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A Phase 2, Multicenter Study to Determine the Efficacy and Safety of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma

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A PHASE 2, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF BB2121 IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

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Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

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PROTOCOL SUMMARY

Study Title

A Phase 2, Multicenter Study to Determine the Efficacy and Safety of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma

Indication

Relapsed and Refractory Multiple Myeloma

Objectives

Primary Objective:

- Evaluate the efficacy, defined as overall response rate (ORR), of bb2121 in subjects with relapsed and refractory multiple myeloma (RRMM)

Secondary Objectives:

- Assess additional efficacy outcomes, including complete response (CR) rate, time to response (TTR), duration of response (DOR), progression-free survival (PFS), time to progression (TTP) and overall survival (OS)
- Assess the safety of bb2121 in subjects with RRMM
- Characterize the expansion of chimeric antigen receptor (CAR) + T cells in the peripheral blood (cellular kinetics- pharmacokinetics [PK])
- Evaluate the development of an anti-CAR antibody response
- Evaluate the proportion of subjects who attain minimal residual disease (MRD) negative status by next generation sequencing (NGS)
- Describe changes in health related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC-QLQ-C30), the European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L) and the European Quality of Life Multiple Myeloma Module (EORTC-QLQ-MY20)

Exploratory Objectives:

- Characterize the expansion of chimeric antigen receptor (CAR) + T cells in the bone marrow
- Evaluate the immunophenotype of bb2121 CAR T and endogenous T cells in the blood, bone marrow and/or tumor tissue
- Evaluate cytokine/chemokine induction in the blood of subjects after infusion of bb2121
- Evaluate the percentage of B-cell maturation antigen (BCMA)-expressing (BCMA+) cells and levels of BCMA expression in bone marrow, and the level of circulating soluble BCMA
- Evaluate mechanisms of tumor sensitivity/resistance to bb2121

- Evaluate the development of an anti-CAR cellular immune response
- Characterize the subject experience on bb2121 using patient interviews
- Measure hospital resource utilization
- Evaluate the proportion of subjects who attain minimal residual disease (MRD) negative status by EuroFlow

Study Design

Study BB2121-MM-001 is an open-label, single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of bb2121 in subjects with RRMM.

The study will enroll up to 140 subjects (up to 119 subjects treated with bb2121) with RRMM to evaluate the efficacy and safety of bb2121.

Pre-treatment:

After informed consent has been obtained, subjects will undergo screening procedures to determine eligibility. After screening eligibility has been met, subjects will be enrolled and undergo leukapheresis to enable bb2121 product generation. Subjects may receive bridging multiple myeloma (MM) therapy following leukapheresis as long as the last dose is administered ≥ 14 days prior to initiation of lymphodepleting (LD) chemotherapy.

Bridging therapies may include corticosteroids, alkylating agents, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 antibodies as single agents or in combination. Experimental agents and myeloma therapies to which the subject has not been previously exposed should not be used as bridging therapy. In subjects who receive bridging myeloma therapy, baseline disease staging assessments need to be repeated following completion of bridging therapy and prior to starting LD chemotherapy.

Treatment:

Subjects eligible for treatment will receive 3 consecutive days of LD chemotherapy starting on Day -5 with fludarabine and cyclophosphamide, followed by 2 days of rest and bb2121 infusion on Day 0.

bb2121 will be administered at a dose ranging from 150 to 450 x 10^6 CAR+ T cells/infusion. Subjects must be admitted for inpatient monitoring from Day 0 through Day 14 post-bb2121 infusion, to monitor the risk of developing cytokine release syndrome (CRS) and neurotoxicity.

Post-treatment:

Safety, myeloma response, disease status, bb2121 expansion and persistence, utility values measured using the EORTC-QLQ-C30, EQ-5D-5L and EORTC-QLQ-MY20 questionnaires, and other secondary and exploratory endpoints will be assessed on all subjects for a minimum of 24-months from bb2121 infusion or until documented disease progression (PD), whichever is longer. Subjects with documented PD within 24-months of bb2121 infusion will remain on the study and have select assessments collected until M24.

Retreatment

Retreatment with a second infusion of bb2121, including a second course of LD chemotherapy, with or without bridging therapy, may be considered if protocol specified eligibility criteria are

met and if sufficient cryopreserved bb2121 drug product is available. There is no drug class restriction for bridging therapy used prior to retreatment, but bridging therapy should be completed at least 14 days prior to starting LD chemotherapy. Retreated subjects will follow the Table of Events starting with the baseline visit and will be followed on study for a minimum of 6 months after the second infusion or until documented PD, whichever is longer.

Study Population

The study will enroll adult subjects with RRMM. Up to 140 subjects will be enrolled with an expectation that there will be up to 119 bb2121 treated subjects.

Length of Study

Subjects will be followed in the study for a minimum of 24 months after bb2121 infusion and the study will consist of 3 periods:

- The pre-treatment period of the study will consist of screening for eligibility, leukapheresis and baseline evaluations (prior to LD chemotherapy).
- The treatment period will start with LD chemotherapy, followed by bb2121 infusion 3 days from the last day of LD chemotherapy on Day 0.
- The post-treatment period will consist of efficacy and safety follow-up visits monthly until month 6, then every 3 months for a minimum of 24-months post-bb2121 infusion or until PD, whichever is longer. Subjects who have PD prior to 24-months post-bb2121 infusion, and are not retreated, will continue to be followed until M24. Subjects who have PD after 24-months post-bb2121 infusion will be evaluated for retreatment or discontinued from the study at the time of PD. A first response evaluation will be performed at approximately 1 month after bb2121 infusion.

The decision to discontinue a subject from study treatment or follow-up is the responsibility of the investigator or designee. The Sponsor will not delay or refuse this decision. However, prior to discontinuing a subject, the Investigator should contact the medical monitor for discussion. The reason for discontinuation will be documented.

Upon discontinuation from this study, all subjects who received bb2121 will participate in a separate long term follow-up (LTFU) study, to be monitored for delayed toxicities related to bb2121, viral vector safety, disease status, quality of life, survival status, and subsequent anti-MM therapies. Subjects will be monitored in the LTFU study for up to 15 years from the date of their last bb2121 infusion as per competent authority guidelines.

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.

The study will have an Independent Response Committee (IRC) who will review data for response assessment. The IRC will determine the response to therapy based on the IMWG Uniform Response Criteria for each subject.

The study will have an independent Data Safety Monitoring Board (DSMB) who will monitor the study data in an ongoing manner.

The study will be conducted in compliance with International Council on Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Procedures and Treatments

Once screening eligibility has been met, a leukapheresis collection will be performed on each subject to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of bb2121.

If necessary, selected anti-myeloma bridging treatment is allowed while bb2121 is being manufactured, for disease control, as long as the last dose is administered ≥ 14 days prior to the initiation of LD chemotherapy. After bb2121 drug product has been manufactured, baseline evaluations are performed prior to initiation of LD chemotherapy. Bridging therapies may include corticosteroids, alkylating agents, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 antibodies as single agents or in combination. Experimental agents and myeloma therapies to which the subject has not been previously exposed should not be used as bridging therapy. In subjects who receive bridging myeloma therapy, select baseline evaluations for disease staging are repeated following completion of bridging therapy and prior to starting LD chemotherapy.

Subjects will receive three days of fludarabine intravenously (IV) (30 mg/m^2) and cyclophosphamide IV (300 mg/m^2) for LD chemotherapy starting on Day -5. After the completion of LD chemotherapy, bb2121 will be administered as an IV infusion at a dose ranging from 150 – 450 x 10^6 CAR+ T cells on Day 0.

Overview of Key Efficacy Assessments

- Myeloma paraprotein in blood and 24-hour urine collection
- Quantitative serum immunoglobulins
- Serum free light chains
- Bone marrow aspiration/biopsy
- Radiographic assessments of lytic bone lesions
- Extramedullary plasmacytoma (EMP) assessments
- Minimal residual disease (MRD) assessment

Overview of Key Safety Assessments

- Complete physical examination including neurologic examination and vital signs
- Mini Mental State Evaluation (MMSE)
- Clinical laboratory evaluations
- Pregnancy testing (for females of childbearing potential [FCBP] only)
- Concomitant medications and procedures
- Replication Competent Lentivirus (RCL)
- Adverse events, including adverse events of special interest (AESIs)

Statistical Methods

The primary objective of the study is assessment of bb2121 efficacy as measured by ORR with a key secondary assessment of CR rate. The primary analysis of efficacy is planned when all subjects have had sufficient follow-up time for analysis, eg, a minimum of 10 months of post-bb2121 infusion follow up. The primary analysis will be based on bb2121 treated subjects.

The ORR is defined as the proportion of subjects with a best overall response of at least a partial response (PR) or better. Complete response rate is defined as the proportion of subjects with best overall response of CR.

The ORR will first be tested against the null hypothesis of an ORR of ≤50% at a one-sided alpha level of 0.025. If the ORR test is significant, CR rate will subsequently be tested against the null hypothesis of a CR rate of ≤10% at the same one-sided alpha level of 0.025.

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1. INTRODUCTION

1.1. Disease Background

1.1.1. Multiple Myeloma and Current Therapies

Multiple myeloma (MM) is a rare and incurable plasma cell neoplasm characterized by clinical features of renal failure, bone lesions, hypercalcemia and bone marrow (BM) suppression resulting from excessive production of monoclonal proteins as well as direct tumor cell effects. MM accounts for approximately 10% to 15% of all hematologic malignancies and primarily affects older individuals – it is extremely rare in patients less than 30 years old (Kumar, 2017; Moreau, 2013). Multiple myeloma is at the aggressive end of a spectrum of diseases referred to as plasma cell dyscrasias (PCD) and is often preceded for months/years by an asymptomatic condition known as monoclonal gammopathy of undetermined significance (MGUS) (Rajkumar, 2016). Data from GLOBOCAN in 2012 estimate a global incidence of 114,000 patients with 80,000 deaths (Ferlay, 2015).

Dramatic progress has been made in the treatment of MM patients and median survival in randomized clinical trials can now extend past 7 years (Attal, 2016). This increase in survival has been driven by more effective combination induction regimens composed primarily of proteasome inhibitors, immunomodulatory agents (IMiD) and dexamethasone coupled with consolidation using autologous stem cell transplantation (ASCT) (Kumar, 2017; Moreau, 2013; Rajkumar, 2016). Unfortunately, even with optimal up-front therapy the vast majority of MM patients relapse and further treatment is needed. For these RRMM patients, treatment options have also improved over time. With the introduction of newer classes of approved anti-myeloma agents, including monoclonal antibodies (daratumumab and elotuzumab), advanced generation proteasome inhibitors (carfilzomib, ixazomib), immunomodulatory compound (pomalidomide) and histone deacetylase inhibitors (panobinostat), RRMM patients can expect some degree of response (Botta, 2017). Many of these newer agents received full approval based on progression-free survival (PFS) benefits in randomized trials (carfilzomib, ixazomib, panobinostat and elotuzumab) but conditional approval was granted for daratumumab based on two trials showing overall response rates (ORR) ranging from 29% to 36% in RRMM subjects (Darzalex, 2017). This underscores the benefit of these newer agents in the treatment of a heavily refractory myeloma population and the desire to expedite novel therapies using ORR as a relevant measure of reduction of tumor burden and based on its correlation to standard approval outcomes such as progression-free survival (PFS) and overall survival (OS) (Lonial, 2015). Although effective, these salvage therapies still fall far short of cure evidenced by complete remission (CR) rates for combination regimens that include daratumumab, ixazomib, panobinostat or elotuzumab of less than 25% (Dimopoulos, 2016; Lonial, 2015; Moreau, 2016; Palumbo, 2016; San-Miguel, 2014). This highlights the need for potentially curative therapies for MM patients.

1.1.2. Immunotherapy in Oncology

Immunotherapy aims to leverage a series of complex interactions between malignant cells and the immune system where surveillance is a critical mechanism for restraining tumor development and one that is exploited in malignancy (Chen, 2013). As an example, dramatic remissions have been observed using immunotherapeutics such as checkpoint inhibitors in advanced

malignancies (Balar, 2017). In MM, immunotherapies in development encompass monoclonal antibodies, checkpoint inhibitors, bispecific T cell engagers, tumor vaccines and engineered T cells (Jung, 2017). All of these approaches are in various stages of clinical development. Given impressive efficacy and acceptable safety profiles in other hematologic malignancies, including acute lymphoblastic leukemia, non-Hodgkin's lymphoma and chronic lymphocytic leukemia (Kalos, 2011; Kochenderfer, 2015; Maude, 2014), engineered chimeric antigen receptor T cells (CAR T cells) have the potential to shift the treatment paradigm in MM. CAR T cells are genetically engineered autologous ex vivo cultured T cells that contain a CAR composed of an antigen-recognizing single chain variable fragment fused to a transmembrane domain and then to an intracellular region comprised of costimulatory and T-cell activation domains (Chang, 2017).

1.2. Product Background

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

Anti-BCMA02 CAR lentiviral vector is used to transduce autologous T cells. This vector uses the murine leukemia virus-derived myeloproliferative sarcoma virus enhanced promoter (MND) 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.

Preclinical pharmacology of bb2121 showed desirable specificity against BCMA and potent activity of the CAR T cells leading to rapid and complete elimination of BCMA expressing tumors. In vitro, bb2121 was cytotoxic against a range of MM cell lines with varying levels of BCMA expression and this activity was not inhibited by soluble BCMA at physiologic concentrations in the cultures. There was no tonic signaling of bb2121 in the absence of BCMA target engagement and no in vitro cytotoxicity induced in cell lines lacking BCMA, underscoring the specificity of bb2121 for BCMA-expressing target cells. In vivo models showed a selective and higher anti-tumor activity of bb2121 in comparison to bortezomib in treatment of immune-deficient mice with large established BCMA-expressing tumors with complete remission and survival rates as high as 100% in mice after a single dose of bb2121.

Figure 1: Anti-BCMA Chimeric Antigen Receptor

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

Refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational product (IP).

1.3. Rationale

1.3.1. Study Rationale and Purpose

1.3.1.1. Rationale for BCMA as a Target for CAR T Therapy

Similar to the use of anti-CD19 CAR T cells to treat CD19-expressing tumors, BCMA is a potential target for CAR T cells in MM for several reasons. First, BCMA is consistently expressed on plasma cells and myeloma cells from MM patients and is thought to provide protection for myeloma cells in the bone marrow niche (Carpenter, 2013; Novak, 2004). Second, BCMA expression increases with disease progression and soluble BCMA in serum acts as a prognostic factor for survival and indicator of response to therapy (Sanchez, 2012). Finally, BCMA has limited distribution in normal non-hematopoietic tissue. Reports have demonstrated BCMA expression on differentiated plasma cells and a subset of mature B cells in normal lymphoid tissue (eg, bone marrow, spleen, lymph nodes and tonsil) but lack of expression on naïve B cells, other hematopoietic cells including neutrophils, macrophages, and T cells or other non hemato-lymphoid tissues (Carpenter, 2013). Plasma cell-restricted expression was further supported in a recent nonclinical report describing a BCMA-targeting therapeutic antibody, in which specific cytolysis of BCMA-expressing (BCMA+) MM cells was observed after in vitro co-culture with this antibody while sparing normal bone marrow and other immune cells (Tai, 2014).

