cerebrospinal fluid (CSF) are usually elevated in patients with neurotoxicity, compared with baseline measurements, suggesting disruption of the blood-brain barrier. Other organ dysfunction (hepatic and renal), as well as hypoxemia, and infection, might also contribute to the encephalopathy (Neelapu, 2018). In another study, it has been reported that evidence for cytokine-mediated endothelial activation causes coagulopathy, capillary leak, and blood-brain barrier disruption allowing transit of high concentrations of systemic cytokines into the CSF (Gust, 2017).

8.1.2.2. Clinical Management of Neurological Toxicities

The optimal management of CAR T cell-induced neurotoxicity is unknown at this time. These management guidelines represent the current state of knowledge and additional information will be provided to Investigators as it becomes available. Management should also be guided as per institutional or standard clinical practice, and as determined by the Investigator or treating physician and/or consulting neurologist. A thorough neurologic evaluation, including electroencephalogram (EEG), magnetic resonance imaging (MRI) or computer tomography (CT) scan of the brain and diagnostic lumbar puncture and frequent monitoring of cognitive function (eg, mini mental status exams or handwriting tests) should be considered.

Treatable causes of neurologic dysfunction, such as infection or hemorrhage should be ruled out. Common manifestations of neurotoxicity (eg, confusion, seizure, aphasia), can also be seen with infection, electrolyte imbalances, metabolic acidosis, uremia, concomitant medication use (eg, narcotics), and other medical conditions. Other causes for such symptoms should be considered.

Magnetic resonance imaging and CT scans of the brain are usually negative for any anatomical pathology that would account for the neurotoxicity symptoms observed in subjects treated with CAR T cell therapy, although rare cases of reversible T2/fluid attenuated inversion recovery (FLAIR) MRI hyperintensity involving the thalami, dorsal pons, and medulla, and cerebral edema have been reported (Neelapu, 2018).

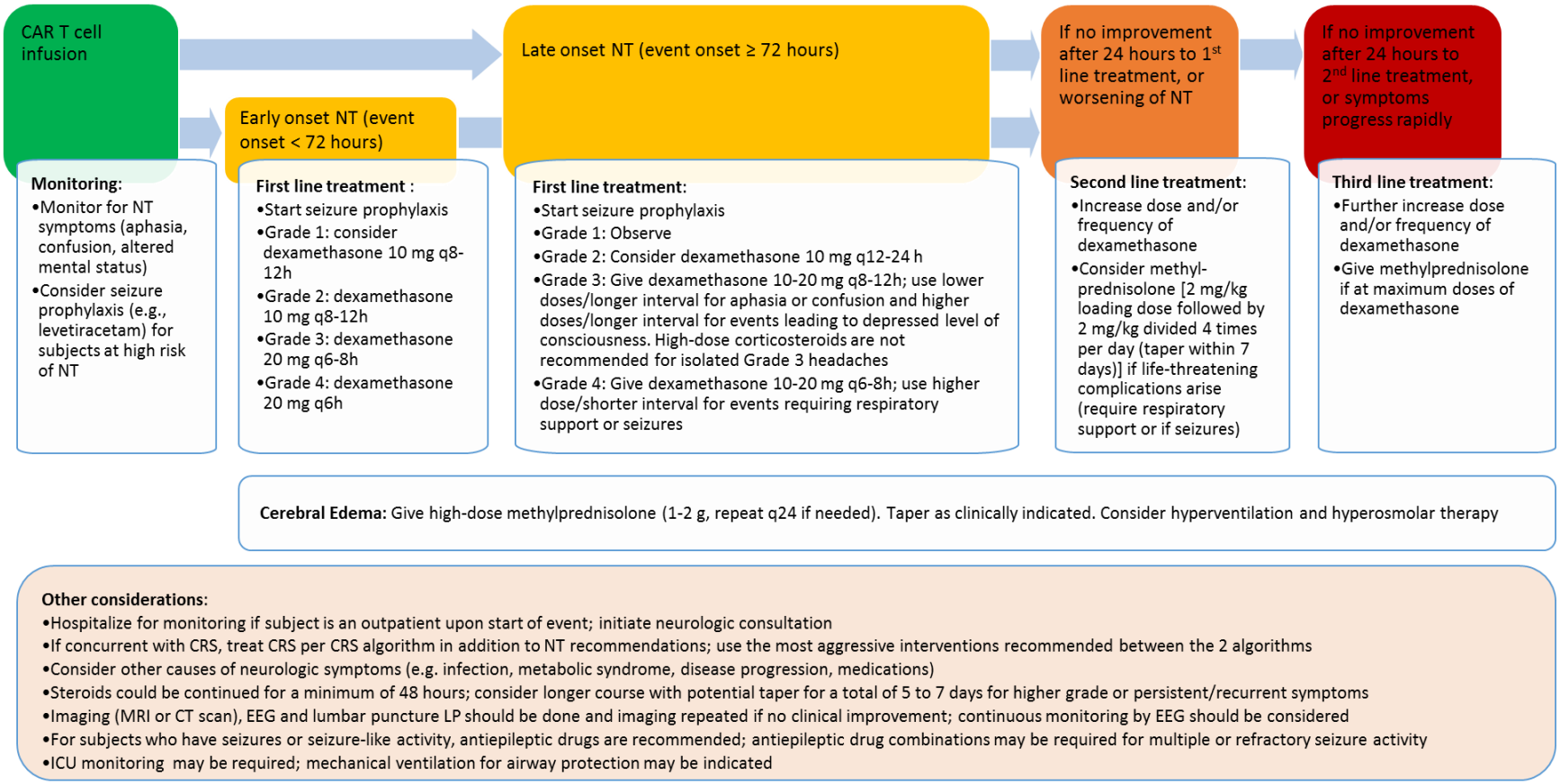
For subjects who have neurologic toxicity in the presence of CRS, the CRS should be managed following the guidelines provided in Figure 8-1.

Neurotoxicity should be evaluated following the guidelines provided in Figure 8-2. For concurrent CRS and neurotoxicity, the most aggressive intervention recommended by either guideline should be employed (if the recommendations for steroid doses differ, use the highest dose and/or frequency). For subjects with Grade 4 neurotoxicity with cerebral edema, high-dose corticosteroids, hyperventilation and hyperosmolar therapy has been recommended (Neelapu, 2018).

Note: Tocilizumab is not recommended for the treatment of neurotoxicity related to CAR T cell therapy, unless CRS or MAS/HLH is also present. Results from 2 studies, one of preemptive use of tocilizumab shortly after anti-CD19 CAR T cell therapy in relapsed/refractory NHL subjects (Locke, 2017), and the other mandatory use of tocilizumab at first fever [> 38.5 °C] in pediatric ALL patients treated with anti-CD19 CAR T cells (Gardner, 2017), demonstrated that early tocilizumab use either increased overall neurotoxicity and Grade ≥ 3 neurotoxicity rates (85% vs 62% overall; 35% vs 26% Grade ≥ 3) or provided no improvement in neurotoxicity rates, respectively. These findings support the hypothesis that tocilizumab does not improve and may worsen isolated neurotoxicity (Locke, 2017).

Neurotoxicity management guidelines are provided in Figure 8-2.

Figure 8-2 Neurotoxicity Treatment Algorithm



Abbreviations: CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CT = computed tomography; EEG = electroencephalogram; ICU = intensive care unit; LP = lumbar puncture; MRI = magnetic resonance imaging; NT = neurotoxicity; q = every.

8.1.3. References

Abramson JS, Palomba ML, Gordon LI, Lunning MA, Arnason JE, Wang M, et al. High durable CR rates in relapsed/refractory (r/r) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort. Blood. 2017 Dec 7;130(1): Abstract No. 581.

Actemra® [Prescribing Information]. South San Francisco, USA: Genentech Inc. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125276s092lbl.pdf

Berdeja JG, Lin Y, Raje N, Munshi N, Siegel D, Liedtke M, et al. Durable clinical responses in heavily pretreated patients with relapsed/refractory multiple myeloma: updated results from a multicenter study of bb2121 anti-BCMA CAR T cell therapy. Blood. 2017 Dec 7;130(1): Abstract 740.

Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127(26):3321-30.

Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014 Feb 19;6(224):224-5.

Frey N. Cytokine release syndrome: Who is at risk and how to treat. Best Pract Res Clin Haematol. 2017 Dec;30(4):336-40.

Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017;129(25):3322-31.

Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov. 2017 Oct 12. [Epub ahead of print]

Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood. 2017 Nov 23;130(21):2295-306.

Heipel M, Smith J, Brown W, Karimi M, Xie B, Li D, et al. Pharmacokinetic, pharmacodynamic and blood analytes associated with clinical response and safety in relapsed/refractory aggressive B-NHL patients treated with JCAR017. Blood. 2017;130:2835.

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10;124(2):188-195. Erratum in: Blood. 2015;126(8):1048.

Locke FL, Neelapu SS, Bartlett NL, Lekakis LJ, Jabobson CA, Braunschweig I, et al. Preliminary results of prophylactic tocilizumab after axicabtagene ciloleucel (axi-cel; KTE-C19) treatment for patients with refractory, aggressive non-Hodgkin lymphoma (NHL). Blood. 2017 Dec 7;130(1): Abstract 1547.

Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017 Dec 28;377(26):2531-44.

Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62.

Park JH. Managing Cytokine Release Syndrome. Clinical Care Options Oncology [Internet]. 2017; https://www.clinicaloptions.com/Oncology/Treatment Updates/Managing AEs/Modules/Managing_CRS.aspx.

RoActemra® [Summary of Product Characteristics]. Welwyn Garden City, United Kingdom: Roche Products Limited. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf.

Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Primary Analysis of Juliet: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Blood. 2017;130(1): Abstract 577.

Siddiqi T, Abramson JS, Li D, Brown W, Devries T, Dave K, et al. Patient characteristics and pre-infusion biomarkers of inflammation correlate with clinical outcomes after treatment with the defined composition, CD19-targeted CAR T cell product, JCAR017. Blood. 2017; 130(1): Abstract 193.

Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR–T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126(6):2123-38.

STATISTICAL ANALYSIS PLAN

Protocol Title: A PHASE 1 STUDY OF bb2121 IN BCMA-EXPRESSING MULTIPLE MYELOMA

SAP Version:	**1**
SAP Date:	**29 AUG 2016**
Study Drug:	**bb2121**
Phase of Study:	**Phase 1**
Protocol Number:	**CRB-401**
Protocol Version:	**Version 1.0**
Protocol Date:	**19 JUL 2016**
Sponsor:	**bluebird bio, Inc.** **150 Second Street** **Cambridge, MA 02141**
CRO Preparing SAP:	**Ce3 Inc.**

TABLE OF CONTENTS

1. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this study is to determine the maximally tolerated dose (MTD) of bb2121 in subjects with multiple myeloma (MM) whose tumors express BCMA, and to determine the recommended Phase 2 dose for future studies; and to confirm the safety of this selected dose.

There are two parts to this study:

- Part A: Dose Escalation Part
- Part B: Cohort Expansion Part.

1.1. Objectives

1.1.1. Primary Objectives

The primary objective of the dose escalation part of the study (Part A) is to:

- Determine the maximally tolerated dose (MTD) of bb2121 in subjects with MM whose tumors express BCMA and a recommended Phase 2 dose (RP2D) for future studies.

The primary objective of the cohort expansion part of the study (Part B) is to:

- Confirm the safety of the dose chosen in Part A.

1.1.2. Secondary Objectives

The secondary objective of the study is to:

- Provide preliminary efficacy data on the anti-tumor effects of treatment with bb2121 in subjects with MM whose tumors express BCMA.

1.1.3. Exploratory Objectives

The exploratory objectives of the study are to:

- Evaluate the overall survival and progression-free survival of subjects treated with bb2121.
- Evaluate the persistence, immune phenotype, and function of bb2121 in the blood, bone marrow and/or tumor tissue.
- Evaluate cytokine/chemokine induction in the blood of subjects after infusion of bb2121.
- Evaluate the level of BCMA+ cells in blood and bone marrow, and the level of circulating soluble BCMA.
- Evaluate minimal residual disease (MRD) in subjects achieving a complete response.

1.2. Endpoints

1.2.1. Primary Endpoint

The primary endpoint of the study is the incidence of adverse events (AEs) and changes in laboratory test results, including dose-limiting toxicities (DLTs).

1.2.2. Secondary Endpoints

The secondary endpoints of the study are disease-specific response criteria including, but not limited to: complete response (CR), very good partial response (VGPR), and partial response (PR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma.