Given the nearly uniform expression of BCMA in MM (ranging from ~ 400 to 4000 receptors per cell) and the low level of target expression observed in nonclinical models sufficient to trigger bb2121 activation in response to BCMA+ target cell engagement (< 250 receptors per cell) (Lee, 2016), restriction of the treated population in both the clinical and marketing setting to a BCMA-positive subset of MM is not planned.

1.3.1.2. Rationale for the Study Design

Treatment options for RRMM have expanded greatly in the past several years and encompass advanced generation immunomodulatory compounds, proteasome inhibitors, monoclonal antibodies, histone modulators and alkylating chemotherapy. The CR rate for many of these drugs when administered in combination can approach 25% but leaves a significant fraction of patients with suboptimal remissions. Deep responses in this patient population including minimal residual disease (MRD) negative states are rare.

In an ongoing Phase 1 first-in-human clinical trial of bb2121 (CRB-401) in RRMM subjects, encouraging preliminary efficacy results have been observed with an acceptable safety profile. In this study, subjects with heavily pretreated RRMM (with high BCMA expression) were treated with escalating doses (50, 150, 450, 800 x 10^6 CAR+ T cells) of bb2121 following lymphodepletion with fludarabine and cyclophosphamide. The dose escalation and initial expansion phase of this trial is completed and includes an expansion cohort in approximately 20 subjects at the recommended Phase 2 dose range that includes subjects who have high and low BCMA expression in the bone marrow.

As of 29 March 2018, 43 subjects have been treated in the dose escalation and expansion phase of the CRB-401 trial. In 36 subjects evaluable for tumor response, with at least 2 response assessments or with progressive disease, treated at dose levels greater than or equal to 150 x 10^6

CAR+ T cells, the ORR was 81%, with a median duration of response of 10.9 months. Among 16 responding subjects evaluable for minimal residual disease (MRD) status, all 16 subjects (100%) were MRD negative. The principal toxicity observed was cytokine release syndrome (CRS) in 27 of 43 (63%) treated subjects which was mild to moderate in the majority of subjects with only two cases of transient Grade 3 CRS. No dose-limiting toxicities were observed during dose escalation (Raje, 2018). Neurotoxicity of any grade was observed in 14 of 43 (33%) subjects including one reversible grade 4 event (2.3%) and no grade 3 events. The one serious adverse event (SAE) of reversible Grade 4 neurotoxicity associated with tumor lysis syndrome and CRS was reported in the expansion cohort.

Another Phase 1 trial is ongoing at the National Cancer Institute with BCMA-targeted CAR T cells including the same anti-BCMA binding domain, but with a CD28 rather than 4-1BB costimulatory domain. This trial has also reported deep and durable (> 24 weeks) remissions in heavily pre-treated RRMM patients with high BCMA expression, but with dose-limiting Grade 3/4 CRS in 2 of 2 patients treated at 9 x 10^6 CAR+ T cells/kg (Kochenderfer, 2016).

In addition, preliminary results of a third clinical program of BCMA-targeted CAR T cells (different anti-BCMA binder with a 4-1BB costimulatory domain) at the University of Pennsylvania reported clinical responses in 3 of 10 subjects with RRMM treated at a dose of 1 to 5 x 10^6 CAR+ T cells/kg in the absence of lymphodepletion, with one sCR ongoing at 12 months and one VGPR followed by disease progression with BCMA negative MM at 5 months, suggestive of antigen loss escape. CRS was reported in 8 of 9 (89%) subjects including 2 Grade 3 and 1 Grade 4 CRS events, including concurrent Grade 3 and 4 neurotoxicity in one patient each (Cohen, 2016). Finally, recent results published from a Phase 1 clinical trial in China presented at ASCO 2017 (Fan, 2017) using a bi-specific BCMA-targeted CAR T (lentiviral vector with unclear costimulatory domain) in 35 RRMM subjects treated at doses from 0.6 to 7 x 10^6 cells/kg showed 100% ORR with CR achieved in 15 of 35 (43%) subjects. In this trial, CRS was observed in 29 of 35 subjects, including two Grade 3 events. No treatment-related deaths or irreversible CRS or neurotoxicity has been observed to date in any of these BCMA-targeted CAR T cell trials. These data provide evidence for acceptable tolerability and encouraging preliminary efficacy of bb2121 and other BCMA-targeted CAR T cells and provide the rationale for the current Phase 2 multi-center, open-label single-arm study designed to confirm the safety and efficacy of bb2121 in RRMM subjects.

1.3.2. Rationale for Dose, Schedule and Regimen Selection

In the CRB-401 first-in-human clinical trial with bb2121, CAR+ T cell doses ranging from 150 to 800 x 10^6 CAR+ T cells per subject showed encouraging efficacy and acceptable tolerability.

Based on a data cut-off of 29 March 2018 in Study CRB-401, updated information is available on 43 subjects enrolled in the dose escalation and expansion phase of this trial. bb2121 doses (x 10^6 CAR+ T cells) administered included: 50 (N = 3), 150 (N = 18), 200 (N = 1), 450 (N = 18) and 800 (N = 3). CRS of any grade was observed in 27 of 43 (63%) subjects with grade 3 CRS events reported in 2 of 43 subjects (4.6%). These included 1 reversible grade 3 CRS event at a dose of 450 and 800 x 10^6 CAR+ T cells, respectively. The median time to onset of CRS was 2 days and median duration was 6 days. The overall frequency of CRS across the dose range of 150 to 450 x 10^6 CAR+ T cells was 60%, including 39% at a dose of 150 x 10^6 CAR+ T cells and 83% at a dose of 450 x 10^6 CAR+ T cells. All cases of CRS were reversible. Neurotoxicity

of any grade was observed in 14 of 43 (33%) subjects including one reversible grade 4 event (2.3%) and no grade 3 events. The overall frequency of neurotoxicity across the dose range of 150 to 450 x 10^6 CAR+ T cells was 30% with a grade ≥ 3 frequency of 2.7%. This includes an overall frequency of 11% at a dose of 150 x 10^6 CAR+ T cells (with no grade ≥ 3 events) and 50% at a dose of 450 x 10^6 CAR+ T cells (with one grade ≥ 3 events, 5.6%). All cases of neurotoxicity were reversible. For this analysis of neurotoxicity, a broad inclusion of observed events within the neurologic System-Organ-Class (SOC) were included (dizziness, bradyphrenia, somnolence, confusional state, nystagmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination). Most neurologic events were grade 1/2 and likely multifactorial in nature, while only one grade ≥ 3 event clearly attributable to CAR T cell associated encephalopathy was reported. To address the grade ≥ 3 neurotoxicity event observed in Study CRB-401, both the CRB-401 and BB2121-MM-001 protocols were modified to update the eligibility criteria to exclude patient with history or presence of clinically relevant central nervous (CNS) pathology and the protocol safety monitoring plan, including a mandatory 14-day hospitalization, twice weekly outpatient visits in weeks 3 and 4 and a detailed CAR T toxicity management guideline to ensure adequate safety oversight. To date no additional grade 3/4 events have been observed.

Based on a data cut-off of 29 March 2018 in CRB-401, efficacy data is available from 39 evaluable subjects with at least 2 months of tumor response assessments or with disease progression within 2 months. Of these, 33 were treated across the dose range of 150 to 450 x 10^6 CAR+ T cells. The reported overall tumor response rate (ORR) at doses of 150 to 450 x 10^6 CAR+ T cells in 33 evaluable subjects was 79% with a median duration of response of 10.8 months. A dose response was observed across the 150 – 450 x 10^6 CAR+ T cell dose range with an ORR of 57% at the 150 x 10^6 CAR+ T cells and 95% at the 450 x 10^6 CAR+ T cell dose. Within the active dose cohorts (150 to 800 x 10^6 CAR+ T cells) tumor response was more frequent in patients with CRS than without CRS (ORR 92% vs 55%, respectively). Based on these updated results, a dose range of 150 to 450 x 10^6 CAR+ T cells is planned for the Phase 2 trial.

1.3.3. Rationale for Pharmacodynamics and Potential Predictive Biomarkers

The efficacy of bb2121 CAR T cells against BCMA+ plasma cells in MM patients relies on the expansion of the CAR T cell population after infusion into the patient. The rate and magnitude of the expansion and the persistence of the CAR T cells may be critical correlates of safety, efficacy and durability of response (Davila, 2014). Pharmacodynamic biomarkers will be used to correlate expansion and persistence of the CAR T cells with anti-tumor efficacy and safety. Additionally, the sampling plan and downstream analyses of the exploratory endpoints aim to address major open questions centered around the biology governing the durability and persistence of the CAR T cells as well as potential mechanisms of resistance to bb2121 CAR T cell therapy: mechanisms driven by either the CAR T cell immunophenotype, the tumor microenvironment, or direct resistance by the tumor.

The pharmacokinetics of bb2121 CAR T cell expansion after infusion will be measured by quantitative PCR (qPCR) and correlated to clinical response including reduction in BCMA+ myeloma cells in the bone marrow and changes in soluble BCMA in the blood. Cytokine mediated toxicities have been observed with CAR T cell therapies and risk of severe CRS (sCRS) is highest during the expansion phase of the CAR T cells. While the severity of CRS has

not been clearly shown to be predictive of response, it is typically observed to some degree in responding subjects and has been positively correlated with level of disease burden in acute lymphoblastic leukemia (ALL) (Maude, 2014). To understand the pathophysiology and/or retrospectively understand the drivers of patient-specific CAR T cell mediated toxicity, an extensive soluble factor panel will be tested on a multiplex assay platform in addition to clinical laboratory monitoring. This includes clinical markers of inflammation, such as C-reactive protein (CRP) and ferritin, as well as an extensive panel of over 25 cytokines and chemokines characteristic of a robust T cell response and/or neurotoxicity, including IL-2, IL-6, IFNγ and IL-15.

MRD in the bone marrow will be measured using both 8-color flow cytometry (standardized EuroFlow) and next generation sequencing (NGS) techniques measuring immunoglobulin gene rearrangements of the malignant clone.

The magnitude and durability of anti-tumor response may be governed by multiple factors including persistence, immunophenotype of the BCMA+ CAR T cells, exhaustion, tumor resistance to the BCMA-directed CAR T therapy, or immunogenicity of the bb2121 CAR T cell leading to CAR T cell clearance. As continued anti-tumor response may be dependent on persistence of functional BCMA-directed CAR T cells, we will evaluate the persistence and immunophenotype of the bb2121 CAR T cells throughout the study using multi-parameter flow cytometry. A comprehensive panel of T cell immunophenotypic markers of activation, exhaustion, regulatory T cell (Treg) status, and memory are in place to characterize the immunophenotype of the CAR T cell population in vivo. Analysis of the bb2121 CAR T cell manufacturing and final product characteristics will help to identify key features associated with clinical safety and efficacy. Persistent bb2121 CAR T cells may become hypofunctional in vivo. As an example, the expression of programmed cell death protein 1 (PD-1) is a marker of T cell exhaustion/dysfunction and may explain the mechanism of ineffective CAR T cell subsets. PD-1 and other markers of exhaustion/hypofunctionality, such as TIGIT, ICOS, TIM3, and LAG-3 will be evaluated along with the traditional T cell subset markers (eg, CD3, CD4, CD8, CD25, and Foxp3). Bone marrow will be evaluated for immune cell subsets (CAR T cells and endogenous immune cells) and presence of myeloma cells. Understanding the full complexity of the CAR T cell, myeloma cell, and tumor microenvironment may provide granularity into the patient-specific responses as well as inform potential combination therapies to ensure maintenance of functional CAR T cells or to reactivate exhausted subsets.

Tumor-specific mechanisms of treatment resistance will be evaluated. BCMA antigen and epitope loss will be assessed by immunologic and gene expression profiling. Examples of compensatory mechanisms that can be evaluated through gene expression profiling include upregulation of, or compensation by, expression of transmembrane activator CAML interactor (TACI), a B cell survival signaling receptor, or by alternative splicing of the BCMA transcript which provides a functional receptor lacking the bb2121 CAR T epitope. Additionally, the soluble factors, B-cell activating factor of the TNF family (sBAFF) and a proliferation-inducing ligand (sAPRIL), which can provide alternative survival signals through compensatory plasma cell receptors related to BCMA, such as TACI, will be monitored (Chiu, 2007). Upregulation of checkpoint molecules on the tumor will also be evaluated by flow cytometry and gene expression profiling. Bioinformatic analysis of longitudinal gene expression profiles provides an unbiased dataset informing both novel mechanisms of resistance as well as potential new targets for MM therapy, including next generation CAR T cell therapies.