1.2.3. Exploratory Endpoints

The exploratory endpoints of the study are:

- Overall survival
- Progression-free survival
- Detection and quantification of bb2121 in blood, bone marrow and/or tumor tissue over time
- Detection and quantification of circulating soluble BCMA over time
- Measurement of serum and urine immunoglobulin levels (e.g., IgG, IgA, IgM) and kappa and lambda free light chains
- Evaluation of minimal residual disease in subjects achieving a complete response
- Assessment of baseline IHC BCMA expression as it correlates to clinical response

2. STUDY DESIGN

2.1. General Study Design and Plan

2.1.1. Part A: Dose Escalation, Overview

In Part A of the study, up to approximately 30 adults with BCMA+ MM will be enrolled using a 3+3 dose escalation approach:

- Three subjects are entered per dose level.
  - If none of the 3 subjects enrolled at the first dose level experience a DLT, then dose escalation will proceed to the next dose level.
  - If 1 of these 3 subjects experiences a DLT, up to 3 more evaluable subjects will be enrolled at this dose level. If that 1 subject remains the only one to experience a DLT out of 6 subjects, then dose escalation will proceed to the next dose level.
  - If 2 or more of the subjects at this dose level experience a DLT, then dose escalation will be halted and the previous lower dose level will be declared the MTD. If the MTD cohort included only 3 subjects, up to an additional 3 subjects will be enrolled at that dose level to confirm that < 2 of 6 subjects experience a DLT at that dose.
- Dose escalation will not proceed until the appropriate number of subjects at that dose level have met the requirements for MTD determination, which includes a minimum of 21 days of follow-up post bb2121 infusion for DLT determination.

Subjects during the dose escalation portion of the study will be enrolled sequentially, and bb2121 infusions will be staggered with a minimum of 14 days between each subject. The start of lymphodepletion of each new subject may begin no fewer than 9 days after the preceding subject's bb2121 infusion. In addition, there will be a minimum of 28 days between escalating dose levels from the time of the last subject's bb2121 infusion on the lower dose level to the first subject's bb2121 infusion on the higher dose level. This will allow for review of the full 21-day DLT assessment period to determine the appropriate 3+3 dose escalation procedure.

A subject is evaluable for DLT if the subject received at least the minimum planned bb2121 dose, and either completed 21-days of follow-up on this study after drug product infusion, or experienced a DLT. Enrolled subjects who are not evaluable for DLT during dose escalation (Part A) will be replaced.

A Safety Review Committee (SRC) will be made up of at least one investigator from each active clinical site as well as the Medical Monitor from the Sponsor and other ad hoc members as appropriate. At the discretion of the SRC, the dose escalation cohorts may be divided into independent groups based upon tumor burden (e.g., low versus high tumor burden), and the distinct groups would continue independent dose escalation in the described standard 3+3 manner. The decision to divide dose cohorts into groups may occur during an ongoing cohort or

at the start of the next dose level. If subjects of only 1 of the divided groups have been included in dose escalation and the decision is made to divide into 2 groups, whichever group has not been included in dose escalation must start at least 1 dose level lower than the most recently successfully completed combined cohorts. Any alteration to the cohorts based on tumor burden will be agreed upon by the study SRC and included in an amendment to the study protocol.

The dose escalation scheme is described in Table 1. Intermediate dose levels may be explored based upon pharmacokinetics, pharmacodynamics, clinical observations, and/or drug product manufacturing data. Any alteration to the dose levels in Table 1 will be agreed upon by the study SRC. Regular teleconferences will occur between the Sponsor, SRC, and study staff prior to dose escalations to discuss the ongoing safety of bb2121.

Table 1: Dose Escalation Cohorts

Dose Level	Target Total Fixed Dose[a] CAR+ T Cells (± 20%)
-1	2.5×10^7
1 (Starting Dose)	5.0×10^7
2	15×10^7
3	45×10^7
4	80×10^7
5	120×10^7

[a] bb2121 dose is expressed as the number of anti-BCMA CAR+ T cells per subject; the total number of T cells in the dose will be greater.

Note: Subjects may receive more than one cycle of treatment, but subsequent treatments may not occur until at least 8 weeks after the first treatment, and will not be considered in determining the DLT.

The Maximally Tolerated Dose (MTD) is the highest dose that causes DLTs in < 2 of 6 subjects. For a dose level to be declared the MTD, at least 5 evaluable subjects must be enrolled with no DLTs reported, or 6 evaluable subjects if 1 subject experiences a DLT.

A MTD may not be determined in this study. A decision to move to expansion cohorts may be made in the absence of a MTD provided the dose is at or below the maximum dose studied in Part A of the study.

The SRC will meet at least monthly (typically by teleconference), prior to dose escalation and to discuss any protocol-related death or occurrence of Grade 4 CRS. The SRC will also review accumulated safety data. The SRC will assist in determining whether any particular AE qualifies as a CRS event retrospectively. At the appropriate time (typically once the MTD is defined) the SRC will meet to determine the dose to be used in Part B (Expansion Cohort). This dose must be at or below the MTD. Notably, the SRC may allow several doses to be evaluated in Part B as long as they are at or below the MTD. Any disagreements that occur in the SRC will be adjudicated by the Sponsor.

2.1.2. Part B: Expansion Cohorts

Part B encompasses an expansion cohort of patients with BCMA+ MM.

The SRC will decide when to open the cohort, the cohort size, and the dose to be used (must be at or below the MTD). The expansion cohort will include 20 evaluable subjects. This decision will be based on a review of the preliminary safety and efficacy data generated in Part A of the study and in discussion with Regulatory Authorities.

2.1.3. Retreatment

Subjects who experience a DLT will not be eligible for retreatment. Subjects who are retreated will be treated at their original dose during study participation unless it exceeds an established MTD, in which case the MTD will be administered. Subjects may only undergo retreatment once. Subjects may undergo retreatment with bb2121 only if the following criteria are met:

- At least 8 weeks since their last bb2121 infusion
- Best response to bb2121 was no change/stable disease, partial response (PR), or complete response (CR) based on standard response criteria according to the IMWG Uniform Response Criteria for Multiple Myeloma. For those subjects whose best response was CR, the subject must be positive for MRD or have demonstrated subsequent progression prior to retreatment.
- Eligibility criteria continue to be met (except for the exclusion of subjects who have received treatment with any gene therapy-based therapeutic for cancer)
- No evidence of persistent, high titer anti-CAR antibodies that may block bb2121 BCMA recognition
- Continued evidence that the tumor is BCMA positive based on tissue biopsy
- At least a 10-fold reduction in circulating anti-BCMA CAR+ T cells from peak
- Additional manufacture of bb2121 is not required (i.e., retreatment is done using unused drug product from first drug product manufacture)

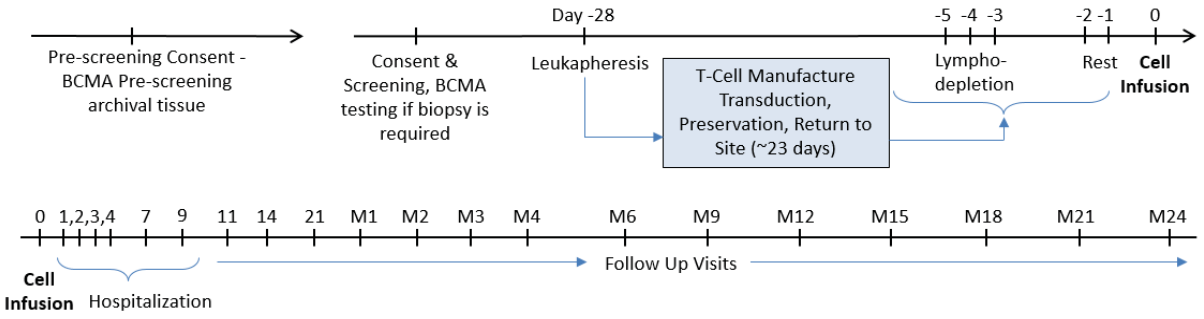
2.1.4. Longterm Follow-up

All subjects who complete the study, as well as those who withdraw from the study after receiving bb2121 for reasons other than death or meeting the early termination criteria, will be asked to continue to undergo longterm follow-up in a companion study for up to 15 years after their last bb2121 infusion, with a focus on longterm safety and efficacy.

2.1.5. Schematic of Study Design

Figure 1 describes the timeline of the study, including pre-screening, cell infusion, and follow-up visits.

Figure 1: Schematic of Study



Top row: BCMA Pre-screening through Day 0 cell infusion
Bottom row: Day 0 cell infusion, follow-up visits

2.2. Study Population

2.2.1. Selection of Study Population

Inclusion and Exclusion criteria are provided in the study Protocol.

2.2.2. Subject Withdrawal and Replacement

It is expected that the most common reason for withdrawal from the study will be disease progression. Subjects, however, may withdraw from this study at any time, for any reason.

It is strongly requested that subjects who respond, but then develop progressive disease, undergo a tumor biopsy prior to study discontinuation.

Subjects who withdraw from the study at any time after receiving bb2121 will be asked to continue to undergo longterm follow-up in a companion study for a total of 15 years after their last bb2121 infusion.

Subjects enrolled in the companion longterm follow-up study may be withdrawn from the longterm gene therapy safety follow up requirements (e.g., visits for clinical assessments and vector copy number [VCN] testing) provided the subject has undetectable VCN (< 0.0003 copies per diploid genome) in peripheral blood cells for 2 consecutive measurements at least 1 month apart at least 12 months after drug product infusion. These subjects will still be followed for progressive disease, relapse, and survival as appropriate.

Subjects withdrawn from the study prior to treatment with bb2121 may be replaced.

2.3. Randomization and Blinding

This is a non-randomized, open label study.

2.4. Study Assessments

Scheduled study assessments are displayed in Table 5-1, Table 5-2, and Table 5-3 of the study protocol.

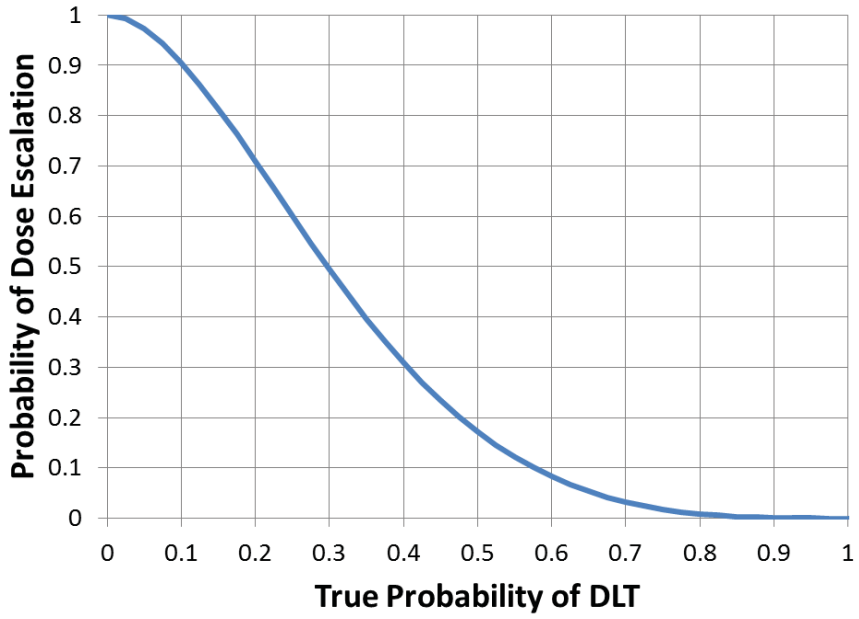
3. SAMPLE SIZE DETERMINATION

The sample size for this study was not determined by formal statistical methods, but will be sufficient to provide preliminary information on safety, as well as efficacy and pharmacodynamic parameters. This sample size would provide 95% assurance for the detection of at least one safety event with a true rate of occurrence of approximately 10%.

Based on the planned dose escalation scheme (Section 2.1.1), up to approximately 30 evaluable subjects will be enrolled in part A of the study. An additional 20 subjects will be enrolled in part B of the study.

The figure below presents the probability of escalation from a lower dose to the next higher dose for a range of true rates of DLT in the standard 3+3 dose-escalation design. For example, if the true DLT rate were 20%, then the chance of dose escalation would be approximately 70%.

Figure 2: Probability of Dose Escalation for the 3+3 Design



In Part B, a minimum sample size of 25 subjects (the 20 additional subjects from Part B plus at least 5 subjects treated at the MTD from Part A) would allow the detection of at least 1 AE with a true incidence of 11.3% with 95% confidence. With this sample size and a true incidence of 11.3% for a specific AE, there is a 95% chance of observing at least one occurrence of that AE.

With at least 5 subjects treated at the MTD in Part A and 20 additional subjects in the expansion study, there are potentially 25 subjects who are evaluable for efficacy. The study would have at least 80% power to reject the null hypothesis that bb2121 therapy has a $\leq$ 10% objective response rate (ORR) assuming a one-sided test with alpha = 0.05 and a minimum efficacy of

30%. A 30% ORR would justify further studies of bb2121 therapy in subjects with relapsed or refractory MM.

4. ANALYSIS POPULATIONS

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: All subjects who initiate any study procedures beginning with leukapheresis. This is the primary set for the analysis of safety data with the exception of determining the MTD and for the analysis of efficacy data. Safety will be evaluated based on specific study periods as noted below.
- The MTD Population: All subjects in Part A of the study who were infused with bb2121 and either completed 21-days of follow-up on this study after drug product infusion or who experienced a DLT. Subjects for whom the minimal dose could not be manufactured (Protocol Section 2.6) will not be included in the MTD population unless it was necessary to expand the size of a lower dose cohort in order to determine the MTD in accordance with Protocol Section 2.1. This is the primary data set for the analysis of safety data for determining the MTD.
- The Efficacy Population (EP): All subjects in Part A of the study treated at the MTD and all subjects enrolled in Part B of the study. This is the primary set for analysis of efficacy data.
- CAR T Population (CP): All subjects who undergo bb2121 infusion, should the number of subjects included in this population be different than that in the ITT population. It is anticipated that the ITT Population and CP will be identical, in which case, analyses performed using the ITT Population will not be repeated for the CP. This is the primary data set for evaluation of exploratory CAR T parameters.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Interim Analyses and Data Monitoring

There will be no formal interim analyses of the data. Interim safety reviews will be conducted by the Safety Revie Committee (SRC) following completion of each dosing cohort prior to dose escalation and enrollment in the next cohort. The SRC will also evaluate all safety data prior to determining the dose(s) to be used in Part B of the study.

5.2. Multi-Center Studies

Given the small sample size in this multi-center study, no adjustment or stratification by study sites will be employed in the summarization or analysis of the data.

The data listings for demographics, baseline characteristics, and disposition of subjects will be augmented to include separate listings by study site.

5.3. Multiple Comparisons / Multiplicity

No adjustments for multiple comparisons are planned.

5.4. Examination of Subgroups

No subgroup analysis is planned.

5.5. Handling of Dropouts or Missing Data

No imputation will be performed for data from missed visits or for evaluations that are not performed.

Subjects in the ITT Population, the EP, or the CP will be considered treatment failures in any efficacy analyses if they have no follow-up after drug product infusion.

Sensitivity analyses will be performed to determine the impact of missing efficacy data.

5.6. Outlier handling

Potential data entry errors manifested as outliers will be handled in the data management process through edit checks.

5.7. Adjustments for covariates

Not applicable.

6. SUMMARY OF STUDY POPULATION DATA

6.1. Subject Disposition

A tabulation of the disposition of subjects will be presented, including the number enrolled, the number treated with bb2121, and the reasons for study discontinuation. Tables and listings will be provided for subjects in each analysis data set. Subject data will also be displayed by site.

Deviations from protocol treatment and assessment specifications will be tabulated and listed.

6.2. Protocol Deviations

Protocol deviations will be tabulated and listed.

6.3. Demographics and Baseline Characteristics

Demographic data will include gender, age, race, and ethnicity.

Baseline physical characteristics will include height, weight, and BMI. Other baseline characteristics will include medical and disease history, and prior treatment.

The data handling convention for missing or partial dates will be applied if needed in the determination of time from initial diagnosis to baseline.

Summaries of demographic and baseline physical characteristics data will be provided. Tabulated summaries will also be provided for medical history, disease history, and prior treatment. These summaries will be provided by Part A dose cohort and overall, and for all patients in Part B. Separate summaries will be provided for each study population, and for tumor burden groups (if necessary).

Individual subject data on demographics, baseline physical characteristics, and for medical history, disease history, and prior treatment will be provided. In addition, separate listings of these data will be provided for each study site.

6.4. Dosing and Extent of Exposure

A summary of drug exposure will be produced for each part of the study. This summary will indicate the frequency and percentage of subjects who were infused per protocol, who completed infusion without interruption, and who were retreated. Summary stastics for infusion details such as volume infused, total number of cells infused, and total number of CAR+ cells infused will also be provided.

Individual study drug administration records and deviations in administration will be displayed in a listing.

6.5. Prior Cancer Therapy

Data on prior cancer therapies will be tabulated for the Safety Population. These summaries will include the frequency and percentage of subjects who received any prior anti-myeloma therapy; who underwent prior cancer surgeries; and who received prior radiation therapy. Descriptive summaries (mean, SD, median, minimum, maximum) for the number of therapries will also be provided.

Indivdual data on prior cancer therapy will be displayed in a listing.

7. EFFICACY ANALYSES

The efficacy analyses will be provided for the efficacy population.

The proportion of subjects who meet disease-specific response criteria after treatment with bb2121 will be tabulated along with a 90% exact binomial confidence interval. A one-sided, alpha = 0.05, Fisher's exact test will be performed to test the null hypothesis that the ORR is 10% or less. This information will be provided by cohort and overall for subjects. Disease-specific response includes, but is not limited to:

- complete response (CR), very good partial response (VGPR), and partial response (PR) according to the IMWG Uniform Response Criteria for Multiple Myeloma.

Subjects who are lost to follow up or who die prior to meeting the above criteria will be considered non-responders for the purpose of this analysis.

Overall survival will be defined as the time (in months) from Day 0 to death. For patients for whom death is not reported, the patient will be censored at the earlier of (1) date of end of study; (2) date on which new therapy is initiated.

Progression free survival (PFS) will be defined as the time (in months) from Day 0 to either first observation of progressive disease or occurrence of death due to any cause within XX days (approximately 2 time intervals for tumor assessments) of either infusion or the last response assessment. In subjects without a progression date or with a death date more than XX days after the first administration of study drugs or the last tumor assessment, the PFS time should be censored on the date of last response assessment or date of bb2121 infusion. Progression free survival analyses should consider tumor assessments after treatment discontinuation or metastatic surgery.

Estimates of overall survival and progression-free survival will be presented using Kaplan-Meier curves.

8. SAFETY ANALYSES

All safety analyses will be performed based on the ITT Population, except for DLT related analyses which will be performed using MTD population. If the CP population is different from ITT population, safety analyses will be repeated in the CP population.

For Part A, the primary safety summaries will be by dose level (originally assigned level) and overall. For Part B, the primary safety summaries will be by cohort and overall. Subjects in Part A will also be grouped with subjects in Part B for those subjects in Part A that receive the same dose of study treatment as subjects in Part B (recommended Phase 2 dose, RP2D), and safety will be summarized for this group of subjects ('Combined RP2D Cohort').

For the Combined RP2D Cohort, primary safety summaries will also be provided separately for subjects classified at screening as low tumor burden and as high tumor burden. This classification will be determined by CD138+ as follows:

Low Tumor Burden: [STATE CRITERION]

High Tumor Burden: [STATE CRITERION].

Additionally, for the Combined RP2D Cohort, primary safety summaries will also be provided separately for subjects classified at screening as high or low BCMA as follows:

Low BCMA: BCMA < 50%

High BCMA: BCMA ≥ 50%.

8.1. Adverse Events

8.1.1. Summaries to be Provided

All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of analysis. AEs will be summarized for those events that occur during three time periods (which will be referred to as Reporting Periods A, B, and C) as follows:

1. After initiating any study procedure (not including pre-screening for BCMA by archival tissue), through leukapheresis, and up to but not including the day of the first dose of lymphodepletion ("Reporting Period A")
2. From the day of the first dose of lymphodepletion up to but not including Day 0 (the day of bb2121 infusion) ("Reporting Period B")
3. From the day of bb2121 infusion (Day 0) through 24 months after drug product infusion (all AEs) ("Reporting Period C").

Adverse events will be summarized by MedDRA system organ class (SOC) and preferred terms.

The following summaries of AEs will be provided:

- An overall summary of AEs, including number of subjects in the population, number of subjects with one or more AEs, number of subjects with one or more Serious AEs, number of deaths (if any), number of subjects experiencing AEs resulting in discontinuation, and number of subjects experiencing Medical ESIs (defined as Grade 3 or greater Cytokine Release Syndrome [CRS] events, and Grade 3 or greater events of neurologic toxicity);
- Frequency and percentage of AEs by SOC and PT;
- Frequency and percentage of AEs by PT;
- Frequency and percentage of AEs by SOC and PT by maximum severity;
- Frequency and percentage of ≥ Grade 3 AEs by SOC and PT;
- Frequency and percentage of Related AEs (i.e., AEs assessed as Possibly Related, Probably Related, or Related to study treatment) by SOC and PT;
- Serious adverse events (SAEs) by SOC and PT;

- Events of special interest (ESIs, as defined above) by SOC and PT;
- AEs resulting in study discontinuations by SOC and PT.

The denominator used for calculation of the percentages will be the number of subjects in the Safety population per treatment group being summarized.

Summaries of the number and incidence of CRS AEs by SOC and PT by severity will also be produced. These will be prepared in five different manners, respectively summarizing AEs that meet each of the following five criteria:

- All AEs except those which are designated as symptoms of CRS on the case report form;
- AEs that are coded as SOC = Immune System Disorders, PT = Cytokine Release Syndrome;
- AEs that are designated as symptoms of CRS on the case report form;
- AEs that meet either of the previous two criteria;
- AEs for which [CRITERIA TO BE PROVIDED BY SPONSOR]

All AEs will be listed in by-subjects, by-time data listings, including any events that may have occurred after signing informed consent but prior to leukapheresis. This listing will include a field for Study Day calculated as [(AE start date, minus date of first dose of study medication) +1].

Additional listings will be provided for:

- SAEs;
- Deaths;
- AEs that led to discontinuation;
- ESIs.

8.1.2. Conventions Regarding Adverse Events

Missing or Partial Dates: The data handling convention for missing or partial dates will be applied in the reporting of adverse events

Relationship: Adverse events will be considered related to study drug (bb2121) if relationship is reported as ‘Possibly related’, ‘Probably related’, or ‘Related’.

Reporting of Multiple Events: The following conventions will be followed in summarizing multiple occurrences of an adverse event for a certain assessment period when summarizing data from individual patient:

- Each subject will be counted only once within a body system (SOC) or a preferred term;

- The highest known severity within a body system or a preferred term will be assigned to the event;

For multiple events within a body system or a preferred term that have differing overall relationships to study drug (i.e., not related and related) will be considered assessed as related to study drug when summarizing treatment-related AEs.

Pooling of Similar Terms: Hematologic abnormalities reported as AEs that were coded to preferred terms in the Investigations SOC will be pooled with appropriate clinical terms in the Blood and Lymphatic System SOC (e.g., thrombocytopenia) for tabulation as follows:

Coded Term	**Pooled with**
Platelet count decreased	Thrombocytopenia
Hemoglobin decreased	Anaemia
Neutrophil count decreased	Neutropenia
White blood cell count decreased	Leukopenia

8.2. Dose-Limiting Toxicities

DLTs are defined as any bb2121-related Grade 3 to 5 toxicity occurring within the 21 days immediately after infusion of the drug product, with the following exceptions:

- Grade 3 CRS that responds to appropriate medical intervention within 3 days (see Protocol, Table 2-3) (recovers to ≤ Grade 2)
- Grade 3 to 4 Tumor Lysis Syndrome (TLS) lasting < 7 days
- Hematologic toxicities:
  - Grade 3 neutropenia of any duration or Grade 4 neutropenia lasting < 28 days
  - Grade 3 anemia of any duration or Grade 4 anemia lasting < 28 days
  - Grade 3 thrombocytopenia of any duration or Grade 4 thrombocytopenia lasting
  - < 28 days
  - All cytopenias except neutropenia, anemia, and thrombocytopenia as described above
- Non-hematologic toxicities:
  - Fever of any grade, including febrile neutropenia
  - Grade 3 diarrhea lasting < 72 hours
  - Grade 3 nausea and/or vomiting lasting < 72 hours
  - Grade 3 fatigue lasting < 7 days

- Grade 3 to 4 transaminase, bilirubin, creatinine kinase, blood urea nitrogen (BUN), or creatinine elevation lasting < 7 days
- Asymptomatic lipase elevation in the absence of any clinical signs or symptoms of pancreatitis
- Any non-hematologic Grade 3 clinical laboratory AE that is asymptomatic and rapidly reversible (returns to baseline or to ≤ Grade 2 within 7 days).

For Part A, a summary of the number and type of DLTs experienced by subjects will be produced per dose group, accompanied by a detailed subject listing of DLT events, with the description, severity and relationship of the event for patients in MTD population.

8.3. Clinical Laboratory Evaluations

Clinical laboratory evaluations to be performed during the study are presented in the table below:

Table 2: Clinical laboratory evaluations to be performed during the study

Hematology	Serum Chemistry	Coagulation	Enzymes & Liver Studies
CBC with differential ferritin fibrinogen	sodium potassium chloride bicarbonate creatinine glucose blood urea nitrogen calcium uric acid phosphate magnesium C-reactive protein Creatinine phosphokinase	prothrombin time (PT)/ partial thromboplastin time (PTT) international normalized ratio (INR)	AST ALT alkaline phosphatase total and direct bilirubin albumin LDH

Abbreviations: CBC, complete blood count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase

CBC includes hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

Descriptive summaries of laboratory parameters will be provided by assessment time point. Additionally, summaries will be provided for changes across the study, as well as for all laboratory parameters in which out of range values were noted.