Humoral and cellular immune responses against bb2121 CAR T cells will be monitored throughout the study. Additional correlative analyses may be conducted to understand features of bb2121 CAR T and circulating immune cells and their association with bb2121 CAR T cell persistence and function, clinical efficacy and toxicity. Further biomarker assessments, such as gene expression profiling, whole exome sequencing, or single-cell mass cytometry (CyTOF), may be conducted on immune or tumor cells to correlate disease features and bb2121 efficacy.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the efficacy, as defined as overall response rate (ORR), of bb2121 in subjects with relapsed and refractory multiple myeloma (RRMM)
Secondary Objective(s)
The secondary objectives are to: • Assess the safety of bb2121 in subjects with RRMM • Assess additional efficacy outcomes including complete response (CR) rate, time to response (TTR), duration of response (DOR), progression-free survival (PFS), time to progression (TTP) and overall survival (OS) • Characterize the expansion of chimeric antigen receptor (CAR) + T cells in the peripheral blood (cellular kinetics- pharmacokinetics [PK]) • Evaluate the development of an anti-CAR antibody response • Evaluate the proportion of subjects who attain minimal residual disease (MRD) negative status by next generation sequencing (NGS) • Describe changes in health-related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC-QLQ-C30), the European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L) and the European Quality of Life Multiple Myeloma Module (EORTC-QLQ-MY20)
Exploratory Objective(s)
The exploratory objectives are to: • Characterize the expansion of chimeric antigen receptor (CAR) + T cells in the bone marrow • Evaluate the immunophenotype of bb2121 CAR T and endogenous T cells in the blood, bone marrow and/or tumor tissue • Evaluate cytokine/chemokine induction in the blood of subjects after infusion of bb2121 • Evaluate the percentage of B-cell maturation antigen (BCMA)-expressing (BCMA+) cells and levels of BCMA expression in bone marrow, and the level of circulating soluble BCMA • Evaluate mechanisms of tumor sensitivity/resistance to bb2121 • Evaluate the development of an anti-CAR cellular immune response • Characterize the subject experience on bb2121 using patient interviews • Measure hospital resource utilization • Evaluate the proportion of subjects who attain minimal residual disease (MRD) negative status by EuroFlow

Table 2: Study Endpoints

Endpoint	Name	Description
Primary	Overall Response Rate (ORR)	Percentage of subjects who achieved partial response (PR) or better according to IMWG Uniform Response Criteria for Multiple Myeloma (Kumar, 2016) as assessed by an independent response committee (IRC)
Key Secondary	Complete Response (CR) Rate	Percentage of subjects who achieved CR or sCR according to IMWG Uniform Response Criteria for Multiple Myeloma (Kumar, 2016) as assessed by an IRC
Other Secondary	Time to Response	Time from first bb2121 infusion to first documentation of response of PR or better
	Duration of Response (DOR)	Time from first documentation of response or PR or better to first documentation of disease progression or death from any cause, whichever occurs first
	Progression-free Survival (PFS)	Time from first bb2121 infusion to first documentation of progressive disease (PD), or death due to any cause, whichever occurs first
	Time to Progression (TTP)	Time from first bb2121 infusion to first documentation of PD
	Overall Survival (OS)	Time from first bb2121 infusion to time of death due to any cause
	Safety	Type, frequency, and severity of adverse events (AEs), adverse events of special interest (AESI), serious adverse events (SAEs), cytokine release syndrome, neurotoxicity, infection and laboratory abnormalities
	PK	Maximum transgene level (Cmax), time to peak transgene level (Tmax), area under the curve of the transgene level (AUC), including maximum expansion and duration of persistence of bb2121 CD3+ cells
	Immunogenicity	Evaluate the development of an anti-CAR antibody response
	Minimal Residual Disease (MRD)	Evaluate subjects for MRD status using next generation sequencing (NGS)
	Health Related Quality of Life (HRQoL)	Subject-reported outcomes as measured by EORTC-QLQ-C30, EQ-5D-5L and EORTC-QLQ-MY20

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description
Exploratory	Biomarker	Characterize the expansion of chimeric antigen receptor (CAR) + T cells in the bone marrow
	Biomarker	Evaluate immunophenotype of bb2121 CAR T and endogenous T cells in the peripheral blood, bone marrow and/or tumor tissue
	Biomarker	Evaluate cytokine/chemokine induction in the blood of subjects after infusion of bb2121
	Biomarker	Evaluate mechanisms of tumor sensitivity/ resistance to bb2121 CAR T cell therapy
	Biomarker	Evaluate the percentage and level of expression of BCMA+ plasma cells in the bone marrow, as well as the level of circulating soluble BCMA
	Biomarker	Evaluate the development of an anti-CAR cellular immune response
	Subject experience on bb2121	Qualitative data obtained from completion of patient interviews
	Hospital resource utilization	Number of inpatient intensive care unit (ICU) days, and outpatient visits and concomitant medications
	Minimal Residual Disease (MRD)	Evaluate subjects for MRD status using flow cytometry (EuroFlow)

The primary study analysis is planned when all bb2121 treated subjects have completed sufficient follow-up, eg, a minimum of 10 months post-bb2121 infusion follow up. An updated analysis will be performed at 24 months after the last subject has received bb2121 infusion, or at other time points as needed.

3. OVERALL STUDY DESIGN

3.1. Study Design

This is an open label, single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of bb2121 in subjects with RRMM. The study will consist of 3 periods: pre-treatment (screening and leukapheresis), treatment (lymphodepleting chemotherapy [LD] and bb2121 infusion) and post-treatment (for a minimum of 24-months post-bb2121 infusion or until documented disease progression, whichever is longer).

Prior to initiation of any study procedures, subjects will complete an informed consent form and undergo screening procedures to determine eligibility. Following confirmation of eligibility, a leukapheresis collection will be performed on each subject to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of the bb2121 investigational product (IP).

If necessary, anti-myeloma bridging treatment is allowed for disease control while bb2121 is being manufactured, for disease control, prior to LD chemotherapy as long as the last dose is administered ≥ 14 days prior to initiation of LD chemotherapy.

Bridging therapies may include corticosteroids, alkylating agents, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 antibodies as single agents or in combination. Experimental agents and myeloma therapies to which the patient has not been previously exposed should not be used as bridging therapy. In subjects who receive bridging myeloma therapy, baseline disease staging assessments need to be repeated following completion of bridging therapy and prior to starting LD chemotherapy.

After bb2121 drug product has been successfully manufactured, additional baseline evaluations are performed to assess continued eligibility and safety prior to initiation of LD chemotherapy (refer to Section 6.1.3 and Table 3).

Subjects will receive three consecutive days of fludarabine intravenously (IV) (30 mg/m^2) and cyclophosphamide IV (300 mg/m^2) for LD chemotherapy starting on Day -5. After the completion of LD chemotherapy, bb2121 will be administered by IV infusion at a dosing range from 150 - 450 x 10^6 CAR+ T cells/infusion on Day 0. Due to the risk of CRS and neurotoxicity, subjects treated on this protocol must be admitted for inpatient monitoring through Day 14 post-bb2121 infusion; subjects may receive bb2121 as an outpatient, and then be hospitalized following the infusion on Day 0.

After infusion with bb2121, subjects will enter the post-treatment phase and will be followed for myeloma response and disease status for a minimum of 24-months post-bb2121 infusion or until documented PD, whichever is longer. Additional follow-ups will include safety, disease status, bb2121 pharmacokinetics, utility values measured using the EORTC-QLQ-C30, EQ-5D-5L and EORTC-QLQ-MY20 questionnaires, other secondary and exploratory endpoints.

All subjects will be followed for survival status on the MM-001 study from time of documented disease progression until last subject last visit (LSLV).

Retreatment with a second infusion of bb2121, including a second course of LD chemotherapy, with or without bridging therapy may be considered if all required selected eligibility criteria are met (refer to Section 6.2.1, Section 7.2.3 and Table 4) and if sufficient cryopreserved bb2121

drug product is available. There is no drug class restriction for bridging therapy used prior to retreatment, but bridging therapy should be completed at least 14 days prior to the start of LD chemotherapy. Retreated subjects will follow the Table of Events starting with the baseline visit and will be followed on study for a minimum of 6 months after the second infusion or until documented PD, whichever is longer.

The decision to discontinue a subject from study treatment or follow-up is the responsibility of the investigator or designee. The Sponsor will not delay or refuse this decision. However, prior to discontinuing a subject, the investigator should contact the Medical Monitor. The reason for discontinuation will be documented.

An Independent Response Committee (IRC) will review all data for response assessment. The IRC will determine the response to therapy based on the IMWG Uniform Response Criteria (refer to Appendix B) for each subject.

An independent Data Safety Monitoring Board (DSMB) will review cumulative study data over the course of the study to evaluate safety and efficacy, protocol conduct, and scientific validity and integrity of the study.

Safety and efficacy data will be monitored by the Celgene Medical Monitor, Clinical Research Scientist and Safety Physician on an ongoing basis throughout the study. Should a significant safety or efficacy issue be identified, all investigators will be notified immediately and the DSMB will be convened in an expedited fashion to make a recommendation as to the future conduct of the study.

Long-term bb2121-related toxicity, and viral vector safety as well as disease status, survival status and subsequent anti-MM therapies will continue to be monitored under a separate Long-term Follow-up (LTFU) protocol for up to 15 years after the last bb2121 infusion as per competent authority guidelines.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.2. Stopping Rules

Adverse events and serious adverse events (SAEs) are expected to occur frequently in this study based on the subject population being accrued and on the nature of the advanced hematologic malignancy under study. Regular systematic review of SAEs will serve as the basis for pausing or prematurely stopping the study. Unexpected SAEs that are related to bb2121 will be the primary criteria for pausing or stopping the study. Review of these SAEs, and any decision to pause enrollment or terminate the study, will be determined by the DSMB, Celgene and the Medical Monitor. Decisions to pause enrollment or terminate the study will be communicated promptly to investigators, to the Institutional Review Boards (IRBs)/Ethics Committees (ECs), Institutional Biosafety Committees (IBCs) (if applicable), and to the appropriate regulatory authorities.

3.2.1. Criteria for Pausing or Stopping the Study

Further enrollment and treatment in the study will be paused pending review and recommendations of the DSMB and immediate notification to all investigators and appropriate

regulatory authorities if any subject experiences any of the following serious adverse events within 28 days after a bb2121 infusion if not related to disease progression:

- Life-threatening (Grade 4) toxicity attributable to protocol therapy bb2121 infusion (+/- LD chemotherapy) that is unexpected, unmanageable (ie, does not resolve to Grade 3 or lower within 7 days), and unrelated to anticancer treatments between leukapheresis and LD chemotherapy
- Death

Expected toxicities, including observed and potential toxicities, associated with bb2121 and/or lymphodepleting chemotherapy are described in protocol Section 10.7, Section 10.8 and the IB.

The study may be terminated for the following reasons:

- Any subject develops uncontrolled bb2121 proliferation that is unresponsive to treatment
- Any subject develops detectable replication-competent lentivirus (RCL) during the study
- Celgene, IRB/EC, or DSMB decides that subject safety may be compromised by continuing the study
- Celgene decides to discontinue/limit the development of bb2121 in the indications under evaluation.

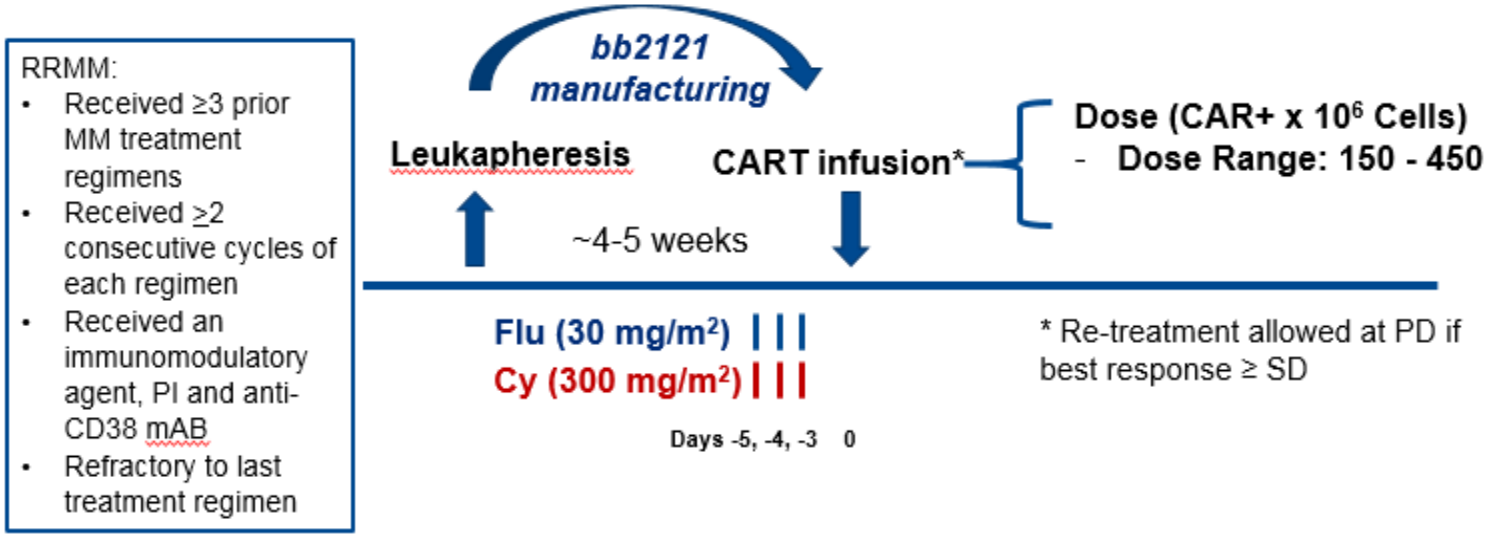
3.3. Study Duration for Subjects

Subjects will be followed in the study for a minimum of 24 months from bb2121 infusion or until documented disease progression, whichever is longer. The study will consist of the following periods: pre-treatment (screening, leukapheresis and baseline), treatment (LD chemotherapy and bb2121 infusion), and post-treatment follow-up. Retreated subjects will be followed on study for a minimum of 6 months following the second infusion or until documented PD, whichever is longer.

3.4. End of Trial

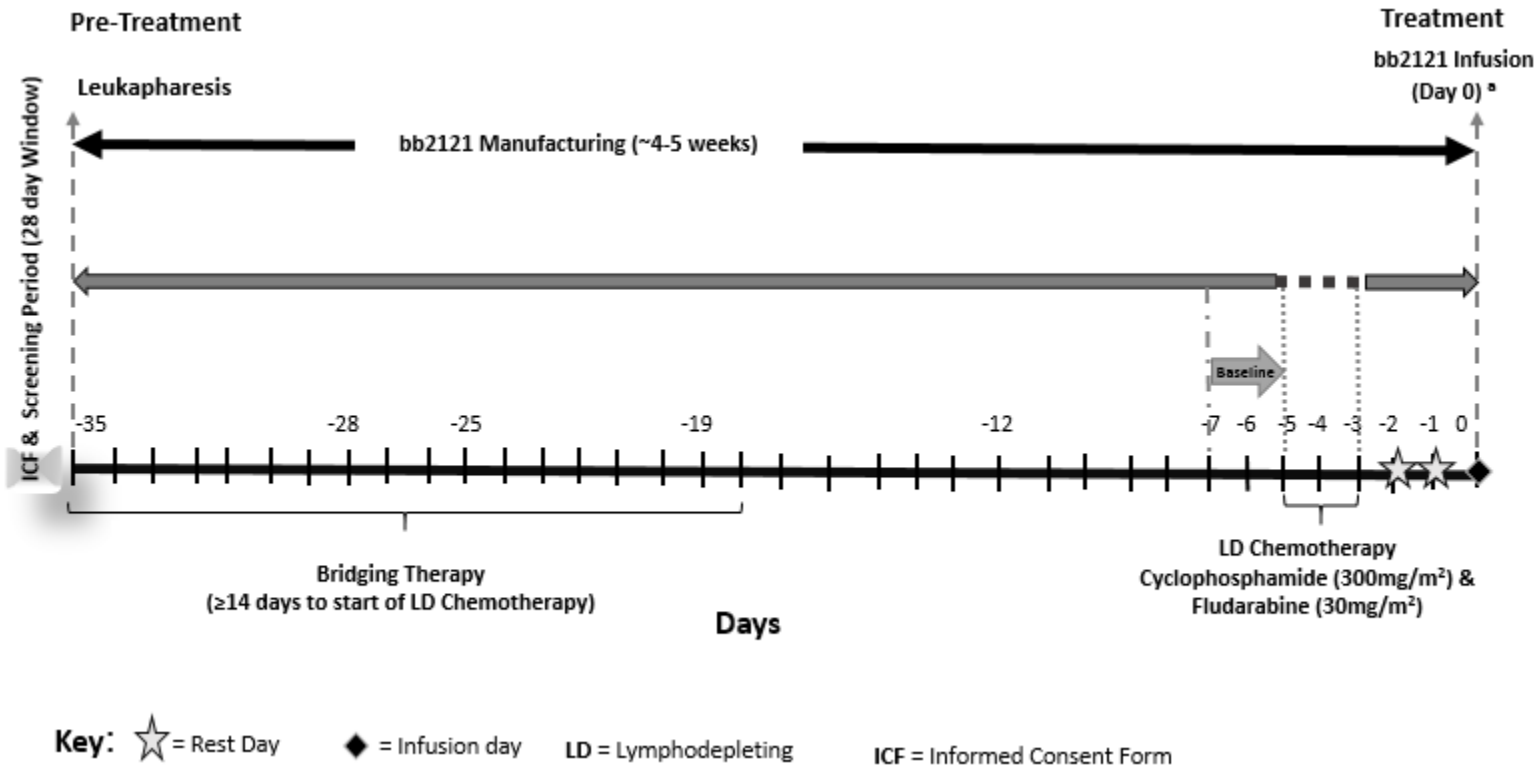
The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever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

Figure 2: Overall Study Design



Abbreviations: CAR = chimeric antigen receptor; Cy = cyclophosphamide; Flu = fludarabine; mAB = monoclonal antibody; PD = progressive disease; PI = proteasome inhibitor; SD = stable disease.