Laboratory measures will also be compared with their corresponding normal ranges and the incidence of abnormally high and abnormally low laboratory values will be calculated for each relevant protocol-specified laboratory test.

A listing (in table format) will be provided for all subjects who experience ALT or AST >3xULN and bilirubin >2xULN, at any duration, even if combination is not simultaneous.

Laboratory values that are of Grade 3 severity or greater will be tabulated by dose and listed on an individual subject basis.

The data for clinical laboratory evaluations will be presented in listings.

8.4. Vital Signs

Vital signs measurements will include systolic/diastolic blood pressure, pulse, respiration rate, and temperature. The vital signs data will be tabulated for each evaluation time point.

The data for vital signs evaluations will be presented in listings.

8.5. Other Safety Measures

Additional tabulations of safety data may be produced, as warranted by the data.

9. EXPLORATORY ANALYSES

The primary data set for exploratory analyses will be the CP.

Tabulations and individual subject data listings will be prepared for each of the exploratory endpoints listed in Section 1.2.3 of this Statistical Analysis Plan.

10. CLINICAL PHARMACOLOGY ANALYSES

10.1. PharmaroKinetics Analyses

PK analyses will be detailed in a separate PK analysis plan.

10.2. Pharmacodynamic (PD) Analyses

The PD analyses is detailed in a separate SAP.

11. OTHER ANALYSES

Other tabulations and analyses may be added as warranted by the study data, and as requested by the study sponsor. Details regarding these methods will be added prior to locking the final study database.

12. REPORTING CONVENTIONS

The table, listing reporting layout will be detailed in companion document, *CRB-401 SAP Table Figure Listing Shell*. A list of required repeat versions of tables, listings, or figures will be maintained in a separate document.

The general reporting conventions are summarized in the two following sections.

12.1. General Reporting Conventions

All tables, figures and data listings will be presented in landscape orientation for easy visual comparison of different dose escalation cohort. If figures presented, legends will be used for all figures with more than one variable or item displayed. Figure lines should be wide enough to see the line after being copied.

All titles will be centered on a page. The ICH numbering convention will be used for all TLFs. All tables, figures, and data listings will have the name of the relevant SAS program and a date-time stamp on the bottom of each output.

Number precision will be specified in the companion documents.

12.2. Statistical Conventions

For tables, sample sizes for each treatment group will be presented as totals in the column header (N=xxx), where appropriate. Sample sizes shown with summary statistics are the number (n) of patients with non-missing values.

Summaries for categorical variables will include only categories that subjects had a response in. Percentages corresponding to null categories (cells) will be suppressed. All summaries for continuous variables will include: N, mean, and SD. Other summaries (e.g., median, quartiles, 5%, 95% intervals, CV or %CV) will be used as appropriate. All percentages should be rounded and reported to a single decimal place (xx.x%). If percentages are reported as integers, percentages greater than 0% but < 1% will be reported as < 1%, whereas percentages greater than 99% but < 100% will be reported as > 99%. A percentage of 100% will be reported as 100%. No value of 0% should be reported. Any computation of percent that results in 0% is to be reported as a blank.

12.3. Software

All statistical summaries and analyses will be produced using SAS®[1], release 9.4.

13. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

No changes from protocol.

14. REFERENCES

1. SAS Institute Inc., Cary, NC, USA.

15. TABLES, FIGURES, LISTINGS

Tables, listings and, if applicable, figures will be generated according to the companion document which detailed the layout of the output. Minor style variation in the final production is permissible.

STATISTICAL ANALYSIS PLAN

A Phase 1 Study of bb2121 in BCMA-Expressing Multiple Myeloma

STUDY DRUG: bb2121 (Autologous Anti-BCMA CAR T Cells)

PROTOCOL NUMBER: CRB-401

DATE FINAL: 01 October 2018 (Version 3.1)

Prepared by:

Celgene Corporation

86 Morris Avenue

Summit, NJ 07901

SUMMARY OF CHANGES

The statistical analysis plan (SAP, version 3.1, 01 October 2019) replaced previous version 1.0 (29 August 2016). The main reasons for this new version are to (1) update the SAP to be in accordance with the latest protocol amendment 5.0 (09 May 2018) in terms of study design and subject cohorts for analysis, and (2) align with Celgene conventions for clinical trial terminology, statistical analysis and data handling rules.

The major changes include:

- Updates to the study analysis population definitions according to the protocol
- Add more safety and efficacy endpoints according to the protocol and include additional specifications for their analysis algorithms (e.g., progression-free survival and overall survival censoring rules)
- Introduce subgroup analyses
- Add content to the pharmacokinetics (PK) section and add a biomarker and correlation analyses section
- Align the data handling rules according to Celgene conventions (e.g., imputation rules for partially missing dates, lab data handling conventions)

TABLE OF CONTENTS

1. STUDY OBJECTIVES

1.1. Primary Objectives

The primary objective of the dose escalation part of the study (Part A) is to:

- Determine the MTD of bb2121 in subjects with MM whose tumors express BCMA and a RP2D for future studies

The primary objective of the cohort expansion part of the study (Part B) is to:

- Confirm the safety of the dose chosen in Part A

1.2. Secondary Objectives

The secondary objective of the study is to:

- Provide preliminary efficacy data on the anti-tumor effects of treatment with bb2121 in subjects with MM whose tumors express BCMA

1.3. Exploratory Objectives

The exploratory objectives of the study are:

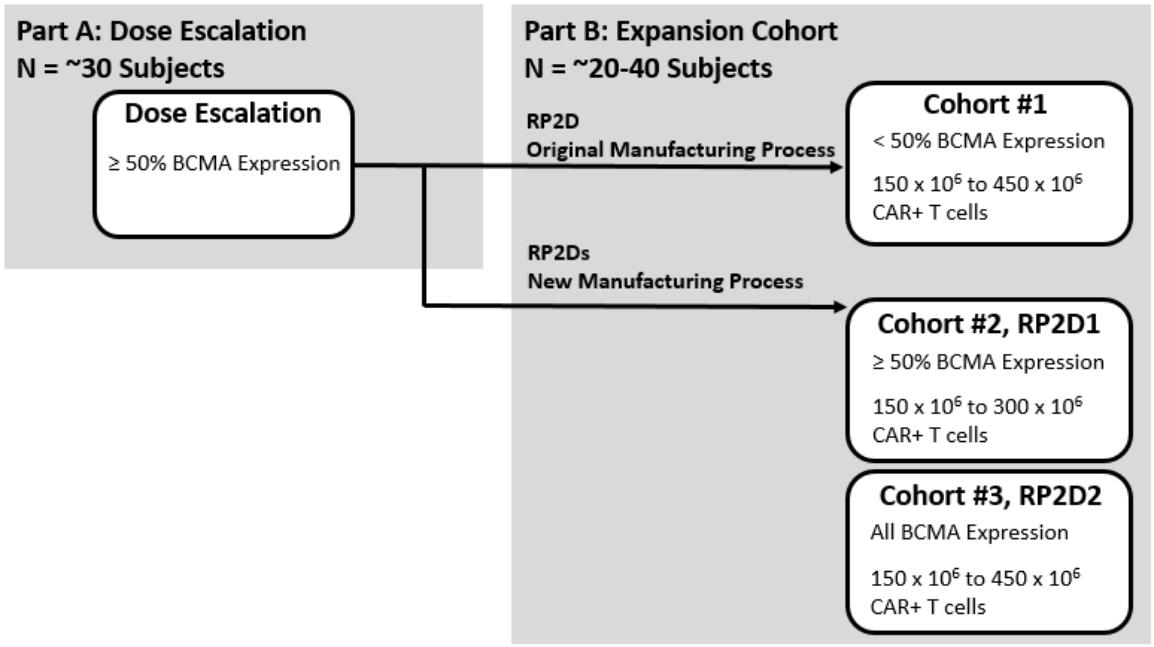
- Evaluate the overall survival and progression-free survival of subjects treated with bb2121
- Evaluate the persistence, immune phenotype, and function of bb2121 in the blood, bone marrow and/or tumor tissue
- Evaluate cytokine/chemokine induction in the blood of subjects after infusion of bb2121
- Evaluate the level of BCMA+ cells in blood and bone marrow, and the level of circulating soluble BCMA
- Evaluate minimal residual disease (MRD)

2. INVESTIGATIONAL PLAN

2.1. Overall Study Design and Plan

This is a 2-part, non-randomized, open label, multi-site, Phase 1 study. A schematic of the study design depicts 2 parts: Part A (Dose Escalation), in which the RP2D is determined, and Part B (Expansion Cohorts), in which subjects are treated with the determined RP2D (Figure 1).

Figure 1: Schematic of Study Design



2.1.1. Part A: Dose Escalation

In the dose escalation phase (Part A) of the study, up to approximately 30 adults with BCMA+ MM will be enrolled using a 3+3 dose escalation approach.

- Initially, 3 subjects are entered at Dose Level 1.
  - If none of the 3 subjects enrolled at the first dose level experience a dose limiting toxicity (DLT), then dose escalation will proceed to the next dose level.
  - If 1 of these 3 subjects experiences a DLT, up to 3 more evaluable subjects will be enrolled at this dose level. If that 1 subject remains the only one to experience a DLT out of 6 subjects, then dose escalation will proceed to the next dose level.
  - If 2 or more of the subjects at this dose level experience a DLT, then dose escalation will be halted and the previous lower dose level will be declared the MTD. If the MTD cohort included only 3 subjects, up to an additional 3 subjects will be enrolled at that dose level to confirm that < 2 of 6 subjects experience a DLT at that dose.
- Dose escalation will not proceed until the appropriate number of subjects at that dose level have met the requirements for MTD determination, which includes a minimum of

21 days of follow-up post bb2121 infusion for DLT determination. An RP2D may be determined without determining an MTD.

The MTD is the highest dose that causes DLTs in < 2 of 6 subjects. For a dose level to be declared the MTD, at least 5 evaluable subjects must be enrolled with no DLTs reported, or 6 evaluable subjects if 1 subject experiences a DLT.

An MTD may not be determined in this study. A decision to move to expansion cohorts using the RP2D may be made in the absence of an MTD provided the dose is at or below the maximum dose studied in Part A of the study. Several doses may be evaluated in Part B as long as they are at or below the MTD.

Subjects during the dose escalation portion of the study will be enrolled sequentially, and bb2121 infusions will be staggered with a minimum of 14 days between each subject. The start of lymphodepletion for each new subject may begin no fewer than 9 days after the preceding subject's bb2121 infusion. In addition, there will be a minimum of 28 days between escalating dose levels from the time of the last subject's bb2121 infusion on the lower dose level to the first subject's bb2121 infusion on the higher dose level. This will allow for review of the full 21-day DLT assessment period to determine the appropriate 3+3 dose escalation procedure.

A subject is evaluable for DLT if the subject received at least the minimum planned bb2121 dose, and either completed 21-days of follow-up on this study after drug product infusion, or experienced a DLT. Enrolled subjects who are not evaluable for DLT during dose escalation (Part A) will be replaced. The definition of DLT is specified in Section 3.4 of the protocol.

At the discretion of the Safety Review Committee (SRC), the dose escalation cohorts may be divided into independent groups based upon tumor burden (eg, low versus high tumor burden), and the distinct groups would continue independent dose escalation in the described standard 3+3 manner. The decision to divide dose cohorts into groups may occur during an ongoing cohort or at the start of the next dose level. If subjects of only 1 of the divided groups have been included in dose escalation and the decision is made to divide into 2 groups, whichever group has not been included in dose escalation must start at least 1 dose level lower than the most recently successfully completed combined cohorts. Any alteration to the cohorts based on tumor burden will be agreed upon by the study SRC. Independent dose escalation groups will be investigated in parallel and the applicable stagger between infusions will be implemented within the independent groups (low versus high tumor burden), but not between groups. Separate MTDs or RP2Ds may be identified for low and high tumor burden groups. In order to declare RP2D(s), 6 subjects will be treated at that dose; if the RP2D(s) is not dependent on tumor burden, the 6 subjects may consist of low and high tumor burden patients.

The dose escalation scheme is described in Table 2. Intermediate dose levels may be explored based upon pharmacokinetics (PK), pharmacodynamics (PD), clinical observations, and/or drug product manufacturing data. Any alteration to the dose levels in Table 2 will be agreed upon by the study SRC. Regular teleconferences will occur between the Sponsor, SRC, and study staff prior to dose escalations to discuss the ongoing safety of bb2121.

Table 1: Dose Escalation Cohorts

Dose Level	Target Total Fixed Dose[a] CAR+ T Cells (± 20%)
-1	25×10^6
1 (Starting Dose)	50×10^6
2	150×10^6
3	450×10^6
4	800×10^6
5	1200×10^6

[a] bb2121 dose is expressed as the number of anti-BCMA CAR+ T cells per subject; the total number of T cells in the dose will be greater.
Note: Subjects may receive more than one dose of treatment, but subsequent treatments may not occur until at least 8 weeks after the first treatment, and will not be considered in determining the DLT.

2.1.2. Part B: Expansion Cohorts

Part B encompasses an expansion cohort of subjects with MM.

The SRC will decide when to initiate Part B and the RP2D(s) (at or below the MTD) to be implemented in 3 cohorts. As depicted in Figure 3 1, the expansion cohorts will include approximately 20 to 40 evaluable subjects.

In Cohort 1, the original manufacturing process will be used, and the dose range will be 150 x 10^6 to 450 x 10^6 CAR+ T cells (+20%). BCMA expression is targeted at < 50% in at least 10 subjects.

After 18 Oct 2017, the current manufacturing process will be implemented for subjects in Cohort 2 and Cohort 3.

- The dose range for Cohort 2 will be 150 x 10^6 to 300 x 10^6 CAR+ T cells (+ 20%). Treatment of the initial 3 subjects will be staggered by 2 weeks between infusions
- The dose range for Cohort 3 will be 150 x 10^6 to 450 x 10^6 CAR+ T cells (+ 20%)

For all expansion cohorts, a specified dose range assumes an allowance of ± 20%.

2.1.3. Retreatment

Subjects who experience a DLT will not be eligible for retreatment. Eligible subjects will only receive a second infusion of bb2121 if protocol specified criteria are met (protocol section 3.11).

Subjects who are retreated:

- Will be administered a dose within the protocol specified dose range, not to exceed the MTD
- Will receive a course of lymphodepletion before the second infusion of bb2121
- Blood should be analyzed for CD4+/CD8+ cell analysis at retreatment Baseline

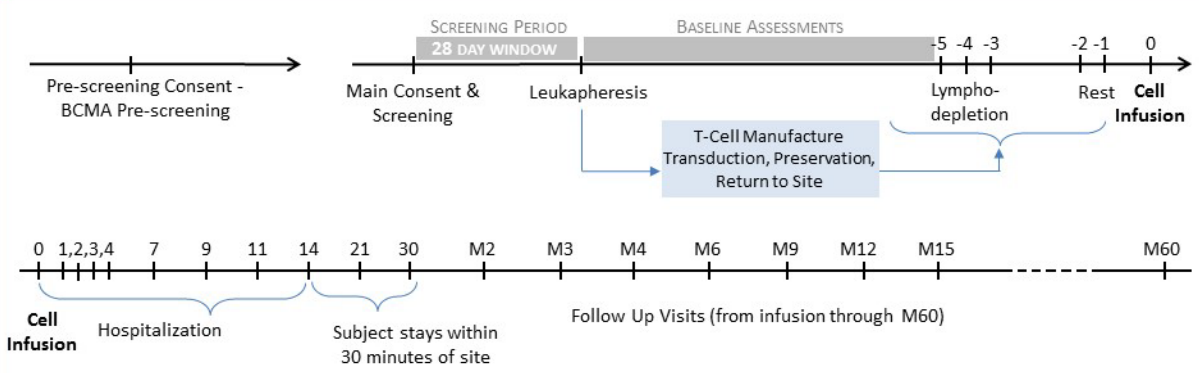
2.1.4. Long-term Follow-up

All subjects who complete the study, as well as those who withdraw from the study after receiving bb2121 for reasons other than death, will be asked to participate in a long-term follow-up study. Long-term bb2121-related toxicity, and viral vector safety as well as survival status and subsequent anti-MM therapies will continue to be monitored under the separate long-term follow-up study for up to 15 years after the last bb2121 infusion as per competent authority guidelines.

2.1.5. Schematic of Study Design

Figure 2 describes the timeline of the study, including pre-screening, cell infusion, and follow up visits.

Figure 2: Schematic of Study



Top row: BCMA Pre-screening through Day 0 cell infusion
Bottom row: Day 0 cell infusion, follow-up visits

2.2. Study Endpoints

The primary endpoints of the study are:

- Incidence of adverse events (AEs) and abnormal laboratory test results, including DLTs

The secondary endpoints of the study are:

- Disease-specific response criteria including, but not limited to: complete response (CR), very good partial response (VGPR), and partial response (PR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma (Kumar, 2016)

The exploratory endpoints of the study are:

- Overall survival (OS)
- Progression-free survival (PFS)

- Detection and quantification of bb2121 in blood, bone marrow and/or tumor tissue over time
- Detection and quantification of circulating soluble BCMA over time
-
- Measurement of serum and urine immunoglobulin (Ig) levels (eg, IgG, IgA, IgM) and kappa and lambda free light chains
- Evaluation of MRD
- Assessment of baseline IHC BCMA expression as it correlates to clinical response

2.3. Stratification, Randomization, and Blinding

This study is an open-label, single arm study. Treatment assignment does not require randomization, blinding or stratification.

2.4. Sample Size Determination

The sample size for this study is determined based on clinical considerations, in addition to the 3+3 dose escalation approach for the dose escalation portion. It is considered sufficient to provide preliminary information on safety, as well as efficacy and pharmacodynamic parameters.

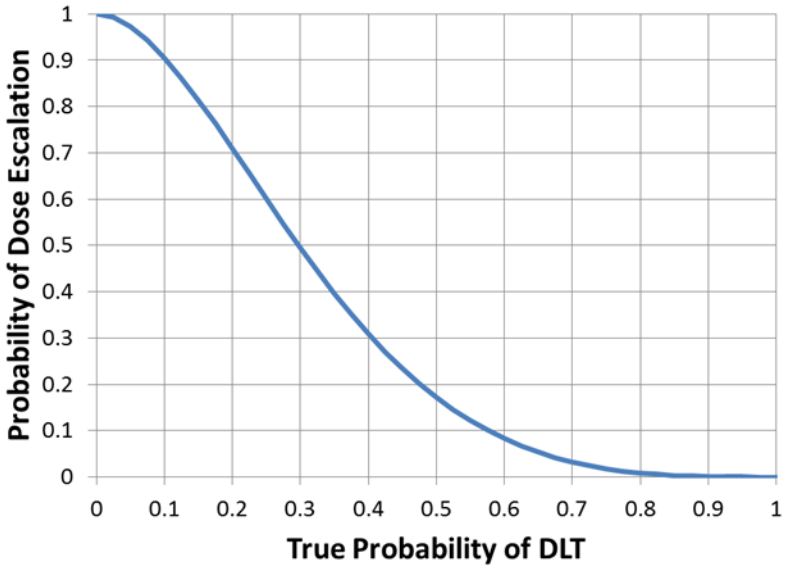
Based on the planned dose escalation scheme (Section 2.1.1), up to approximately 30 evaluable subjects will be enrolled in Part A of the study. Approximately 20 to 40 additional subjects will be enrolled in Part B of the study.

Figure 3 presents the probability of escalation from a lower dose to the next higher dose for a range of true rates of DLT in the standard 3+3 dose-escalation design. For example, if the true DLT rate were 20%, then the chance of dose escalation would be approximately 70%.

In Part B, a minimum sample size of 25 subjects (approximately 20 to 40 additional subjects from Part B plus at least 5 subjects treated at the MTD from Part A) for each of the RP2D(s) would allow the detection of at least 1 AE with a true incidence of 11.3% with 95% confidence. With this sample size and a true incidence of 11.3% for a specific AE, there is a 95% chance of observing at least one occurrence of that AE.

With at least 5 subjects treated at the MTD in Part A and approximately 20 to 40 additional subjects in Part B, there are potentially 25 subjects who are evaluable for efficacy for each of the RP2D(s). The study would have at least 80% power to test the null hypothesis that bb2121 therapy has a $\leq$ 10% objective response rate (ORR) assuming a one-sided test with alpha = 0.05 and a target efficacy of 30% ORR for each of the RP2Ds. A 30% ORR would justify further studies of bb2121 therapy in subjects with relapsed or refractory MM.

Figure 3: Probability of Dose Escalation for the 3+3 Design



DLT = dose limiting toxicity

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. Reporting Conventions

- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001,' and p-values that round to 1.0000 will be presented as '>0.9999.'
- Confidence intervals (CIs) will be presented as two-sided 95% CIs unless specified differently in specific analysis.
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, standard deviation (STDEV), minimum, and maximum for continuous variables.
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value.
- The number and percentage will be presented in the form XX (XX.X%), where the percentage is in the parentheses. All percentages will be rounded to one decimal place.
- All listings will be sorted for presentation in order of part (A vs B), dose cohort, subject, and date of procedure or event, unless specified otherwise.

Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the following:

- Program and data source (eg, SAS program name and SAS dataset name, including the path, that generates the output).
- Data extraction date (eg, data cutoff date or database lock date, and data extract date).
- Output date (eg, run date).

The purpose of the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference. An output date will also appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listings will display all the relative values supporting corresponding table and figure.

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the "Date9." date format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

The analysis specified by this SAP will summarize subjects by dose cohorts and overall in the dose-escalation and in the dose-expansion phase. In addition to by dose cohort analysis, the subjects treated with RP2Ds in both dose escalation and expansion phase as well as other select dose cohorts such as active dose (defined as dose level above 50×10^6 CAR T cells) will be combined for analysis. Subgroups analyses of key clinical and manufacturing characteristics will be conducted to support the main analyses.

For bb2121-retreated subjects, their data before retreatment will be analyzed together with those subjects who did not undergo retreatment; however, their data after retreatment will be analyzed separately from the initial bb2121 infusion in general unless specified otherwise. The populations specific for bb2121 retreatment (Section 3.2.7) will be used.

The day of the first dose of bb2121 will be defined as Study Day 1 (corresponding to Day 0 in the Protocol).

3.2. Analysis Populations

3.2.1. Screened Population

The screened population includes all subjects who have signed the main informed consent.

Reasons for screen failures will be presented using the screened population.

3.2.2. Enrolled Population

The enrolled population includes all subjects in the screened population who undergo leukapheresis.

Summary of analysis population and subject disposition, and listings will be based on the enrolled population unless specified otherwise. Selected safety analysis may also be analyzed using the enrolled population.

3.2.3. bb2121-treated Population

The bb2121-treated population includes all subjects in the enrolled population who have received bb2121 infusion.

The primary analysis for efficacy and safety will be based on bb2121-treated unless specified otherwise.

3.2.4. Efficacy Evaluable (EE) Population

The EE population is defined as all subjects in the bb2121-treated population who had a baseline and at least one valid post-baseline (ie post bb2121 infusion) efficacy assessment.

Selected key efficacy analyses (eg, response rate assessments, PFS) may be performed using the EE population. A subject is regarded as having a baseline assessment as long as there is a valid post baseline assessment (eg, not recorded as “not done” or “not evaluable”).

3.2.5. Dose Limiting Toxicity (DLT)-evaluable Population

The DLT evaluable population is defined as all subjects in Part A of the study who were infused with at least the minimum planned bb2121 dose and either completed 21 days of follow-up on this study after drug product infusion or experienced a DLT.

Subjects for whom the minimal dose could not be manufactured will not be included in the DLT-evaluable population unless it was necessary to expand the size of a lower dose cohort in order to determine the MTD in accordance with Protocol Section 3.1.

The DLT evaluable population will be used for the analysis of safety data related to DLT and the determination of the MTD in Part A.

3.2.6. Pharmacokinetic (PK) Analysis Population

The PK analysis population includes subjects who received at least one bb2121 infusion and have evaluable CAR T data (i.e. at least one measurable time point).

The PK analysis population for retreatment includes subjects who received the retreatment bb2121 infusion and have evaluable CAR T data (i.e. at least one measurable time point) for the retreatment period.

The PK analysis population will be used for all PK related analysis. The PK analysis population for retreated subjects can be derived in the same way with regard to retreatment bb2121 infusion.

3.2.7. bb2121-Retreated Population

The bb2121-retreated population will be defined as follows.

The bb2121-retreated population includes all subjects who enrolled for bb2121 retreatment and have received bb2121 retreatment.

The subject disposition, and the efficacy/safety analyses, if warranted, after retreatment will be based on bb2121 retreated population.

4. SUBJECT DISPOSITION

The total number of subjects with screen failure will be summarized by dose escalation and expansion phases and a listing for subjects with screen failures will be provided for subjects who were screened, but not enrolled. The number of subjects will be presented for the following analysis populations:

- Enrolled population
- bb2121-treated population
- EE population
- DLT-evaluable population
- PK analysis population
- bb2121-retreated population

A summary of subjects in the enrolled population by investigation site will be presented.

The enrolled population will be tabulated (number and percentage) by dose cohorts and overall for the following categories for initial bb2121 infusion. The tabulation will be repeated for the bb2121-treated population and other populations with applicable categories.