Figure 3: Study Schematic



NOTES:

a. Subjects will be hospitalized post-bb2121 infusion through Day 14. After hospital discharge, subjects must remain within a 30-minute transportation ride to the treating hospital and must have a dedicated caregiver(s) from Day 15 through Month 1 post-bb2121 infusion.

Figure 3: Study Schematic (Continued)

NOTES:

a. Retreated subjects will follow events starting with the baseline visit.
b. Subjects will be followed for disease status until documented PD, or for a minimum of 24 months, whichever is longer, (or minimum of 6 months for subjects retreated with a second bb2121 infusion) after last dose of bb2121. Please refer to Table 3 for safety and efficacy evaluation schedule.
c. Subjects will be hospitalized post-bb2121 infusion through Day 14. After hospital discharge, subject must remain within a 30-minute transportation ride to the treating hospital and must have a dedicated caregiver(s) from Day 15 through Month 1 post-bb2121 infusion.

4. STUDY POPULATION

4.1. Number of Subjects

Up to 140 subjects with RRMM will be enrolled, with up to 119 bb2121-treated subjects.

4.2. Inclusion Criteria

Eligibility is determined prior to leukapheresis. Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Documented diagnosis of multiple myeloma
   - Must have received at least 3 prior MM treatment regimens. Note: induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single regimen.
   - Must have undergone at least 2 consecutive cycles of treatment for each regimen, unless PD was the best response to the regimen.
   - Must have received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.
   - Must be refractory to the last treatment regimen. Refractory is defined as documented progressive disease during or within 60 days (measured from the last dose) of completing treatment with the last anti-myeloma drug regimen before study entry.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
4. Subjects must have measurable disease, including at least one of the criteria below:
   - Serum M-protein greater or equal to 1.0 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. Recovery to Grade 1 or baseline of any non-hematologic toxicities due to prior treatments, excluding alopecia and Grade 2 neuropathy.
6. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
7. Subject is willing and able to adhere to the study visit schedule and other protocol requirements within this protocol as well as agrees to continued follow-up for up to 15 years as mandated by the regulatory guidelines for gene therapy trials.

8. Females of childbearing potential (FCBP[1]) 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 lymphodepleting chemotherapy. Contraception methods must include 1 highly effective and 1 additional effective (barrier) method of contraception from screening until at least 1 year following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with bb2121. Any decision regarding contraception after bb2121 infusion should be discussed with the treating physician.
   - Agree to abstain from breastfeeding during study participation. There are insufficient exposure data to provide any recommendation concerning the total duration of abstaining from breastfeeding following treatment with bb2121. Any decision regarding breastfeeding after bb2121 infusion should be discussed with the treating physician.
   - Refrain from tissue donation including egg donation or any other tissue/blood/organ donations for at least 1 year following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of refraining from tissue donation following treatment with bb2121. Any decision regarding tissue donation after bb2121 infusion should be discussed with the treating physician.

   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 1-year post lymphodepleting chemotherapy, even if he has undergone a successful vasectomy. Subjects will be followed from screening until at least 1 year following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with bb2121. Any decision regarding contraception after bb2121 infusion should be discussed with the treating physician.

[1] A female of childbearing potential is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

* 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.

- Refrain from tissue donation including sperm or any other tissue/blood/organ donation for at least 1 year following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of refraining from tissue donation following treatment with bb2121. Any decision regarding tissue donation after bb2121 infusion should be discussed with the treating physician.

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
- Hormonal (birth control pill, injections, implants)
- Bilateral tubal ligation
- Successful vasectomy
- Male condom (additional effective method)
- Diaphragm (additional effective method)
- Cervical cap (additional effective method)

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subjects with known central nervous system involvement with myeloma.
2. History or presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, seizure, paresis, aphasia, stroke, subarachnoid hemorrhage or other 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. Subjects with active or history of plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or clinically significant amyloidosis.
4. Subjects with solitary plasmacytomas or non-secretory myeloma without other evidence of measurable disease.
5. Inadequate hepatic function defined by AST and/or ALT > 2.5 × upper limit of normal (ULN) and total bilirubin > 1.5 × ULN (unless due to Gilbert’s syndrome and direct bilirubin is ≤ 1.5 x ULN).
6. Inadequate renal function defined by CrCl ≤ 45 ml/min using Cockcroft-Gault equation.
7. International ratio (INR) or partial thromboplastin time (PTT) > 1.5 × ULN, or history of Grade ≥2 hemorrhage within 30 days, or subject requires ongoing treatment with chronic, therapeutic dosing of anti-coagulants (eg, warfarin, low molecular weight heparin, or Factor Xa inhibitors).

8. Inadequate bone marrow function defined by absolute neutrophil count (ANC) < 1000 cells/mm^3 in the absence of growth factor support (filgrastim within 7 days or peg-filgrastim within 14 days of screening) and platelet count < 50,000 mm^3 in the absence of transfusion support (platelet transfusion within 7 days of screening).
9. Echocardiogram or MUGA with left ventricular ejection fraction < 45%.
10. Inadequate pulmonary function as defined as oxygen saturation ($Sa0_2$) < 92 % on room air.
11. Ongoing treatment with chronic immunosuppressants (eg, cyclosporine or systemic steroids at any dose). Intermittent topical, inhaled or intranasal corticosteroids are allowed.
12. Previous history of an allogeneic hematopoietic stem cell transplantation or treatment with any gene therapy-based therapeutic for cancer or investigational cellular therapy for cancer or BCMA targeted therapy.
13. Evidence of human immunodeficiency virus (HIV) infection.
14. Seropositive for and with evidence of active viral infection with hepatitis B virus (HBV)
    - Subjects who are hepatitis B surface antigen (HBsAg) negative and HBV viral DNA negative are eligible
    - Subjects who had hepatitis B but have received an antiviral treatment and show non-detectable viral DNA for 6 months are eligible
    - Subjects who are seropositive because of hepatitis B virus vaccine are eligible
    - Subjects with known HBV infection should have undetectable HBV viral load and be maintained on anti-viral therapy to prevent HBV reactivation.
15. Seropositive for and with active viral infection with hepatitis C virus (HCV)
    - Subjects who had hepatitis C but have received an antiviral treatment and show no detectable HCV viral RNA for 6 months are eligible.
16. Subjects with a history of class III or IV congestive heart failure (CHF) or severe non-ischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months prior to starting study treatment.
17. 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, carcinoma in situ of the cervix, carcinoma in situ of the breast, or incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor nodes, metastasis clinical staging system]) or prostate cancer that is curative.
18. Subjects who are pregnant, or who intend to become pregnant during participation in the study.
19. Subject with known hypersensitivity to any component of bb2121 product, cyclophosphamide, fludarabine or tocilizumab.

20. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
21. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study. This includes systemic fungal, bacterial, viral, or other infection that is uncontrolled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antimicrobial treatment) or requiring IV antimicrobials for management.
22. Subject has any condition that confounds the ability to interpret data from the study.

5. TABLE OF EVENTS

Table 3: Table of Events

	Pre-treatment Period			Treatment Period		Post-treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Disease History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum/urine pregnancy test	X	-	X[f]	-	-	-	-	-	-	-	X[ee]	-	-	X[ee]	-	-	-	-	X[ee]	-	-	-	-	-	-
Physical examination including routine neurologic examination and vital signs[dd]	X	X	X	-	Daily (Days 0 through 14)[cc]						X[bb]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	-	X	-	X	-	-	X	X[bb]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Height	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	X	-	X	-	Daily						X	X	-	-	-	-	-	-	-	-	-	-	-	-	-
MMSE	-	-	X	-	-	Every other day[g]					X	X	-	X	-	-	-	-	-	-	-	-	-	-	-
Hematology Panel	X	X	X	-	Daily (Days 0 through 14)						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel	X	X	X	-	Daily (Days 0 through 14)						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TLS/CRS panel[h]	-	-	X	-	Daily (Days 0 through 14)						X	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphocyte subset panel[i]	X[i]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Coagulation Panel	X	-	X	-	Daily (Days 0 through 14)						X	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral Serology Testing[j]	X[k]	X[l]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HBV DNA/HCV RNA Testing[m]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	X	-	X	-	X	-	-
ECHO/MUGA/ECG[n]	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BNP	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urinalysis	X	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Leukapheresis	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepletion	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
bb2121 infusion	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Temperature monitoring	-	-	-	-	Every 6 – 8 hours [o]							-	-	-	-	-	-	-	-	-	-	-	-	-	-
Efficacy Assessments[hh]																									
Serum PEP/IFE and urine PEP (24-hour urine collection) and urine IFE	X	-	X	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum free light chains	X	-	X	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative serum immunoglobulins	X	-	X	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum β-2 microglobulin	X	-	X[x]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Skeletal survey[p]	X	-	-	-	-	-	-	-	-	-	-	As clinically indicated for response assessment												-	-
Clinical Examination for extramedullary disease	X	-	X	-	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PET/CT, CT or MRI for extramedullary disease[q]	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X	-	X	X	X
Bone marrow biopsy	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	-	-	X	X	X
Bone marrow aspirate	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[r]	-	X	X	X
Morphology	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[r]	-	X	X	X
Cytogenetics/FISH	X	-	X[x]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X[r]	-	-	X[z]	X[z]
BMA Immunophenotyping	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[r]	-	X	X	X

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Bone marrow CAR+ T cells	X	-	-	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[r]	-	X	X	X
MRD	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-	-	X	-	X	-	X[r]	-	X	X	X
Gene expression profiling	X	-	X[x]	-	-	-	-	-	-	-	-	X	-	X	-		X	-	X	-	X[r]	-	X	X	X
Biomarker Assessments (research samples)																									
Peripheral blood sample for cytokine (plasma)	X	-	-	-	X	X[u]	X	X	X	X	X[bb]	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Peripheral blood for Immunophenotyping by flow cytometry	X	-	-	-	X	X[s]	X	-	X	X	-	X	-	X	-	-	X	-	-	-	-	-	-	X	X
Peripheral blood sample for biomarkers (PBMC)	X	-	-	-	X	X[s]	X	-	-	X	-	X	-	X	-	-	X	-	X	-	X	-	X	X	X

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
						Safety Monitoring[ff]						Follow-up													
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]																				
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Peripheral blood sample for soluble BCMA (serum)	X	-	-	-	X	X[s]	X	-	X	X	X[bb]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood for immunogenicity (serum)	X	-	X[gg]	-	X	-	X	-	-	X	-	X	-	X	-	-	X	X	X	X	X	X	X	X	X
Peripheral blood for PK (CD3+ cells)[jj]	X	-	-	-	-	X[s]	X	X	X	X	X[bb]	X	X	X	X	X	X	X	X[w]	X	X	X	X	X	X
Peripheral blood for RCL testing[t,jj]	X	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	X	-	X	-	-	-	X	X	-
Peripheral blood for cellular immunogenicity (PBMC)	X	-	X[gg]	-	-	-	-	-	-	-	-	X	X	X	X	-	-	-	-	-	-	-	-	X	X
Extramedullary plasmacytoma biopsy[ii]	(X)	-	-	-	-	At time of disease progression (optional)																			-
Tumor Biopsy[jj]	-	-	-	-	-	Will be requested if a subject develops a new neoplasm while enrolled in this study; the Sponsor may request a sample of the neoplastic tissue for safety analysis of the bb2121 cells.																			

Table 3: Table of Events (Continued)

	Pre-Treatment Period			Treatment Period		Post-Treatment Period																			
	Screening[a]	Leukapheresis[b]	Baseline Evaluations[c]	LD Chemotherapy[d]	bb2121 infusion[e]	Safety Monitoring[ff]						Follow-up													
Study Days				D -5, -4 and -3	D0	D 1-6	D7	D9	D 11	D 14	D 17, 21, 24	M1	M2	M3	M4	M5	M6	M9	M 12	M 15	M 18	M 21	M 24/ EOS	PD[y]	CR[y]
Visit Window (Days)					+7					±1	±1	±3	±3	±3	±3	±3	±3	±14	±14	±14	±14	±14	±14	+28	+28
Other Assessments																									
Adverse Events and concomitant medications	AEs related to protocol-mandated procedures and associated concomitant medications; ALL SAEs			All AEs and associated concomitant medications								All Grade ≥ 3 AEs, all SAEs, all AESIs and associated concomitant medications (starting at M7)												
HRQoL	X	-	X	-	X	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X[aa]	X[aa]
Hospital resource utilization	-	-	X	-	-	Collected continuously																			
Survival Status	-	-	-	-	-	-	-	-	-	-	-	Every 3 months after PD[v]													

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BCMA = B-cell maturation antigen; β = beta; BMA = bone marrow aspirate; BNP = brain natriuretic peptide; CAR = chimeric antigen receptor; CD3 = cluster of differentiation 3; CR = complete response; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EM = extramedullary; EMP = extramedullary plasmacytoma; EOS = end of study; FISH = fluorescence in-situ hybridization; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV-1 = human lymphocytic T-cell virus type 1; HRQoL = health related quality of life; ICF = informed consent form; IFE = immunofixation; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PBLs = peripheral blood lymphocytes; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PEP = protein electrophoresis; PET = positron emission tomography; PK = pharmacokinetic; RCL = replication competent lentivirus; TLS = tumor lysis syndrome.