1. Subjects who enrolled (underwent leukapheresis), but discontinued without lymphodepletion
2. Subjects who received initial lymphodepletion
3. Subject who discontinued after initial lymphodepletion, but before bb2121 infusion
4. Subjects who received initial bb2121 infusion
5. Subject who discontinued after initial bb2121 infusion without retreatment lymphodepletion
6. Subjects who received retreatment lymphodepletion
7. Subject who discontinued study after retreatment lymphodepletion, but before bb2121 infusion
8. Subjects who received bb2121 retreatment infusion
9. Subjects who discontinued after bb2121 retreatment infusion

In addition, the following categories will be presented for all subjects in the designated population:

10. Subjects who discontinued the study
11. Subjects who are still ongoing in the study
12. Subjects who completed study per protocol requirements
13. Subjects who enrolled in the long-term follow up studies (bb2121-LTF-305 or GC-LTFU-001)

The primary reason for study discontinuation will be summarized (number and percentage) by dose cohorts and overall using the following categories as collected on the case report form (CRF):

- Adverse event
- Withdrawal by subject
- Loss to follow-up
- Physician decision
- Progressive disease, with at least 6 months of follow up post bb2121 infusion(s)
- Study terminated by Sponsor
- Death
- Adequate cells are not collected during harvests, or failure of transduced cells to be dispositioned for clinical use

Similarly, the analysis for subject disposition (item 10 to 13 above) and primary reason for study discontinuation will be provided for subjects who discontinued from study after leukapheresis but before initial bb2121 infusion, after initial bb2121 infusion only without retreatment and after retreatment, as applicable.

A listing will be provided for subject disposition.

5. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations and/or violations were identified and reported by site, and assessed by the study physician or designee. The major protocol deviations/violations will be summarized by dose cohorts and overall using the enrolled population.

A by-subject listing of subjects with protocol deviations/violations in the enrolled population will be provided.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized by dose cohorts and overall using the enrolled and bb2121-treated populations. Summaries for medical history, prior anti-myeloma therapies, prior radiation therapies, prior anti-cancer surgeries, concomitant medications/non-drug therapies and concomitant procedures will be presented for the bb2121-treated population. Individual subject listings will be provided to support the summary tables.

6.1. Demographics

Continuous demographic variables (eg, age) will be summarized using descriptive statistics (eg, mean, standard deviation, median, minimum and maximum), while the sex and other categorical variables will be summarized with frequency tabulations by dose cohorts and overall.

Age will be calculated as follows:

Age = Integer part of [(Date of inform consent – Date of Birth + 1) / 365.25].

6.2. Baseline Disease Characteristics

Continuous baseline disease characteristics (including disease history) will be summarized using descriptive statistics (eg, mean, standard deviation, median, minimum and maximum), while the ISS stage and other categorical variables will be summarized with frequency tabulations by dose cohorts and overall.

6.3. Medical History

A summary of medical and surgical history will be presented by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 20.0) by dose cohorts and overall using the bb2121-treated population.

6.4. Prior Anti-Cancer Therapies

Prior anti-cancer therapies, including prior anti-myeloma therapies, prior radiation therapies and prior anti-cancer surgeries, are the therapies that were started before the initial bb2121 infusion. The number of prior anti-cancer therapies in each category (ie, prior anti-myeloma therapies including autologous stem cell transplant (ASCT), prior radiation therapies and prior cancer surgeries) and overall will be summarized by frequency tabulations for the bb2121-treated population. Summary statistics such as the median number of prior anti-cancer therapies in each category and overall will be provided. The prior anti-myeloma therapy with the same sequence/regimen number are counted as one prior therapy.

Individual drugs in the prior anti-myeloma therapies will be coded according to the Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) Drug Dictionary (WHO DD) (Enhanced Version September 2016) and will be summarized by drug class and preferred name. Subjects refractory to select prior anti-myeloma therapies will be summarized by frequency count and percentage. Refractory to prior anti-myeloma therapy is defined as progression during treatment or within 60 days after the end date of the last regimen containing the designated drug.

Listings of prior anti-cancer therapies will also be presented by categories for the enrolled population.

6.4.1. Anti-myeloma Bridging Therapies

Anti-myeloma bridging therapies are the non-protocol anti-myeloma therapies that administered between main informed consent and baseline/lymphodepletion and before bb2121 retreatment. Individual drugs in the bridging therapies will be coded according to the ATC coding scheme of the WHO. Anti-myeloma bridging therapies will be summarized in frequency tabulations by WHO DD therapeutic drug class and preferred name.

7. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided initial treatment and retreatment separately, based on the bb2121-treated population bb2121-treated population and bb2121-retreated population, respectively. Descriptive statistics will be provided for dosing related parameters by dose cohorts and overall. Summary of dose modifications will also be provided.

7.1. Lymphodepletion (LD) Chemotherapy

7.1.1. Drug Exposure

Details of exposure to lymphodepletion chemotherapies – fludarabine and cyclophosphamide will be presented for bb2121-treated population.

Descriptive statistics will be provided for duration of treatment, number of days dosed, body weight adjusted cumulative dose (in mg/m^2) and total cumulative dose (mg), and average daily dose.

Treatment duration is defined as follows:

last lymphodepletion dose date – first lymphodepletion dose date + 1

The average daily dose is defined as body weight adjusted cumulative actual dose divided by number of days dosed.

7.1.2. Dose Modification

Dose reduction or increase is defined as a non-zero dose change compared with protocol planned lymphodepletion chemotherapy dose (300 mg/m^2 for cyclophosphamide and 30 mg/m^2 for fludarabine).

Dose modification will be summarized by dose cohort and overall including the following:

- Number of days with dose reductions
- Number of days with dose increase
- Number of days with dose not administered

7.2. bb2121 Infusion

Exposure of bb2121 will be summarized in bb2121-treated population. Descriptive statistics will be provided for the following:

- Total number of cells infused
- Volume infused
- Total number of CAR T cells infused

In addition, the following parameters of bb2121 administration will be presented:

- Frequency count and percentage of subjects who were infused with bb2121 per protocol

- Frequency count and percentage of subjects who completed bb2121 infusion without interruption
- Frequency count and percentage of subjects who underwent bb2121 infusion with interruption along with the reason for interruption
- Frequency count and percentage of subjects who received re-treatment

Individual study drug administration records and deviations in administration will be displayed in a listing.

7.3. Retreatment

Number of subjects who received bb2121 retreatment will be summarized. LD chemotherapy and exposure to bb2121 will also be summarized as described above in bb2121-retreated subjects.

8. EFFICACY ANALYSES

All efficacy evaluations will be conducted by dose cohorts and overall using the b2121-treated population. Supportive analysis of select efficacy endpoints using the EE population will be conducted as well. Two-sided CIs for intended point estimates will be reported. Analyses for bb2121 initial infusion and retreatment will be performed separately. The efficacy analysis will be based on the response assessments determined by the investigators using the IMWG response criteria (Kumar, 2016).

8.1. Response Rate

The proportion of subjects whose best response based on disease-specific response criteria with bb2121 will be tabulated along with a 95% exact binomial CI. This information will be provided by dose cohorts and overall. To select the best response, the following order of response will be used: stringent complete response (sCR) > complete response (CR) > very good partial response (VGPR) > partial response (PR) > minimal response (MR) > stable disease (SD) > progressive disease (PD). The objective response rate (ORR) based on the best response among all response assessments after bb2121 infusion will be reported. The ORR is calculated as the number of subjects who achieved PR or better, divided by the number of subjects in the specific analysis population. Both the unconfirmed response and the response that is confirmed by a consecutive assessment with the same response category or better is considered for the calculation of response rate. Similarly, the rate of other response categories for subjects whose best response is CR or better, VGPR or better with 95% CI will also be presented.

Subjects who are lost to follow up or who die prior to any response will be considered non-responders. Responses that are documented after the subjects receive any subsequent anti-myeloma treatment, including any bridging therapy between initial and retreatment bb2121 infusions, will not be counted in the numerator as responses; however, these subjects will be included in the denominator per bb2121-treated population. Response analysis will be performed separately for bb2121 initial infusion and re-treatment (ie response rate for initial infusion will not consider the responses achieved after bb2121 retreatment). A listing of response by investigator assessment will be provided as well.

8.2. Progression-free Survival

Progression-free survival (PFS) is defined as the time (in months) from bb2121 infusion date (Day 0) to the date of either first observation of progressive disease or occurrence of death due to any cause, whichever occurs first. Complete censoring rules (both United States Food and Drug Administration (US FDA) Guidance for Clinical Trail Endpoints for the Approval of Cancer Drugs and Biologics [FDA, 2007] and European Medicines Agency (EMA) Guideline on the evaluation of anticancer medicinal products in man [EMA, 2012]) are specified in Table 3.

The primary analysis will be based on the FDA censoring rule; the analysis based on the EMA censoring rule will be considered as a sensitivity analysis. For PFS analysis purpose, all subjects treated with bb2121 is considered as having baseline assessment. The Kaplan-Meier method (KM) will be used to estimate the survival distribution functions by dose cohorts and overall. The median of PFS along with the two-sided 95% CI will be estimated. In addition, the event rates (or event-free) at specific timepoints (eg, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months,

etc.) will be computed, along with the standard errors (Greenwood's formula; Klein, 2003). The plots of survival curves using the KM method will be presented for subjects grouped by dose cohorts, response types and other baseline characteristics as appropriate (eg, tumor burden, BCMA level, see Section 8.5).

Progression-free survival will be analyzed for bb2121 retreated subjects using the same rules as described for initial treatment, with retreatment infusion date as the first dose date for retreatment PFS calculation.

Table 2: Censoring Rules for PFS

Scenario	**FDA Censoring Rule**		**EMA Censoring Rule**	
	Censor/Event	**Date**	**Censor/Event**	**Date**
No Baseline (to be used for post baseline response assessment) and no death within the first 2 scheduled assessments	Censor	Infusion date	Censor	Infusion date
Death or Documented Progressive Disease (PD) a) Death within the first 2 scheduled assessments	Event	Death date	Event	Death date
b) PD or death right after missing 2 (or more) consecutive scheduled assessments	Censor	Last adequate efficacy assessment date with no evidence of PD; if missing the first 2 assessments, then infusion date	Event	Documented PD or Death date whichever is earlier
c) Otherwise	Event	Documented PD or Death date whichever is earlier	Event	Documented PD or Death date whichever is earlier
Start new anti-tumor drug/non-protocol treatment before PD/death	Censor	Last adequate assessment date with evidence of	Event	PD date/Death date whichever is earlier,

Scenario	FDA Censoring Rule		EMA Censoring Rule	
	Censor/Event	Date	Censor/Event	Date
		no progression before starting new drug/treatment		independent of starting new AMT
No documented PD and No Death	Censor	Last adequate assessment date with evidence of no progression	Censor	Last adequate assessment date with evidence of no progression

8.3. Overall Survival

Overall survival is defined as the time from bb2121 infusion date to the date of death due to any cause. Subjects who die before or on the date of data cutoff will be considered to have had an OS event. Subjects who do not have a death record prior to or on the cutoff date will be censored at the "last date known alive."

Last date known alive is defined as the last valid date of subject assessment prior to or on the data cutoff date in the clinical database. For subjects who have withdrawn consent from the study, the last date known alive will be the date of consent withdrawal from the study. For all other subjects, the last date known alive will be derived by searching through all valid assessment dates in all study datasets to identify the last valid subject assessment date available for each subject. If the last valid subject assessment date available is on or prior to the data cutoff date, it is used as the last date known alive. If the last valid subject assessment date available is after the data cutoff date, the data cutoff date is used as the last date known alive.

The median of OS along with the two-sided 95% CI will be estimated using KM method. In addition, the event rates (or event-free) at specific timepoints will be computed, along with the standard errors (Greenwood's formula; Klein, 2003).

8.4. Analyses of Other Efficacy Endpoints

8.4.1. Time to First Response

The time to first response is defined as the time from infusion date to the time the myeloma response criteria for sCR, CR, VGPR or PR is first met. Subjects who are non-responders will be excluded from this analysis. Responses that occur after receiving any other anti-myeloma therapy initiated after baseline (including retreatment for initial infusion time to first response analysis) will be excluded. Summary statistics will be used to summarize the time to response. Time to first VGPR or better for subject who achieved VGPR or better, time to first CR or better for subjects who achieved CR or better, and time to best response for subjects who achieved PR or better will also be assessed with the same method as described above. Only responses confirmed by

Time to first response can be analyzed in the same manner after retreatment starting from the retreatment infusion date, if the data possess sufficient responders that warrant such an analysis.

8.4.2. Duration of Response

Duration of response is defined as the duration from the time when the myeloma response criteria are first met for sCR, CR, VGPR or PR until the first date the response criteria are met for PD or until the subject dies due to any cause, whichever occurs first. Duration of response for subjects last known to be alive with no progression after an sCR, CR, VGPR or PR will be censored at the last adequate assessment. Subjects receiving any other anti-myeloma therapy before progression or death will be censored at the last adequate assessment prior to the initiation of such treatment. Subjects with PD or death right after missing 2 (or more) consecutive scheduled assessment will be censored at last adequate efficacy assessment date with no evidence of PD. Subjects who are non-responders or achieved response only after other anti-myeloma therapy will be excluded from this analysis. Duration of response will be analyzed using the same method as used for PFS as described in Section 8.2.