[a] Screening procedures must be completed within 28 days of leukapheresis.
[b] Leukapheresis will be approximately 4 -5 weeks before planned bb2121 infusion on Day 0. All safety evaluations will be performed locally ≤ 3 days prior to leukapheresis.
[c] Baseline evaluations performed within 72 hours prior (or on the same day) to LD chemotherapy.
[d] LD chemotherapy to start 5 days before Day 0.
[e] bb2121 infusion is targeted for Day 0 and must be infused no more than 7 days from the planned infusion day (Day 0). If bb2121 infusion cannot take place by day 7, subjects must wait 4 weeks to receive a second LD chemotherapy prior to bb2121 infusion. Refer to Section 6.2.2 and Section 7.2.1.1 on minimum assessments required to receive LD chemotherapy and bb2121 infusion; Subjects that are enrolled and unable to receive bb2121 infusion will be followed for 30 days for safety from the last study procedure (eg, leukapheresis, LD chemotherapy and bridging therapy). Tocilizumab must be available at the site prior to infusion of the subject.
[f] Serum or urine pregnancy test within 72 hours of LD chemotherapy; in the event of a positive urine pregnancy test, a serum pregnancy test should be performed to confirm result.
[g] MMSE will be performed every other day for the first 14 days (on Days 2, 4, 6, 8, 10, 12 and 14) and then twice weekly through M1 (on Days 17, 21, 24 and M1).
[h] TLS/CRS panel will include total bilirubin, magnesium, uric acid, phosphorus, ferritin, CRP, and creatine phosphokinase. Evaluations will continue until abnormal laboratory values returned to baseline (refer to Appendix F).
[i] Lymphocyte subset panel includes CD3, CD4, CD8 and CD19/CD20; Screening assessment should be performed within 7 days prior to leukapheresis.
[j] Viral serology testing to include HIV, Hepatitis B, Hepatitis C, syphilis and HTLV-1 antibody.
[k] Viral serology testing at screening for US and Canadian sites (include HIV, Hepatitis B, Hepatitis C, syphilis and HTLV-1 antibody); HIV, Hepatitis B and Hepatitis C in EU sites.
[l] Viral serology testing prior to leukapheresis for EU sites only.
[m] HBV DNA and HCV RNA testing to monitor for Hepatitis B or C viral reactivation, only in subjects with a history of HBV or HCV infection, respectively.
[n] Repeat ECHO/MUGA within 2 weeks prior to the start of LD chemotherapy if intervening/bridging therapy includes potentially cardiotoxic drugs (eg, carfilzomib, anthracyclines or high dose cyclophosphamide). ECG to be performed for all subjects within 2 weeks of screening and LD chemotherapy.
[o] After hospital discharge, subjects must monitor their temperature, every 6-8 hours (while awake), post-bb2121 infusion through Month 1 in a diary. Subjects must contact their treating investigator for any fever ≥38° C/100.4°. After hospital discharge, subjects must remain within a 30-minute transportation ride to the treating hospital and must have a dedicated caregiver(s) from day 15 through Month 1.
[p] Skeletal survey is done locally at screening and post-bb2121 infusion as clinically indicated. A PET/CT, CT or MRI scan may be done in place of a skeletal survey provided the same modality will be used for all assessments.
[q] PET/CT, CT or MRI of extramedullary disease required for subjects with a history of or clinical indication of EMPs only assessable radiographically. If a PET/CT, CT or MRI was performed within 30 days of screening as standard of care, it will not need to be repeated and can be used as the screening assessment.
[r] Prior to M18, all bone marrow aspirate assessments will be evaluated for MRD regardless of IMWG response. For M18 and beyond, bone marrow aspirate for MRD assessments will only be performed in subjects with responses of VGPR or better and in subjects with MRD negative status at the last prior assessment.
[s] Blood samples will be collected on Day 2 and Day 4 only; collection of peripheral blood sample for PBMC is not required on Day 4.
[t] Blood RCL collection will be stopped in the event of 2 consecutive undetectable results. Subjects with any +RCL will be monitored closely.
[u] Cytokines to be performed daily on Days 1 through 6. Additional assessments can be performed at time of suspicion of CRS (ie, at time of high fever onset, 24 hours after fever onset and 48 hours after fever onset).
[v] All subjects will be followed for survival every 3 months from the time of documented PD, until last subject last visit on the MM-001 study.
[w] If CAR transgene is detected in ≥ 1% of cells at any time point ≥12 months after last bb2121 infusion, the pattern for vector integration sites will be analyzed. If integration pattern suggests a predominant clone, the specific locations on the host chromosome will be determined, if a predominant integration site is identified a repeat analysis will be conducted within 3 months (refer to Section 6.4.4.1).
[x] Additional baseline assessments must be repeated if a subject received bridging therapy after leukapheresis. Assessments must be performed following bridging therapy and prior to LD chemotherapy. Bone marrow morphology and all other bone marrow assessments will be required. In subjects that did not receive bridging therapy and had inadequate screening bone marrow samples, an additional baseline bone marrow evaluation may also be requested
[y] 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.
[z] Subjects with genetic abnormalities at screening (or baseline for subjects that received bridging therapy), repeat cytogenetics/FISH at CR and at the time of PD. Subjects without defined genetic abnormalities at screening (or baseline for subjects that received bridging therapy), repeat cytogenetics/FISH at the time of PD.

[aa] HRQoL should be performed at the time of the PD or CR visit assessment, regardless if it was performed at the last scheduled visit.
[bb] Assessments are performed on D21 only.
[cc] On the day of bb2121 infusion, vital signs are collected prior to infusion, once midway through infusion, once at the end of infusion, and then every 15 minutes thereafter for the first hour then hourly for a total of 4 hours.
[dd] Oxygen saturation via pulse oximetry will be performed at screening, within 3 days of leukapheresis, at baseline, Day 0, M1, M2 and M3.
[ee] Serum or urine pregnancy test performed on Day 24, M3 and M12.
[ff] Safety monitoring period is 30 days. Each subsequent month is defined as 30 days post-bb2121 infusion.
[gg] Only required at baseline prior to start of LD chemotherapy for subjects that are retreated.
[hh] An additional Unscheduled visit may be required proximate to the primary analysis.
[ii] Subject has radiologically measurable EMP (soft tissue or bone related) at the time of PD that is amenable to biopsy. Optional at time of Screening.
[jj] If a subject develops a new neoplasm any time post bb2121 infusion, the Sponsor will request a sample of the tumor biopsy to evaluate the presence of a transgene. In addition to tumor biopsy, a peripheral blood sample for RCL testing and a peripheral blood sample for PK at the time of a new neoplasm will be requested. Refer to the lab manual for tissue collection instructions for liquid and solid hematological malignancies and solid tumors.

Table 4: Table of Events – Retreatment Evaluations

	Retreatment Screening evaluations[a]	Refer to Table 3 for baseline, treatment and post-treatment period evaluations
Study Procedures		
Inclusion/Exclusion criteria	X	
Serum/urine pregnancy test	X	
Physical examination including routine neurologic examination, weight and vital signs	X	
ECOG	X	
MMSE	X	
Hematology Panel	X	
Chemistry Panel	X	
Coagulation Panel	X	
Viral Serology Testing	X[b]	
ECHO/MUGA	X	
Serum PEP/IFE and urine PEP (24-hour urine collection) and urine IFE	X	
Serum free light chains	X	
Quantitative serum immunoglobulins	X	
Serum β-2 microglobulin	X	
Skeletal survey	X	
Clinical Examination for extramedullary disease	X	
Adverse Events and concomitant medications	X	

Abbreviations: ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; HTLV-1 = human lymphocytic T-cell virus type 1; IFE = immunofixation; MMSE = Mini Mental State Examination; MUGA = multigated acquisition; PD = progressive disease; PEP = protein electrophoresis.
Subjects may receive bb2121 product manufactured and stored from the original leukapheresis material and production run. No further manufacturing from either the second leukapheresis or from the stored leukapheresis material is allowed.
[a] If retreatment screening evaluations are performed within 72 hours of LD chemotherapy, the baseline evaluations do not need to be repeated. If bridging therapy is received, a repeat bone marrow biopsy and bone marrow aspirate is required.
[b] Viral serology testing to include HIV, Hepatitis B, Hepatitis C, syphilis and HTLV-1 antibody.

Table 5: Table of Events – Evaluations for Disease Progression after Month 24

Study Days	M27	M30	M33	M36+
Study Procedures				
Physical examination including routine neurologic examination, weight and vital signs[c]	X	X	X	X
ECOG[c]	X	X	X	X
Hematology Panel[c]	X	X	X	X
Chemistry Panel[c]	X	X	X	X
Serum PEP/IFE and urine PEP (24-hour urine collection) and urine IFE[c]	X	X	X	X
Serum free light chains[c]	X	X	X	X
Quantitative serum immunoglobulins[c]	X	X	X	X
PET/CT, CT or MRI for extramedullary disease[a]	-	X	-	X
Bone marrow biopsy[b]		-	-	X
Bone marrow aspirate[b]	-	-	-	X
Morphology[b]	-	-	-	X
Cytogenetics/FISH[b]	-	-	-	X
BMA Immunophenotyping[b]	-	-	-	X
Bone marrow CAR+ T cells[b]	-	-	-	X
MRD[b]	-	-	-	X
Gene expression profiling[b]	-	-	-	X
Peripheral blood for biomarkers (PBMC)[a]	-	X	-	X
Peripheral blood for soluble BCMA[c]	X	X	X	X
Peripheral blood for immunogenicity (serum)	X [b,d]	-	-	-
Peripheral blood for PK (CD3 + cells)[c,f]	X	X	X	X
Peripheral blood for RCL testing[b,f]	X	-	-	X
Extramedullary plasmacytoma biopsy[e]	At time of disease progression (optional)			
Tumor Biopsy[f]	Will be requested if a subject develops a new neoplasm while enrolled in this study; the Sponsor may request a sample of the neoplastic tissue for safety analysis of the bb2121 cells.			
Possibly related Grade ≥ 3 AEs, possibly related SAEs, possibly related AESIs and associated concomitant medications	From M25 through year 5/end of study participation			
HRQoL	X[b]	X	X	X

Abbreviations: ADA = anti-drug antibody; AESI = adverse event of special interest; BCMA = B-cell maturation antigen; BMA = bone marrow aspirate; CD3 = cluster of differentiation 3; CR = complete response; CT = computed tomography; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytoma; FISH = fluorescence in-situ hybridization; IFE = immunofixation; M = Month; MMSE = Mini Mental State Examination; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PEP = protein electrophoresis; PET = positron emission tomography; PK = pharmacokinetic; RCL = replication competent lentivirus; SAE = serious adverse event.

[a] Assessments will be performed every 6 months until disease progression for up to 5 years.
[b] Assessments will be performed at least every 12 months until disease progression for up to 5 years.
[c] Assessments will be performed every 3 months until disease progression for up to 5 years.

[d] If subject had positive ADA in the previous 24 months, assessment will be performed every 3 months until undetectable; if subject was negative ADA in the previous 24 months, no additional sample collection is required.
[e] Subject has radiologically measurable EMP (soft tissue or bone related) at the time of PD that is amenable to biopsy.
[f] If a subject develops a new neoplasm any time post bb2121 infusion, the Sponsor will request a sample of the tumor biopsy to evaluate the presence of a transgene. In addition to tumor biopsy, a peripheral blood sample for RCL testing and a peripheral blood sample for PK at the time of a new neoplasm will be requested. Refer to the lab manual for tissue collection instructions for liquid and solid hematological malignancies and solid tumors.

6. PROCEDURES

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee.

All efficacy and biomarker evaluations will be performed centrally and safety evaluations will be performed locally (unless otherwise indicated).

6.1. Pre-treatment Period

6.1.1. Screening Evaluations (performed within 28 days prior to leukapheresis)

Screening evaluations will be performed to determine study eligibility after the subject signs the IRB/EC approved informed consent form to determine study eligibility. Where applicable, institutional decision boards (eg, tumor board and RCP) should be involved in subject selection. The screening evaluations must be completed within 28 days of leukapheresis unless noted otherwise below.

Waivers to the protocol will not be granted during the conduct of this trial.

The following evaluations will be performed at screening as specified in Table 3 after informed consent has been obtained:

- Assess eligibility per inclusion/exclusion criteria. All inclusion/exclusion criteria must be met in order for subjects to be in the study
- Demographics (eg, date of birth, age, sex, race and ethnicity)
- Obtain medical history, including: disease diagnosis and history, SCT history, chemotherapy, radiation and surgical history. May include history of toxicities related to prior treatments and allergies
- Obtain prior disease history, including pathology reports (BM biopsy, plasmacytoma biopsy), clinical laboratory test (sPEP/IFE, uPEP/IFE, quantitative serum Ig, β-2 microglobulin, hematology and chemistry panel), and radiology reports (skeletal survey, PET/CT, CT or MRI)
- Serum ß-HCG pregnancy test for all females of child-bearing potential
- Physical examination, including routine neurologic examination, height, weight, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- ECOG performance status
- Hematology panel including complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count (with differential), and platelet count
  - Lymphocyte subset panel to include CD3, CD4, CD8 and CD19/CD20
- Chemistry panel including sodium, potassium, calcium, corrected serum calcium, chloride, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, albumin, alkaline phosphatase (ALP), total bilirubin, AST, ALT, lactate

dehydrogenase (LDH), and bicarbonate. Direct bilirubin should be collected if total bilirubin is abnormal

- Coagulation panel including partial thromboplastin time (PTT), international normalized ratio (INR), fibrinogen and d-dimers
- Viral serology testing for HIV, HBV, HCV, syphilis and HTLV-1 antibody (US and Canadian sites); HIV, HBV and HCV (EU sites)
- HBV DNA and HCV RNA testing required for subjects with documented HBV or HCV infection, respectively
- Echocardiogram (ECHO)/MUGA for left ventricular ejection fraction (LVEF)
- Electrocardiogram (ECG)
- Urinalysis
- Clinical disease response assessment:
  - sPEP/IFE
  - uPEP with 24-hour urine collection and urine IFE
  - Serum quantitative free light chains
  - Quantitative serum immunoglobulins
  - Serum beta-2 microglobulin
- Skeletal survey (performed locally) and as clinically indicated. Not required if PET/CT, CT or MRI is performed.
- Clinical evaluation by physical examination for extramedullary disease.
- PET/CT, CT or MRI for extramedullary disease (performed locally; only for subjects with a history of or clinical indication of extramedullary plasmacytoma (EMP), assessable radiographically). May be performed instead of skeletal survey to assess bone involvement.
- Bone marrow biopsy (for morphology and biomarkers)
- Bone marrow aspirate to include:
  - Morphology
  - Cytogenetics/FISH
  - BMA immunophenotyping
  - Bone marrow CAR+ T cells
  - Minimal Residual Disease (MRD)
  - Gene expression profiling
- Tumor tissue biopsy from plasmacytoma (optional)

- Research samples:
  - Peripheral blood for cytokine, immunophenotyping by flow cytometry, biomarkers, soluble BCMA, immunogenicity, cellular kinetics- PK as measured by qPCR, RCL and cellular immunogenicity
- Adverse events that are protocol mandated and associated concomitant medications
- Administer health related quality of life (HRQoL) Questionnaires

6.1.2. Leukapheresis (approximately 4-5 weeks prior to planned bb2121 infusion)

Following the screening assessments, if the subject is eligible to participate in the study, a leukapheresis collection will be performed on each subject to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of the bb2121 investigational product. Should a technical issue arise during the procedure or in the processing of the product, the subject may have a second collection procedure performed. More than one bb2121 product lot may be combined to meet the protocol target dose range. Subjects must continue to meet screening eligibility requirements for repeat leukapheresis (refer to Table 3).

Treatment with the following therapies prior to leukapheresis will not be allowed:

- Any prior systemic therapy, including experimental agents, for MM within 14 days prior to scheduled protocol required leukapheresis.
- Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 14 days prior to leukapheresis. Physiologic replacement, topical, intranasal and inhaled steroids are permitted.

The following safety evaluations will be performed locally ≤ 3 days prior to leukapheresis as specified in Table 3:

- Physical examination, including routine neurologic examination and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- ECOG performance status
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology panel
  - Chemistry panel
  - Viral serology testing (only EU sites will perform serology testing prior to leukapheresis)
- AEs that are procedure related and associated concomitant medications
- Patient interviews (prior to and after leukapheresis)

If necessary, anti-myeloma bridging treatment is allowed after leukapheresis while bb2121 is being manufactured, for disease control, prior to LD chemotherapy. The treatment must be completed at least 14 days before the initiation of the first dose of LD chemotherapy.

Bridging therapies may include corticosteroids, alkylating agents, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 antibodies as single agents or in combination. Experimental agents and myeloma therapies to which the patient has not been previously exposed should not be used as bridging therapy. In subjects who receive bridging myeloma therapy, baseline disease staging assessments need to be repeated following completion of bridging therapy and prior to starting LD chemotherapy.

6.1.3. Baseline Evaluations (performed prior to LD chemotherapy)

Subjects should complete the following assessments within 72 hours or on the same day of LD chemotherapy, as specified in Table 3: Negative serum/urine pregnancy test on female of child-bearing potential

- Physical examination, including routine neurologic examination, weight, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- Mini Mental State Examination (MMSE). Refer to Appendix E
- ECOG performance status
- ECG
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology panel
  - Lymphocyte subset panel
  - Chemistry panel (direct bilirubin should be collected if total bilirubin is abnormal)
  - Tumor lysis syndrome (TLS) panel: magnesium, uric acid, phosphorus
  - CRS panel: ferritin, C-reactive protein, and creatine phosphokinase
  - Coagulation panel
  - Brain natriuretic peptide (BNP)
- Clinical disease response assessment:
  - sPEP/IFE
  - uPEP with 24-hour urine collection and urine IFE
  - Serum quantitative free light chains
  - Quantitative serum immunoglobulins
- A repeat bone marrow aspirate may be requested if the screening sample was inadequate to complete baseline MRD and biomarker assessments
- Clinical evaluation by physical examination for extramedullary disease
- Cellular immunogenicity (only for retreated subjects)
- bb2121 immunogenicity (only for retreated subjects)

- Adverse events that are study procedure related and associated concomitant medications
- Administer HRQoL Questionnaires
- Collection of hospitalization details (refer to Section 6.6.5)

If a subject receives bridging therapy after leukapheresis, the following additional myeloma restaging and cardiac assessments (including all other baseline evaluations) will be performed prior to LD chemotherapy:

- Serum beta-2 microglobulin
- PET/CT, CT or MRI for extramedullary disease (performed locally; only for subjects with a history of or clinical indication of extramedullary plasmacytoma [EMP], assessable radiographically)
- Bone marrow biopsy (for morphology and biomarkers)
- Bone marrow aspirate to include:
  - Morphology
  - Additional baseline MRD and biomarker assessments
- An ECHO/MUGA will be repeated within 2 weeks prior to the start of LD chemotherapy if bridging therapy includes potentially cardiotoxic drugs (eg, carfilzomib, anthracyclines or high dose cyclophosphamide)

6.2. Treatment Period

6.2.1. Lymphodepleting Chemotherapy

Adverse events and associated concomitant medications will be collected from the first dose of LD chemotherapy through 6 months post-bb2121 infusion.

Upon notification from Celgene that bb2121 will be available, LD chemotherapy should be initiated 5 days prior to planned bb2121 infusion. Given that enrolled subjects have RRMM refractory to their last line of therapy it is expected that hematologic and organ function may worsen during the window between leukapheresis and starting LD chemotherapy. To be eligible to start LD chemotherapy the following criteria needs to be met:

1. No bridging anti-myeloma therapy within 14 days prior to start of LD chemotherapy.
2. Adequate hepatic function defined by AST and/or ALT ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN (unless due to Gilbert's syndrome and direct bilirubin is ≤ 1.5 x ULN)
3. Adequate renal function defined by clearance creatinine ≥30 mL/min
4. INR and PTT ≤ 1.5 × ULN
5. Adequate bone marrow function defined by ANC ≥ 500 cells/mm^3 and platelet count ≥ 50,000 mm^3 (unless inadequate bone marrow function is thought to be related to bone marrow myeloma involvement, this should be discussed with the Medical Monitor)
6. No presence of active infections

7. No intercurrent illness or toxicity that would place the subject at undue risk of proceeding to LD chemotherapy and bb2121 infusion (should be discussed with the Medical Monitor)
8. No therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 72 hours prior to LD chemotherapy. Physiologic replacement, topical, intranasal and inhaled steroids are permitted.
9. No active urinary outflow obstruction

Patient Interviews (optional) will be performed according to Table 6.

6.2.2. bb2121 Infusion

Upon completion of LD chemotherapy, subjects will be infused with bb2121 on Day 0. Subjects may receive bb2121 infusion as an outpatient, and then be hospitalized following the infusion on Day 0.

Subjects should not experience a significant worsening in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with bb2121 infusion. Subjects who meet at least one of the following criteria on the day of scheduled bb2121 infusion should have bb2121 administration delayed:

- Suspected or active systemic infection
- Onset of fever ≥ 38ºC/100.4ºF, not related to underlying disease
- Requirement for supplemental oxygen to keep saturation greater than 91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New onset or worsening of other non-hematologic organ dysfunction ≥ Grade 3
- Taking any of the prohibited medications as described in Section 8.2

bb2121 infusion must be postponed until the active infection has resolved (subjects with suspected/active infection must have negative culture for at least 24 hours on appropriate antibiotics or negative rapid viral panel) and the organ toxicities recovered to ≤ Grade 2. In case of delayed infusion, LD chemotherapy may need to be repeated after discussion with the Sponsor (see Section 6.2.1).

If bb2121 cannot be infused on Day 0, a 7-day window is allowed, but should be discussed with the Medical Monitor. If bb2121 infusion cannot occur by Day 7, the Sponsor should be notified. Subjects may receive bb2121 infusion following a second round of LD chemotherapy after a minimum of 4 weeks from last LD chemotherapy. The same criteria listed in Section 6.2.1 needs to be met.

Subjects that are enrolled and unable to receive bb2121 infusion will be followed for 30 days for safety from the last study procedure (eg, leukapheresis, LD chemotherapy and bridging therapy).

The following evaluations will be performed on the day of bb2121 infusion (unless otherwise indicated):

- Physical examination, including routine neurologic examination and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
  - Vital signs will be collected prior to infusion (- 30 minutes), once midway through infusion, once at the end of infusion (+ 10 minutes), and then every 15 minutes (± 5 minutes) thereafter for the first hour (± 10 minutes) then hourly for a total of 4 hours
- ECOG performance status
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology panel
  - Chemistry panel
  - TLS/CRS panel
  - Coagulation panel
- Urinalysis
- Research samples:
  - Peripheral blood for cytokine measurements, soluble BCMA, immunophenotyping, bb2121 immunogenicity, and peripheral biomarkers
- All AEs and associated concomitant medications through 6 months post-bb2121 infusion
- Administer HRQoL Questionnaires
- Patient interviews (optional)

6.3. Post-treatment Period

6.3.1. Post-bb2121 Infusion (Day 1 through Month 1)

Due to the risk of CRS and neurotoxicity, subjects treated on this protocol must remain hospitalized for inpatient monitoring through Day 14 post-bb2121 infusion; subjects may receive bb2121 as an outpatient, and then be hospitalized following the infusion on Day 0. Inpatient monitoring should include a daily physical exam and vital signs every 4 hours unless otherwise clinically indicated. In addition, the schedule of assessments (refer to Table 3) should be followed. Additional clinical assessments or interventions should be performed as clinically indicated.

Based on the risks of adverse events requiring immediate medical intervention, after hospital discharge, subjects must stay within a 30-minute transportation ride to the treating hospital for close monitoring of fever and other signs of CRS or neurotoxicity and have a dedicated full-time caregiver(s) through M1. On Day 14, subjects can be discharged only if they are afebrile for 24 hours, signs and symptoms of CRS and neurotoxicity have completely resolved and CRP is declining, if elevated from baseline, or stable and not rising. Once the subject is discharged, self-monitoring of fever is required every 6 to 8 hours (while awake) for the first month.

Hospitalization is required if there are any signs of fever (≥ 38ºC/100.4ºF), signs or symptoms suggestive of CRS or neurotoxicity, including increase of CRP (> 200 mg/L or rising rapidly) for close monitoring of cardiac and organ function, including routine neurologic exams.

A dedicated triage center with "CAR T" study staff assigned to manage the flow of subjects to the treating physician 24 hours a day must be in place after the required 14-day hospitalization period. If the emergency department is to be utilized instead of a direct bypass to the dedicated triage center, that department and their staff must be trained to triage subjects directly to the bb2121 study staff for immediate management of signs and symptoms suggestive of CRS or neurotoxicity. Each site will implement and provide a detailed expedited triage plan and train all study staff for their respective roles regarding CRS or neurotoxicity detection and management.

Refer to Table 3 for details on assessments to be performed:

- Daily local safety assessments from Day 1 through Day 14 (inpatient) and on Days 17, 21 and 24 (outpatient):
  - Physical examination, including routine neurologic examination, weight and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
  - ECOG performance status
  - Collection of peripheral blood samples for clinical laboratory evaluation:

    Hematology panel

    Chemistry panel

    TLS/CRS panel

    Coagulation panel
- MMSE will be performed on Days 2, 4, 6, 8, 10, 12, 14, 17, 21,24 and M1
- Serum/urine pregnancy test on Day 24
- After discharge from hospitalization, self-temperature monitoring is required to be taken every 6 to 8 hours (while awake), in a diary through M1. The clinical site must be contacted immediately for temperature ≥ 38°C or 100.4°F.
- Research samples:
  - Peripheral blood for cytokine measurement performed on Days 1, 2, 3, 4, 5, 6, 7, 9, 11, 14 and 21. Additional assessments required if signs and symptoms suggestive of CRS.
  - Immunophenotyping performed on Days 2, 4, 7, 11 and 14
  - Peripheral biomarkers performed on Days 2, 7 and 14
  - Soluble BCMA performed on Days 2, 4, 7, 11, 14 and 21
  - bb2121 immunogenicity performed on Days 7 and 14, and
  - Cellular kinetics- PK as measured by qPCR performed on Days 2, 4, 7, 9, 11, 14 and 21

- All AEs and associated concomitant medications through 6 months post-bb2121 infusion
- Patient interviews (optional) on Day 21
- Collection of hospitalization details (refer to Section 6.6.5)

6.3.2. Post-bb2121 Infusion (M1 through Month 24/EOS)

The following assessments will be performed in all subjects from M1 through M24 according to Table 3. If PD occurs within 24 months, refer to assessments in the below section.

- Physical examination, including routine neurologic examination, weight (M1 only) and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
  - Oxygen saturation via pulse oximetry collected at M1, M2 and M3 only
- ECOG performance status
- MMSE will be performed at M1 and M3
- Serum/urine pregnancy test at M3 and M12
- Clinical assessment by physical examination, for extramedullary disease (performed locally)
- PET/CT, CT or MRI scan for extramedullary disease (performed locally)
- Bone marrow biopsy
- Bone marrow aspirate to include:
  - Morphology at M1, M3, M6, M12, M18, M24
  - Cytogenetics/FISH at M18
  - BMA immunophenotyping at M1, M3, M6, M12, M18, M24
  - Bone marrow CAR+ T cells at M1, M3, M6, M12, M18, M24
  - MRD at M1, M3, M6, M12, M18, M24
  - Gene expression profiling at M1, M3, M6, M12, M18, M24
- Tumor tissue from plasmacytoma (optional)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology panel
  - Chemistry panel
  - TLS/CRS panel (M1 or until laboratory values have returned to baseline)
  - Coagulation panel at M1 only
- HBV DNA/HCV RNA assessment at M6, M12, M18 and M24
- Clinical disease response assessment:

  - sPEP/IFE
  - uPEP with 24-hour urine collection and urine IFE
  - Serum quantitative free light chains
  - Quantitative serum immunoglobulins
- Research samples:
  - Peripheral blood for cytokine measurement (M1 only)
  - Immunophenotyping performed at M1, M3, M6, M12, M18, M24
  - Peripheral biomarkers performed at M1, M3, M6, M12, M18, M24
  - Soluble BCMA performed monthly for first 6 months then every 3 months until M24
  - bb2121 immunogenicity performed M1, M3, then every 3 months until M24
  - Cellular kinetics- PK as measured by qPCR performed monthly for first 6 months then every 3 months until M24
  - RCL performed M3, M6, M12, M24
  - Cellular immunogenicity performed M1, M2, M3 and M4
- AEs will be collected as described during the following time periods:
  - All AEs and associated concomitant medications through 6 months post-bb2121 infusion
  - All Grade ≥ 3 AEs, all SAEs and all adverse events of special interest (AESIs) (including new malignancies, CRS, macrophage activation syndrome (MAS), neurologic disorders, hematologic disorders, rheumatic and autoimmune disorders or exacerbation of one of these pre-existing conditions and infections) and associated concomitant medications will be collected from M7 continuously until Month 24/end of study (EOS) visit
- Administer HRQoL Questionnaires
- Patient interviews (optional)
- Collection of hospitalization details (refer to Section 6.6.5)
- Survival status

If a subject has PD within 24-months and it is determined during a scheduled visit according to the TOE and Section 6.3.4, only missing assessments from the PD visit should be performed within 28 days of the last visit. The subject will either be evaluated for retreatment with bb2121 or remain on study and have the following assessments performed starting from the time of PD through the remainder of the 24-months:

- Collection of anti-cancer treatment since bb2121 infusion (if applicable)

- Immunoglobulins (not required if B-cell recovery documented without recent administration of IVIG)
- Cellular kinetics- PK as measured by qPCR
- Collection of peripheral blood for RCL testing
- Record all AEs and associated concomitant medications through 6 months post-bb2121 infusion and afterwards all AEs ≥ Grade 3, all SAEs, all AESIs and associated concomitant medications (refer to Section 10.1)
- Administer HRQoL Questionnaires
- Patient interviews (optional)
- Collection of hospitalization details (refer to Section 6.6.5)
- Survival status

At month 24, the EOS visit will be performed.