Duration of response after retreatment infusion can be analyzed in the same manner, if the data possess sufficient responders that warrant such an analysis.

8.4.3. Subsequent Anti-Myeloma Therapy and Time to Subsequent Anti-Myeloma Therapy

Summaries for subsequent anti-myeloma therapies will be presented for the bb2121-treated population. Summaries will be presented by type of therapy and therapy regimen using frequency counts and percentages. Individual subject listings will be provided to support the tables.

Individual drugs in the subsequent therapies will be coded according to the ATC coding scheme of the WHO and will be summarized by drug class and preferred name.

Time to subsequent anti-myeloma therapy (AMT) is defined as time from initial bb2121 infusion to the start of next non-protocol AMT excluding bridging AMTs applied for bb2121 retreatment. Subjects who do not receive another AMT will be censored at the last assessment or follow-up visit known to have received no new therapy.

The same method used for PFS as described in Section 8.2 will be used to analyze this endpoint.

8.4.4. Minimal Residual Disease (MRD) Negativity

MRD negativity defined at selected sensitivity level (eg, 10^{-4}, 10^{-5} or 10^{-6}) will be analyzed. MRD will be summarized with frequency tabulations. MRD may also be summarized for difference response status (eg those subjects who achieved CR or VGPR) based on data availability.

8.4.5. Graphic Summary of Efficacy

A swimming lane plot will be provided to summarize the status for each subject over time after infusion. The duration of each response status (sCR/CR, VGPR, PR and SD) will be shown by different color or pattern. Milestone events such as MRD negativity will be indicated at when it occurred. Whether the subject is still ongoing in the study (at data cut-off date), or experienced

PD or death will be marked at the end of the lane. Other characteristics (eg, tumor burden at baseline) of the subjects may also be marked in the plot as appropriate.

8.5. Subgroup Analysis

In addition to analyses that include bb2121-treated subjects, additional subgroup analyses will be performed where an adequate number of subjects are available in each subgroup to allow for meaningful interpretation of results. Analyses will be performed within the following subgroups for response assessments. Select subgroup analysis may be performed for PFS and OS based on data maturity.

- Age (< 65 vs ≥ 65 years old)
- Sex (male vs female)
- Race (white vs non-white)
- Dose levels and manufacturing process (150×10^6 cells old process vs 150×10^6 cells current process vs > 150×10^6 cells)
- Daratumumab refractory (yes vs no)
- Number of prior regimen (< median vs ≥ median)
- High risk cytogenetics (yes vs no)
- High risk MM define as R-ISS III at baseline (yes vs no)
- High risk MM defined as ISS III, at baseline (yes vs no)
- Tumor BCMA expression low vs high BCMA+)
- Tumor burden (bone marrow % plasma cells low vs high
- Baseline serum BCMA level (< median vs ≥ median)
- Bridging anti-MM therapies (yes vs no)
- LD chemotherapies (full dose vs modified dose)

Cytogenetic “high-risk” is defined as any of the following at screening or baseline or from historical records: FISH: del17p13, t(14;16), t(4;14) or Cytogenetics: Del 17; “not high risk” is defined as negative in all of the above probes. The cytogenetic risk is “Missing” if the status for the probes are all missing or partially available, but not sufficient to determine “High” or “Not High”. Maximum and minimum value between pre-screening and screening visits reported by the central lab are used to determine BCMA groups (Low BCMA: <50%, High BCMA: >=50%) when the subject was in planned in high BCMA (Part A all cohorts and Part B Cohort 2) and low BCMA cohorts (Part B Cohort 1), respectively. If values from both visits were missing, baseline visit value is used. If there were multiple measurements within the same visit, the maximum measurement in that visit is used.

In addition, any other individual or combination of clinical features identified as possible prognostic and/or manufacturing factors for efficacy may be used in the exploratory analyses.

Corresponding forest plots will be provided for response rate difference and hazard ratio (for certain time to event analysis) in subgroups.

8.6. Analysis Based on the Efficacy-Evaluable (EE) Population

Key efficacy endpoints such as PFS, OS, and response rate may be analyzed based on the EE population as well, using the same methods as those used for the bb2121-treated population.

9. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study and to describe how the safety results of the study will be presented. Primary safety analyses will be performed by dose cohorts and overall using the bb2121-treated population. Summary of AEs that occur before bb2121 infusion will be analyzed based on enrolled population as well as bb2121-treated population as appropriate. DLT related analyses will be performed using DLT evaluable population. Individual subject listings will be provided to support the tables.

9.1. Adverse Events (AEs)

9.1.1. General AE Analysis Conventions

All AEs will be coded using MedDRA version 20.0 at the time of analysis. Adverse events will be summarized by MedDRA SOCs and PTs. If a subject experiences multiple AEs under the same PT/SOC, then the subject will be counted only once for that PT/SOC.

A treatment-related AE is defined as an AE which was considered to be related to the study drug by the investigator. AEs assessed as "Possibly Related", "Probably Related", or "Related" to study treatment per the investigator are considered as treatment-related AEs.

If the relationship to study drug is missing for an AE that occurred after the start of study drug administration (i.e. initial bb2121 infusion), a causality of related will be assigned. The imputed values for relationship to study drug will be used for the incidence summary; the actual values will be presented in data listings.

The severity/intensity of AEs will be assessed by the investigator as graded 1 to 5 according to the current version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). For all other AEs not described in the NCI CTCAE criteria, the severity/intensity will be assessed by the investigator as follows:

Grade 1 Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4 Life-threatening consequences; urgent intervention indicated

Grade 5 Death related to AE.

If a subject experienced the same AE more than once with a different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. In addition, AEs with a missing severity will be presented in the summary table as a severity category of "Missing". No imputation of missing AE severity grade will be applied. The actual reported values for severity (including missing) will be utilized in all AE summaries and listings.

9.1.2. AE Reporting Period

AEs will be summarized for those events that occur during six time periods (which will be referred to as Reporting Period A to F) as follows:

1. From leukapheresis to, but not including, the day of the first dose of lymphodepletion ("Reporting Period A").
2. From the day of the first dose of lymphodepletion up to but not including the day of bb2121 infusion ("Reporting Period B").
3. From the day of bb2121 infusion through ≤ 8 weeks after infusion ("Reporting Period C").
4. From > 8 weeks through 6 months after bb2121 infusion ("Reporting Period D").
5. From >6 months to 24 months after bb2121 infusion ("Reporting Period E").
6. From > 24 months to 60 months after bb2121 infusion ("Reporting Period F").

The denominator used for calculation of the percentages will be the number of subjects in the designated population who entered the corresponding reporting period.

If a subject received retreatment, the AE reporting period will stop at the day before retreatment lymphodepletion date or the planned reporting period end date as specified above, whichever is earlier.

Similar reporting period (B and thereafter) will be used for AE summaries during retreatment. The periods will be determined as above relative to retreatment lymphodepletion date and infusion date.

9.1.3. AE Categories

An overall summary of AEs for AE categories listed below will be provided. Tables summarizing the frequency and percentage of AEs will be generated for each of the following by SOC and/or PT in reporting period C and D. Some selected AE categories from below will be also summarized across other reporting periods (Section 9.1.2).

- All AEs
- All AEs related to study drug
- Serious AEs (SAEs)
- SAEs related to study drug
- Grade 3 or 4 AEs
- Grade 3 or 4 AEs related to study drug
- Grade 5 AEs
- Grade 5 AEs related to study drug
- AEs by maximum severity

9.1.4. Adverse Events of Special Interest (AESIs)

The selected AESIs refers to a group of terms/PTs from one or more SOCs relating to a defined medical condition or area of interest. The AESI phrase or term refers to the group of PTs, rather than the individual PTs. AESIs will be selected using Standardized MedDRA Query (SMQ) definitions or MedDRA SOC and/or PT definitions, plus per medical review. The groupings of AESIs will be determined by safety physicians and provided to statistician prior to database lock. AESIs may include:

- Grade >= 3 Cytokine Release Syndrome [CRS] events
- Grade >= 3 Neurologic toxicity
- New malignancies
- Grade >=3 Macrophage activation syndrome (MAS)
- Hematologic disorders
- Rheumatic and autoimmune disorders
- Grade >= 3 Infections

In addition, any other events of interest for safety concerns in subjects with MM may be used in the exploratory analyses.

AESI analyses will include overall summary of the following AE categories in select reporting period(s) between C and F:

- All AESIs
- AESIs related to study drug
- Serious AESIs
- Grade 3 or 4 AESIs
- Grade 5 AESIs
- AESIs by maximum severity

Time to onset of CRS and duration of CRS will be summarized. In addition, summaries of CRS symptoms for subjects who experienced CRS AEs (coded as SOC = Immune System Disorders, PT = Cytokine release syndrome) will be summarized

An overall summary of AEs not designated as symptoms of CRS on the CRF will also be provided. All AEs, AEs related to study drug, Grade 3/4 AEs and AEs by maximum severity of this type will be summarized by dose cohorts in select reporting period(s) between C and F.

All AEs will be listed in by-subjects, by-time data listings, including any events that may have occurred after signing informed consent but prior to leukapheresis. Additional listings will be provided for the following AEs:

- SAEs
- Grade 3/4 AEs
- AESIs

- AEs before leukapheresis
- AEs for subject who enrolled, but were not treated

9.1.5. Adverse Events Subgroup Analysis

Tables summarizing the frequency of TEAEs by baseline subgroups will be generated (provided the number of subjects is sufficient) for selected AE categories and reporting period(s), including:

- Age (< 65 vs ≥ 65 years old)
- Sex (male vs female)
- Race (white vs non-white)
- Tumor BCMA expression (low vs high)
- Tumor burden (bone marrow % plasma cells low vs high)
- Baseline serum BCMA level (< median vs ≥ median)

In addition, any other clinical features identified as possible factors of interest for safety concerns in subjects with MM may be used in the exploratory analyses.

9.1.6. Dose Limiting Toxicities (DLTs)

DLTs are defined as any bb2121-related Grade 3 to 5 toxicity occurring within the 21 days immediately after infusion of the drug product that meets one of the criteria defined in section 3.4 of the protocol. A summary table of DLTs will be presented by dose cohort including number and percentage of subjects having a DLT. The percentage of subjects having a DLT is based on the number of subjects in the DLT evaluable population. DLT flag may be added to select listings of AEs as appropriate.

9.1.7. AE after Retreatment

AEs started after retreatment infusion will be reported separately with bb2121-retreated population. All or select AE categories and AESIs will be summarized in the same manner as for the initial infusion.

9.2. Deaths

The primary cause of death, as collected in the CRF, will be tabulated by cause of death categories for all deaths, deaths within 30, 60 and 90 days, and deaths form > 90 days to 60 months after bb2121 infusion using the bb2121-treated population. Death after initial bb2121 treatment and retreatment will be summarized in the same manner as for AE analysis.

A listing of all patients who died will be provided for the enrolled population specifying the date of death, the cause, and the relative day to initial infusion and retreatment if applicable.

9.3. Clinical Laboratory Evaluations

Clinical laboratory results of interest include: chemistry, hematology, coagulation and serology. Clinical laboratory values will be graded according to current NCI CTCAE version (version

4.03) for applicable tests. Local laboratory normal ranges will be used to determine the categories of High, Low, and Normal.

Lab results and change from baseline by visit will be summarized using descriptive statistics for continuous variables. Maximum and minimum post-baseline values (including unscheduled visits) and corresponding change from baseline values will be summarized using descriptive statistics.

Shift tables demonstrating the lab parameter status (low/normal/high) changes from baseline to worst post-baseline value will be displayed in cross-tabulations by dose cohorts. Bidirectional shift tables (high and low) demonstrating the change of NCI CTCAE grades from baseline to worst post-baseline will also be presented by dose cohort.

Listings of clinical laboratory data with NCI CTCAE grades (if applicable) and abnormal flags (low or high) will be provided.

For some key lab tests (eg, alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, total bilirubin, total lymphocytes, total neutrophils, leukocytes, hemoglobin, ferritin, C-reactive protein), by subject line plots will be presented to show the pattern of the lab test values over time using the bb2121-treated population. All non-missing lab test values including assessments at scheduled, unscheduled, or end of treatment visits, will be presented. Value for the end of treatment visit will be included in line plots but will be displayed at the nominal visit equal to or immediately after the end of treatment visit.