6.3.3. Post-bb2121 infusion (M25 and Beyond)

If a subject remains progression free at M24, additional quarterly assessments will be performed for up to 5 years until documented PD. Myeloma disease status laboratory assessments will be performed every 3 months, imaging studies (as applicable to monitor EMD) performed every 6 months and bone marrow assessments every 12 months for up to 5 years. Biomarker assessments will be performed; refer to Table 5 for schedule of assessments. At the time of documented PD, subjects will either be evaluated for retreatment with bb2121 or perform the EOS visit assessments within 28 days of the last visit according to Table 3. The EOS assessments will be performed in place of the PD visit assessments.

6.3.4. Post-bb2121 Infusion (Disease Progression/CR)

The following assessments will be performed in all subjects at the time of documented PD or CR. If PD or CR is determined during a scheduled visit according to the TOE, only missing assessments from the PD or CR visit should be performed within 28 days of the last visit (with the exception of HRQoL, which must be performed).

- Physical examination, including routine neurologic examination and vital signs (blood pressure, body temperature, respirations and heart rate)
- ECOG performance status
- Clinical assessment by physical examination, for extramedullary disease (performed locally)
- PET/CT, CT or MRI scan for extramedullary disease (performed locally)
- Bone marrow biopsy
- Bone marrow aspirate to include:
  - Morphology
  - Cytogenetics/FISH

  - BMA immunophenotyping
  - Bone marrow CAR+ T cells
  - MRD
  - Gene expression profiling
- Tumor tissue biopsy from plasmacytoma (optional)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology panel
  - Chemistry panel
- Clinical disease response assessment:
  - sPEP/IFE
  - uPEP with 24-hour urine collection and urine IFE
  - Serum quantitative free light chains
  - Quantitative serum immunoglobulins
- Research samples:
  - Peripheral blood for immunophenotyping
  - Peripheral biomarkers
  - Soluble BCMA
  - bb2121 immunogenicity
  - Cellular kinetics- PK as measured by qPCR RCL testing (at the time of PD only)
  - Cellular immunogenicity (at the time of PD only)
- Record all Grade ≥ 3 AEs, all SAEs and AESIs (including new malignancies, CRS, MAS, neurologic disorders, hematologic disorders, rheumatic and autoimmune disorders or exacerbation of one of these pre-existing conditions and infections)
- Administer HRQoL Questionnaires (must be performed at time of PD/CR)
- Patient interviews (optional)
- Collection of hospitalization details (refer to Section 6.6.5)
- Survival status

6.3.5. Unscheduled Evaluations

If the investigator feels that a subject needs to be evaluated at a time other than the protocol-specified visit, the subject may be asked to come in to the clinic for an unscheduled evaluation, as appropriate. All unscheduled assessments and those performed due to adverse events or study procedures should be captured on the eCRF.

6.3.6. Assessment at Time of Death

In case an autopsy is performed, blood and tissue samples will be collected for central analysis of markers related to safety and efficacy of the CAR T cells.

6.3.7. Assessment at Time of Second Malignancy

If a subject develops a new neoplasm at any time following infusion, the Sponsor requests a sample of the neoplastic tissue (refer to laboratory manual) and blood samples (refer to Section 6.4.4, and 6.4.4.1) for assessment of RCL, CAR+ T cells, and vector integration site analysis, as applicable.

6.3.8. Early Withdrawal

If a subject voluntarily withdraws prematurely from the study, a visit will be scheduled as soon as possible, and all of the assessments listed for Month 24/EOS visit will be performed.

6.3.9. Survival Follow-up

At the time of documented PD, all subjects will also be followed (in the MM-001 study) for survival every 3 months until last subject last visit. Additional survival follow-up information will be collected in the context of the LTFU protocol.

6.3.10. Long-term Follow-up

Because this protocol involves gene transfer, long-term follow-up for lentiviral vector safety will be followed under a separate LTFU protocol, for up to 15 years after bb2121 infusion.

All subjects who have completed follow-up, or are withdrawn from this study will be asked to enroll into the LTFU protocol. A separate informed consent form will be provided for the LTFU protocol. Subjects who do not consent to participate in the LTFU protocol will be followed for survival through public records.

6.4. Safety Assessments

All safety-related laboratory assessments will be performed locally, unless otherwise indicated.

6.4.1. Physical Examination, Vital Signs, ECOG, Height and Weight, Routine Neurologic Examination, MMSE

A physical examination should include assessments of the following body parts/systems: abdomen, extremities, heart, lungs, and neurological. In addition, symptom-directed exams should be performed.

Measurement of vital signs include blood pressure, body temperature, respiration, heart rate, and oxygen saturation via pulse oximetry.

Eastern Cooperative Oncology Group performance status (refer to Appendix D) will be used to evaluate subject eligibility at screening and will be assessed throughout the study at timepoints specified in Table 3. Height in centimeters (cm) or inches (in) and body weight to the nearest kilogram (kg) will be measured according to Table 3.

A routine neurologic examination should include, at minimum, a physical examination to assess mental status, cranial nerves, motor and sensory skills, coordination and balance. The MMSE (refer to Appendix E) may be administered by an appropriately trained provider (ie, physician, nurse); a neurologist is not required. Efforts should be made to have the same provider perform the MMSE on a given subject to maintain consistency of assessment.

6.4.2. Laboratory Assessments for Safety Parameters

Safety assessments will be performed daily during the first 14 days of hospitalization and thereafter as described in Table 3. Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs/SAEs or expected events (refer to Appendix F).

- Hematology laboratory tests include complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count (with differential) and platelet count
  - Lymphocyte subset panel to include CD3, CD4, CD8 and CD19/CD20
- Serum chemistry laboratory tests include sodium, potassium, calcium, corrected serum calcium, chloride, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, albumin, alkaline phosphatase (ALP), total bilirubin, AST/SGOT, ALT/SGPT, lactate dehydrogenase (LDH), and bicarbonate. Direct bilirubin should be added if total bilirubin is abnormal.
  - TLS/CRS panel will include magnesium, uric acid, phosphorous, ferritin, C-reactive protein, and creatine phosphokinase
- Coagulation panel will include partial thromboplastin time, international normalized ratio, fibrinogen and d-dimers
- Urinalysis includes specific gravity, pH, glucose, bilirubin, protein, ketones, blood and, if feasible, microscopic analysis [cast, bacteria, RBCs, and WBCs]. Urinalysis will be performed by local laboratory and as per local practice.
- Renal Function: The creatinine clearance (CrCL) will be calculated based on the Cockcroft-Gault formula or the CrCl directly calculated from the 24-hour urine collection method (refer to Appendix G).

6.4.3. Cardiac Assessments

An assessment of LVEF will be performed locally by ECHO or MUGA to assess the cardiac function of the subject and to confirm study eligibility.

A repeat LVEF assessment is required within 2 weeks prior to start of LD chemotherapy if bridging therapy included potentially cardiotoxic drugs (eg, carfilzomib, anthracyclines and high dose cyclophosphamide).

Additional LVEF assessment studies should be performed as clinically indicated to evaluate subjects suspected of having decreased cardiac function associated with CRS.

An ECG will be performed locally within 2 weeks of the screening visit and repeated at baseline within 2 weeks prior to the start of LD chemotherapy.

Blood assessment for brain natriuretic peptide (BNP) should be performed locally at baseline within 72 hours prior to start of LD chemotherapy.

6.4.4. Replication-Competent Lentivirus Testing

RCL testing will be performed centrally on PBMCs obtained by a peripheral blood draw. Details regarding sample collection and processing are provided in the BB2121-MM-001 laboratory manual. Testing for RCL will utilize an analytically validated polymerase chain reaction based assay.

Samples for RCL testing will be collected at timepoints indicated in Table 3.

If all samples collected within the first year after the dose of bb2121 are negative, subsequent samples will be archived. However, if any of the samples are positive, the test will be repeated to confirm the result. If the repeat test is also positive, further analysis of the RCL will be undertaken, including a coculture assay with subject PBMCs to further characterize replicating lentivirus in order to ascertain the nature of the RCL and potential effects. Any confirmed positive result from RCL testing will be reported as a serious adverse event within 24 hours, and the relevant Health Authorities will be notified.

If a subject has not progressed within 24-months post-bb2121 infusion, RCL assessment will be performed annually for up to 5 years or until disease progression. If at year 5, RCL is negative, no additional samples will be required.

Samples will be archived with appropriate safeguards to ensure long-term stability and an efficient system for the prompt linkage and retrieval of the stored samples with the subject's study records and the production lot records. Archived samples will be destroyed as outlined in the LTFU protocol.

6.4.4.1. Vector Integration Site Analysis

Vector integration site testing will be performed if the CAR transgene is detected in ≥ 1% of PBMC any time point ≥12 months after the last bb2121 infusion. If integration pattern suggests a predominant integration site, a repeat analysis will be conducted within 3 months and further studies including insertion site analysis will be performed. Any observation of clonal outgrowth (clonal dominance), or monoclonality, will be reported as an SAE within 24 hours.

6.5. Efficacy Assessments

Response (efficacy) assessments include: serum and urine myeloma paraprotein protein electrophoresis and immunofixation, serum immunoglobulins, serum free light chain assay, clinical and/or radiological extramedullary plasmacytoma assessments (if applicable), radiographic assessment for bone lesions, minimal residual disease (MRD), and bone marrow aspirate and bone marrow biopsy.

Per IMWG Uniform Response Criteria all response categories require two consecutive assessments (with the exception of radiographic and bone marrow evaluation) made at any time prior to start of new therapy.

6.5.1. Laboratory Assessments for Efficacy Parameters

All efficacy evaluations will be performed centrally (unless otherwise specified):

- Serum protein electrophoresis (sPEP) and urine protein electrophoresis (uPEP) test (performed on 24-hour urine collection) for M-protein measurement. Subjects with negative uPEP/IFE at baseline will have urine collected in the setting of PD or CR.
- Serum and urine immunofixation (IFE)
- Quantitative serum immunoglobulin assessment includes IgG, IgM, and IgA
- Quantitative serum free light chain (FLC, kappa and lambda) with kappa:lambda ratio
- Serum β-2 microglobulin (β2M) will be performed at the screening visit only

6.5.2. Skeletal Survey

A skeletal survey will be performed locally at screening and at any time post-bb2121 infusion at the time of suspected CR, and if the treating investigator believes there are signs or symptoms of increased or new skeletal lesions. This assessment can be performed by X-ray, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, computerized tomography (CT) scan, or PET/CT scan provided the same modality will be used for future assessments.

6.5.3. Extramedullary Plasmacytoma Assessments

For extramedullary plasmacytomas (EMP) that are only assessable radiographically (PET/CT, CT or MRI), the radiographic modality used at screening will be repeated at each assessment time point throughout the study.

- Radiographic disease assessment should be performed locally at screening for any subject with documented extramedullary disease and at M1, M3, M6, M12, M18 and M24. If PD occurs after M24, assessments will be performed every 6 months thereafter for up to 5 years until documented PD. Radiographic assessments should also be performed at the time of suspected CR and PD.
- On-going protocol specified radiological assessments are no longer required following confirmation of PD, unless bb2121 retreatment is given.

6.5.4. Bone Marrow Aspiration and/or Biopsy

- Percent of plasma cells or CD138+ cells and BCMA expression will be assessed on bone marrow biopsy and aspirate samples. Samples will be collected at screening, M1, M3, M6, M12, M18 and M24. If PD occurs after M24, assessments will be performed every 12 months thereafter for up to 5 years or until documented PD. Bone marrow assessments should be performed at the time of suspected CR and PD to accurately assess response, according to the IMWG Uniform Response Criteria for Multiple Myeloma (Kumar, 2016).
- MRD status will be assessed on selected bone marrow aspirates collected throughout the study, including at screening, M1, M3 M6, M12, M18 and M24. If PD occurs after M24, assessments will be performed every 12 months thereafter for up to 5 years or until documented PD. MRD assessments will be performed at all bone

marrow assessment time points through M12 independent of IMWG response. Thereafter, MRD assessments will only be performed in subjects with responses of VGPR or better and in subjects with MRD negative status at the last prior assessment. MRD will be evaluated using "next-gen" multiparameter flow cytometry (EuroFlow), as well as by "next-gen" sequencing (NGS). Negative MRD status will be defined as < 1 in 10^5 nucleated cells per IMWG Uniform Response Criteria for Multiple Myeloma (Kumar, 2016).

Outside of the protocol specified timepoints for bone marrow biopsy and aspirate, if a subject has resolution of serum and urine M-protein and/or FLC consistent with CR, a bone marrow biopsy and aspirate will be performed to confirm CR. A bone marrow aspirate and biopsy should also be obtained at the time of suspected PD. Bone marrow assessments should include morphology and flow cytometry. In subjects with defined genetic abnormalities at screening (or baseline for subjects that received bridging therapy), cytogenetics/fluorescence in situ hybridization (FISH) should be performed at CR and at the time of PD. In subjects without defined genetic abnormalities at screening (or baseline for subjects that received bridging therapy), cytogenetic/FISH only need to be repeated at the time of PD. Ongoing protocol specified bone marrow assessments are no longer required following confirmation of PD unless bb2121 retreatment is given.

If a bone marrow biopsy or an aspirate is performed at any time during the study, biopsy and/or aspirate samples should be collected for the clinical response assessments, MRD, and for biomarker studies. Additional assessments may be performed as part of standard of care as needed for response assessment.

6.5.5. Assessment of Response

6.5.5.1. Investigator Assessment

Starting from month 1, investigators will assess the results from central laboratories using the IMWG Uniform Response Criteria (Kumar, 2016) (refer to Appendix B) at every month for the first 6 months then every 3 months for a minimum of 24-months or until disease progression, whichever is longer. Response is based on the central laboratory data to ensure consistency across investigative sites, except for new or increase in bone lesions or extramedullary plasmacytomas.

6.5.5.2. Independent Response Committee (IRC) Assessment

An IRC will be formed by a group of experts in the MM disease area to review data for response assessment. The IRC will determine the response to therapy based on the IMWG Uniform Response Criteria for each subject.