Time to Grade 3/4 cytopenia and duration of Grade 3/4 cytopenia will be analyzed. Grade 3/4 cytopenia is defined as neutropenia (absolute neutrophil count (ANC) < 1,000/μL) or thrombocytopenia (platelet count < 50,000/μL). Recovery from neutropenia and thrombocytopenia is achieved when ANC is >=1,000/μL and platelet count is >=50,000/μL, respectively. Time to recovery and duration of Grade 3/4 neutropenia is defined as the time from bb2121 infusion date and first onset of Grade 3/4 neutropenia, respectively, to the time when recovery was first met. The median is based on Kaplan-Meier estimate. Subjects who did not recover are censored to last assessment date and subjects who died before recovery are censored to current data cut-off date.

9.4. Vital Sign Measurements

Vital sign values and change from baseline by visit will be summarized using descriptive statistics. Maximum and minimum post-baseline values (including unscheduled visits) and corresponding change from baseline values will be summarized using descriptive statistics.

Shift tables demonstrating the changes (low/normal/high) from baseline to worst post-baseline value will be displayed in cross-tabulations. Normal ranges in Table 4 will be used to determine the categories of low, normal and high.

Table 3: Normal Ranges of Vital Sign Measurements

Test	Normal Range (Unit)
DBP	[60, 90] (mmHg)
SBP	[100, 140] (mmHg)

Pulse	[60, 100] (bpm)
Temperature	[35, 38] (°C)

9.5. Left Ventricular Ejection Fraction (LVEF) Assessment

LVEF assessment values at baseline will be summarized using descriptive statistics as a baseline characteristic. A by subjects listing will be presented for baseline LVEF assessment.

9.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

Shift table from baseline to best and worst post-baseline in ECOG performance score will be displayed by using the bb2121-treated populations. A listing of ECOG grade will be provided as well.

9.7. Other Safety Measurements

Other safety measurements such as physical examination and pregnancy test (for female subjects) will be presented in by subject listings.

10. PHARMACOKINETICS ANALYSES

Pharmacokinetic analysis will be performed with the PK population. PK data collected for retreatment will be analyzed in a similar manner as data collected for initial infusion with respect to retreatment infusion date.

10.1. PK Sample Collection

CD3+ T cells, composed of endogenous and CAR T cells, will be isolated from the whole blood. DNA will be purified from the CD3+ sorted cells and vector copy number (VCN) for only CAR T will be determined by qPCR at the following time points:

Pre-dose, Day 2, Day 4, Day 7, Day 9, Day 11, Day 14, Day 21, Month 1, Month 2, Month 3, Month 6, Month 12, Month 18,Month 24 and every 3 months after Month 24 up to Month 60. PD visit.

10.2. Data Handling for PK Analysis

Concentrations prior to the initial bb2121 infusion or a below the limit of quantitation (BLQ) value at bb2121 retreatment baseline will be assigned a numerical value of zero. A quantifiable concentration at retreatment baseline will be retained for analysis. Post-infusion concentrations that are BLQ will be imputed as ½ of the lower limit of quantification (LLoQ) in the PK analysis.

A concentration value of zero will be excluded from the computation of the geometric mean (geometric CV%) and the plots in log scale. If any subjects are found to be noncompliant with respect to dosing, have incomplete data, or encounter other circumstances that would affect the evaluation of PK, a decision will be made on a case-by-case basis as to their inclusion in the PK analysis. Data excluded from PK analysis will be included in the data listings, but not in the summaries.

In tables and listings for the derived PK data, there should be four decimal places for numerical values below 1, three decimal places for numeric values below 10 but above 1, and two decimal places for numeric values above 10. However, the listing of raw data should not have more decimal places than the actual data.

10.3. Noncompartmental PK Parameters

The bb2121 expansion measured by VCN for CAR T in CD3+ T-cells will be used to estimate the drug exposure parameters. Actual sampling and dosing time will be used in this analysis. The following noncompartmental PK parameters will be derived from VCN in CD3+ T-cells using the software program Phoenix WinNonlin (version 7 or higher)

- C_{max}: The maximum CAR T cell count occurring at T_{max}.
- $AUC_{0-\infty}$: The area under the curve (AUC) of CAR T cells extrapolated to infinity, calculated using the observed value of the last non-zero cell count.
- AUC_{0-t}: The AUC of CAR T cells from the time of dosing to the last measurable cell count.
- $AUC_{0-28days}$: The AUC of CAR T cells from the time of dosing to 28 days

- T_{max}: The time of maximum observed CAR T cell count, obtained directly from the observed CAR T cell count- time
- T_{last}: Time to last measurable CAR T cell count
- DN- $AUC_{0-\infty}$: The AUC extrapolated to infinity, calculated using the observed value of the last non-zero CAR T cell, divided by the dose
- DN- C_{max}: The maximum CAR T cell count occurring at T_{max}, divided by dose.
- $t_{1/2, z}$: Terminal half-life.
- λ_z: The first order rate constant associated with the terminal (log-linear) portion of the curve.

The following PK parameters will be calculated for diagnostic purposes and listed but they will not be summarized:

- λ_z lower: lower limit of time (days) included in the calculation of λ_z
- λ_z upper: upper limit of time (days) included in the calculation of λ_z
- λ_z N: number of data points used in the calculation of λ_z
- Rsq: regression coefficient for calculation of λ_z

VCN in CAR T cells by target dose levels and nominal time points and PK parameters by target dose levels will be summarized using descriptive statistics (N, mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, standard deviation, min, and max). In general, geometric mean and the geometric CV (%) will be derived from non-zero concentration values.

Coefficient of variation CV (%) is calculated as follows: 100 × (standard deviation/mean). Geometric CV (%) is calculated as follows: CV (%)=100 × $\sqrt{\exp(\hat{\sigma}^2) - 1}$, where $\hat{\sigma}^2$ denotes the variance of the log-transformed values.

PK concentration and parameters will be presented in listings by subjects. For each PK concentration collection time, the relative time from bb21221 infusion and the difference between actual and planned collection time will be presented. The sample collected outside the planned collection window as well as unscheduled collections will be marked.

The following figures will be provided:

- Individual subject's VCN per µg genomic DNA (linear scale and semi-logarithmic scale) over time line plot with actual dose level indicated;
- Mean and ± standard deviation of VCN per µg genomic DNA (linear scale and semi-logarithmic scale) by target dose level over time line plot;

10.4. Relationship Between Exposure and Response

The relationship between exposure and response may be explored using the AUC and/or C_{max} estimate from the noncompartmental PK analysis and the clinical data.

The following relationships may be examined graphically using individual or population data from efficacy and safety

- The relationship between C_{max} or AUC and the ORR
- The relationship between C_{max} or AUC and Safety (ie, AE, AESI, SAE, CRS, neurotoxicity, infection and laboratory abnormalities)
- The relationship between C_{max} or AUC and anti-CAR antibody response (immunogenicity)
- The relationship between C_{max} or AUC and various changes biomarkers (cytokine inductions, expression change of BCMA+ plasma cells, exploratory cytokines and chemokines)

The trend of PK parameters among categorical efficacy and safety variables (eg, response vs non-response, AEs occurrence Yes vs No) can be presented using box plot or dot plot as appropriate with response/safety categories in the horizontal axis. Mean or percentiles may be indicated in the plot. The relationship between PK parameters and continuous efficacy/safety endpoints can be presented using scattered plot. Further correlative analyses of exposure-response relationship may be performed in a separate exploratory analysis plan if the graphic analyses indicate a significant trend.

11. BIOMARKER AND CORRELATION ANALYSES

Biomarkers refer to the markers processed from samples obtained for pharmacodynamic analysis and the markers which are of predictive/prognostic values. For CAR T cell infusion, some chemistry and manufacturing controls (CMC) parameters may also help to understand and interpret the efficacy/safety results, and will be included in this biomarker section. Tables and figures derived from this section should use the bb2121-treated population unless specified otherwise. Summaries and analyses will be provided for subjects treated at RP2D as well as in other dose cohort(s) as appropriate. Figures will be provided as appropriate to illustrate the trend of biomarker change over time and their correlation with efficacy/safety and other clinical endpoints including other biomarkers. All listings of this section, presented by tissue or assay type, will use the enrolled population or bb2121 treated population as appropriate. In general, descriptive statistics and non-parametric test will be used for biomarker analyses due to the small sample size. PD biomarker data collected for retreatment will be analyzed in a similar manner as data collected for initial infusion with respect to retreatment infusion date.

11.1. Endpoint Variables Related to Biomarker

Biomarker endpoints to be analyzed in this study include the following:

- Adaptive anti-drug antibody positivity
- Vector copy number measured in the peripheral blood and bone marrow
- Cytokine induction level in the blood of subjects after bb2121 infusion
- Level of expression of BCMA+ plasma cells in the bone marrow by flow cytometry
- Level of circulating soluble BCMA.
- Level of BCMA in plasma cells by IHC

CMC parameters of interest may include parameters for CAR T cells potency measurement such as CD137 induction and IFN-γ secreted, T cells subsets in manufactured CAR T cells, and parameters measured for cells collected from leukapheresis.

For continuous biomarker data, summary statistics (N, mean, StdDev, median, Min, and Max) of observed values and the change from baseline will be presented by visit (if post-baseline data collected); categorical measurements will be summarized using frequency counts and percentages.

The trend of change over time for selected biomarkers will be illustrated by graphic presentation including dot plot, box plot, individual line plot or mean (median) plot. The horizontal axis consists of nominal or actual timepoints of the given biomarkers.

11.2. Correlation between Biomarker and Clinical Endpoints

Correlation between biomarkers and clinical endpoints including efficacy/safety and other biomarkers, as well as correlation between response and safety such as CRS, biomarkers of CRS, and neurotoxicity may be explored for subject treated at RP2D or other select dose level(s).

11.2.1. Correlation between Continuous Biomarkers and Clinical Endpoints

This section will investigate whether efficacy, safety or other clinical parameters of bb2121 could be explained by differences in select continuous biomarkers. If the number of samples available for a biomarker is too limited (ie, less than 30% of the all subjects), no correlation analysis between that biomarker and clinical endpoints will be conducted.

For a binary clinical endpoint (eg, response vs non-response), logistic regression can be performed and odds ratio of unit biomarker change will be provided. A boxplot or dot plot will be presented to compare biomarker change among different response groups to help illustrate the trend. Wilcoxon-Mann-Whitney test may also be conducted with raw p-value provided.

For continuous clinical endpoints, their correlation with biomarkers can be investigated using a Spearman rank correlation test (Sokal and Rohlf, 1995). A scatter plot may be provided to illustrate the trend of correlation with Spearman correlation co-efficiency provided.

11.2.2. Correlation between Categorical Biomarker and Clinical Endpoints

For association of binary clinical endpoints with binary biomarkers, Fisher's exact test will be conducted to examine independence between biomarker and clinical endpoint with raw p-value provided.

For a continuous clinical endpoint, a boxplot or dot plot will be presented to compare clinical endpoints among different biomarker categories to help illustrate the trend. Wilcoxon-Mann-Whitney test may also be conducted with raw p-value provided.

For time to event clinical endpoint such as PFS, the KM estimate of median PFS with its two-sided 95% CI (Brookmeyer and Crowley, 1982) will be provided for each biomarker category. The KM plots of PFS by biomarker categories will be presented. The raw p-value of log rank test may also be provided.

12. QUALITY OF LIFE ANALYSIS

Not applicable.

13. INTERIM ANALYSIS

No formal interim analysis was planned for this study.

14. REFERENCES

Brookmeyer R. and Crowley J., "A Confidence Interval for the Median Survival time," Biometrics 1982, 38, 29-41.

Clopper CJ, Pearson ES. "The use of confidence or fiducial limits illustrated in the case of the binomial," Biometrika 1934; 26: 404-413.

Durie BGM, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006:20(9):1467-73.

European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95/Rev.4. 01 Jul 2013.

Klein JP, Moeschberger ML. Nonparametric estimation of basic quantiles for right-censored and left-truncated data. In: Survival analysis techniques for censored and truncated data. 2nd ed. New York: Springer; 2003. p. 91-104.

Klein, J. and Moeschberger, M., Survival Analysis: Techniques for Censored and Truncated Data, 2nd Edition, Springer-Verlag ISBN: 038795399X, 2003.

Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Bladé J, Mateos MV, Dimopoulos M, Kastritis E, Boccadoro M, Orlowski R, Goldschmidt H, Spencer A, Hou J, Chng WJ, Usmani SZ, Zamagni E, Shimizu K, Jagannath S, Johnsen HE, Terpos E, Reiman A, Kyle RA, Sonneveld P, Richardson PG, McCarthy P, Ludwig H, Chen W, Cavo M, Harousseau JL, Lentzsch S, Hillengass J, Palumbo A, Orfao A, Rajkumar SV, San Miguel J, Avet-Loiseau H. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8): e328-346.

Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-9.

Sokal, R.R., and F.J. Rohlf. 1995. Biometry: The principles and practice of statistics in biological research. 3rd edition. W.H. Freeman, New York.

Storer BE. Design and analysis of phase I clinical trials. Biometrics. 1989 Sep; 45(3):925-37.

U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry Clinical Trail Endpoints the Approval of Cancer Drugs and Biologics. May 2007.