The IRC will adjudicate efficacy data according to IRC Charter during the study. The IRC adjudicated response data will be used for the primary and updated analyses (at 10 months and 24 months post-bb2121 infusion of the last subject, respectively), and for additional analyses if needed.

Primary efficacy analyses will be conducted using response data, that are assessed by the IRC according to the IMWG Uniform Response Criteria (refer to Appendix B). Analyses using Investigator assessment will be supportive.

NOTE: Per IMWG Uniform Response Criteria all response categories and progressive disease require 2 consecutive assessments except for radiographic or bone marrow assessments

6.6. Subject Reported Quality of Life Outcomes or Health Economics

Subject-reported quality-of-life outcomes will be administered according to Table 3.

If the subject withdraws from the study prematurely, all attempts should be made to obtain a final quality-of-life questionnaire prior to subject discontinuation. EORTC-QLQ-C30, EQ-5D-5L and EORTC-QLQ-MY20 will be used to assess the subject's health as well as physical, social, emotional, and functional well-being.

The questionnaire will be completed by the subjects before any clinical assessments are performed at any given visit. If subjects refuse to complete all or any part of a questionnaire, this will be documented. Questionnaires should be completed in the language most familiar to each subject, and subjects should be given adequate time and space to complete the questionnaire. Site personnel should review questionnaires for completeness and ask subjects to complete any missing responses.

Patient interviews will be used to capture the experience on bb2121 from a patient perspective.

6.6.1. EORTC-QLQ-C30

The EORTC-QLQ-C30 questionnaire will be used as a measure of health-related quality of life. The QLQ-C30 is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/health-related quality of life (HRQoL) scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.

The QLQ-C30 employs a week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories "Not at all", "A little", "Quite a bit" and "Very much". The two items assessing global health status/ HRQoL utilize a 7-point scale ranging from 1("Very Poor") to 7 ("Excellent") (Aaronson, 1993).

6.6.2. EQ-5D-5L

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems)

In 2005, a Task Force was established within the EuroQol Group to investigate methods to improve the instrument's sensitivity and to reduce ceiling effects. After much discussion, the Task Force decided that there should be no change in the number of dimensions for a new version of EQ-5D.

However, previously published studies by EuroQol Group members showed that experimental 5-level versions of EQ-5D could significantly increase reliability and sensitivity (discriminatory power) while maintaining feasibility and potentially reducing ceiling effects.

The EQ-5D-5L still consists of 2 pages – the EQ-5D-5L descriptive system (page 2) and the EQ Visual Analogue Scale (page 3). The descriptive system comprises the same 5 dimensions as the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as a cardinal score.

The EuroQol Group had received feedback over the years that respondents sometimes found it difficult to draw a line from the box to the scale. It was also cumbersome for administrators to record their scores. The EQ-5D-5L now asks respondents to simply 'mark an X on the scale to indicate how your health is TODAY' and then to 'write the number you marked on the scale in the box below'.

This should make the task easier for both respondents and users (Herdman, 2011; The EuroQol, 1990).

6.6.3. EORTC-QLQ-MY20

The EORTC has developed a myeloma module referred to as QLQ-MY20, to be administered alongside the core QLQ-C30. The QLQ-MY20 is a 20-item myeloma module intended for use among patients varying in disease stage and treatment modality. The module has been validated and shown to be measuring additional aspects of HRQoL, such as body image and future perspective.

6.6.4. Patient Interviews

Standardized measures of HRQoL have not been widely used in evaluations of CAR-T therapies and due to the novelty of bb2121, much has yet to be learned about its impact on HRQoL, which may currently be missed by these standard HRQoL measures. For this reason, subjects will be invited to be interviewed during the study; the aim being to provide an opportunity for subjects to share their experiences with bb2121 therapy in their own words, capturing insights not usually recorded via the established patient reported outcomes (PRO) scales and questionnaires.

Subjects will be requested to participate in a series of interviews over the 2-year study period. The interviews will be structured by a discussion guide.

The first interview will last up to one hour and will be conducted in-person or via telephone. The remainder of the interviews will be shorter in duration, lasting approximately 30 minutes, and may be conducted either over the telephone or in-person. Interviews will be scheduled at a time convenient to the subjects. During the interviews, subjects may be asked about:

- Their experience of RRMM, including symptoms and how the condition affects their life
- Their experience with the experimental therapy administered in the clinical trial (bb2121)
- Their decision to participate in the trial
- Their experiences during the trial

Table 6: Table of Events - Patient Interviews

	Pre-Treatment Period			Treatment Period								Post-Treatment Period												
						Safety Monitoring						Follow-up												
	Screening	Leukapheresis	Baseline Evaluations	LD Chemotherapy	bb2121 infusion																			
Study Days				**D -5, -4 and -3**	**D0**	**D 1-6**	**D7**	**D9**	**D 11**	**D 14**	**D 21**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M9**	**M 12**	**M 15**	**M 18**	**M 21**	**M 24**	**PD**	**CR**
Patient Interviews[a]	-	X[b]	-	-	X[c]	-	-	-	-	-	X	-	X	X	-	-	X	X	X	-	X	-	X	X	X

[a] Patient interviews are voluntary and will be performed by an external organization with specialist expertise in conducting patient interviews. A window of ± 7 days is allowed for all post infusion interviews.
[b] Patient interview will be conducted prior to and after leukapheresis.
[c] A window of 72-hours post-bb2121 infusion is allowed.

6.6.5. Hospital Resource Utilization

Hospital resource utilization will be assessed based on the numbers of hospitalizations, intensive care unit (ICU) inpatient days and non-ICU inpatient days in addition to outpatient visits. Dates of admission and discharge to the hospital and to the ICU will be collected together with the reasons for the hospitalization(s).

6.7. Pharmacokinetics

At prespecified time points (refer to Table 7), whole blood will be collected from each subject for analysis of bb2121 CAR+ T cell expansion and persistence (cellular kinetic profile). 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. The cellular kinetic profile (PK) will be described by time course of transgene copies per microgram of genomic DNA as measured by quantitative polymerase chain reaction (qPCR) using CD3+ sorted T cells.

The enriched transgene copy number within CD3+ cells will be used for the pharmacokinetic assessment in this study.

The PK data from this study will be listed and summarized by time points, as appropriate. PK data may be analyzed for exposure-response and exposure-AE relationships. In addition, using the PK data, non-compartmental analysis may be performed to calculate parameters such as Tmax, Cmax, Tlast, and AUC.

6.8. Biomarkers, Pharmacodynamics, Pharmacogenomics

6.8.1. Biomarker Assessment

Biomarker assessments will be performed centrally and include immunophenotypic evaluation of cells in peripheral blood and bone marrow, BCMA and related marker expression in blood, bone marrow and plasmacytomas (optional), characterization of tumor microenvironment, and analysis of plasma cytokines.

Sample specimens will be collected for these studies as indicated in Table 7 for biomarkers. Refer to Table 3 for frequency of assessments.

Table 7: Biomarkers Sampling

Biomarker Assessment Type	Sample type
Cytokines and immune-related soluble factors-safety	Plasma
sBCMA, sAPRIL, sBAFF	Serum
Immunophenotyping (circulating T cell subsets and bb2121 CAR T)	Peripheral blood
Immunophenotyping (T cell subsets and tumor cells)	Peripheral blood, bone marrow aspirate and optional plasmacytoma biopsy
PBMC isolation (gene expression profiling, NGS)	Peripheral blood
BCMA target expression and tumor characterization (IHC)	Bone marrow biopsy, aspirate, or optional plasmacytoma biopsy

Table 7: Biomarkers sampling (Continued)

Biomarker Assessment Type	Sample type
Tumor and immune microenvironment characterization (gene expression profiling, NGS)	Peripheral blood, bone marrow aspirate, and optional plasmacytoma biopsy

Bone marrow biopsy/aspirate samples and optional plasmacytoma biopsies will be collected to investigate cellular elements within the tumor and the tumor microenvironment for biomarkers related to clinical efficacy and association with disease features. In addition, gene expression profiling on tumor and immune cells from the bone marrow and optional plasmacytoma biopsies will be evaluated to explore potential mechanisms of treatment resistance at relapse.

Peripheral blood will be collected to evaluate the following:

- Immunophenotyping will be done to characterize the bb2121 cells and circulating immune cell subsets to identify protein markers correlated with bb2121 activation, persistence and possible regulation of bb2121 cells by circulating immune cells.
- Soluble factors from plasma will be measured as a marker of immune activation and to determine potential correlations between cytokine/chemokine production, efficacy and severity of CRS and neurotoxicity.
- Tumor related soluble factors such as sBCMA, sAPRIL, and sBAFF will be measured and correlated with efficacy.

The data collected in these biomarker assessments will be used in aggregate to elucidate relationship between CAR T cell function, persistence, modulation of surface expressed molecules present in the tumor/tumor microenvironment, and peripheral blood and clinical response and toxicity.

Detailed information regarding the collection, handling, and shipment of biomarker samples is provided in the BB2121-MM-001 laboratory manual.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product

7.1.1. bb2121

bb2121 consists of autologous T lymphocytes transduced with an anti-BCMA02 CAR lentiviral vector to express a chimeric antigen receptor targeting the human B cell maturation antigen (anti-BCMA CAR) and suspended in cryopreservative solution as a cellular dispersion for infusion.

A schematic of the lentiviral vector transgene used to transduce the autologous T lymphocytes is shown below.

Schematic Representation of Anti-BCMA02 Chimeric Antigen Receptor

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

Anti-BCMA02 CAR LVV is a replication defective, self-inactivating (SIN), third generation human immunodeficiency virus type 1 (HIV 1) based LVV, pseudotyped with the vesicular stomatitis virus glycoprotein (VSV G) envelope protein, encoding a chimeric antigen receptor (CAR) specific for the human B cell maturation antigen (BCMA) (anti-BCMA CAR). This vector uses the murine leukemia virus-derived myeloproliferative sarcoma virus enhancer, negative control region deleted, dl587rev primer binding site substituted (MND) promoter to drive expression of the CAR. Autologous T cells transduced with anti-BCMA02 LVV results in production of an integral membrane protein composed of: 1) an extracellular single chain variable fragment (scFv) containing the light chain variable region (VL) and heavy chain variable region (VH) from a mouse anti-BCMA monoclonal antibody (mAb C11D5.3); 2) the hinge and transmembrane domain from human CD8α; and 3) the T cell cytoplasmic signaling domains of CD137 (4-1BB) and the CD3ζ chain, in tandem.

7.2. Treatment Administration and Schedule

Treatment period will start with LD chemotherapy on day -5, followed by bb2121 infusion on day 0 (+7 day window).

7.2.1. Lymphodepletion

Upon notification from the Sponsor that bb2121 will be available, LD chemotherapy should be initiated 5 days prior to bb2121 infusion. For details on eligibility for starting LD chemotherapy refer to Section 6.2.1. For details on LD chemotherapy administration, refer to Section 7.2.1.1.

7.2.1.1. Lymphodepleting Chemotherapy

Subjects will receive one 3-day cycle of lymphodepletion starting 5 days prior to bb2121 infusion targeted to be on Day 0 (+ 7 day window) as outlined below.

Table 8: 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. The Cockcroft Gault formula should be used to calculate renal function.
Fludarabine should not be administered to subjects with CrCl <30 mL/min.
Refer to Fludarabine Phosphate Injection package insert.

Chemotherapy should be administered per institutional guidelines. Refer to the most recent package inserts for further details on administration of these agents.

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 per 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.

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.

Chemotherapy-associated cytopenias should be managed with myeloid growth factor and blood product transfusion support according to local institutional guidelines.

7.2.2. bb2121 Infusion Process

7.2.2.1. bb2121 Preparation and Cell Thawing

bb2121 must be delivered to the pre-defined department responsible for receiving cell products, thawed at the infusion site in a ~37°C water bath or approved thawing instrument 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. In the event of a delay in completing the planned bb2121 infusion within one hour of thaw, bb2121 should still be administered; the reason for the delay should be recorded in the eCRF and the Sponsor will be notified.

All procedures involving bb2121 must be performed using aseptic techniques by trained personnel. See bb2121 Product Receipt, Preparation, and Administration Manual for more detail.

7.2.2.2. bb2121 Premedication

Pre-medication should occur approximately 30 minutes prior to the infusion and should include acetaminophen 650 mg orally (or according to institutional standards) and diphenhydramine 12.5 mg IV or 25 to 50 mg orally (or equivalent). Subjects should not receive corticosteroids as pre-medication.

7.2.2.3. bb2121 Infusion

bb2121 will be given on day 0 (+ 7-day window), after lymphodepletion on Days -5, -4 and -3 at a dose ranging from 150 to 450 × 10^6 CAR+ T cells/infusion. Refer to Section 6.2.2 for bb2121 infusion delays > 7 days.

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.

Vital signs are to be monitored prior to bb2121 infusion, midway through the infusion, upon completion of the infusion, and then every 15 minutes thereafter for the first hour, and hourly for the next 4 hours. Infusion reactions, including anaphylaxis, will be managed according to the medical judgment of the physician overseeing the infusion.

Due to the risk of CRS, subjects treated on this protocol must be closely monitored as inpatients post-bb2121 infusion for signs and symptoms of CRS or neurotoxicity. Tocilizumab must be available at the site prior to infusion of the subject. Following bb2121 infusion, subjects must remain hospitalized for a minimum of 14 days to monitor for toxicities (eg, CRS and neurotoxicity). Subjects may receive bb2121 as an outpatient, and then be hospitalized following the infusion on Day 0. A full work-up of fever is recommended including evaluation for an infectious etiology (eg, blood cultures, urine culture, chest X-ray, as required. Blood should be drawn for PK and cytokine assessments along with clinical laboratory tests (hematology, chemistry, coagulation along with TLS/CRS panel). Study sites must have intensive care units (ICU) with the ability to manage CRS, neurotoxicity and other complications from cellular therapies. On Day 14, subjects are discharged only if they are afebrile for 24 hours, signs and symptoms of CRS and neurotoxicity have completely resolved and CRP is declining, if elevated from baseline, or stable and not rising.

After hospital discharge, subjects are required to do self-temperature monitoring every 6 to 8 hours (while awake) through M1 for ongoing fever assessment and record results in a diary. Based on the risks of adverse events requiring immediate medical intervention, subjects must stay within a 30-minute transportation ride to the treating hospital for close monitoring of fever and other signs of CRS or neurotoxicity and have a dedicated full-time caregiver(s) through M1. Once the subject is discharged, hospitalization is required for any signs of fever (≥ 38°C/100.4°F) or other signs or symptoms suggestive of CRS or neurotoxicity, including increase of CRP (> 200 mg/L or rising rapidly) for close monitoring of cardiac and organ function, including routine neurologic exams.

A dedicated triage center with “CAR T” study staff assigned to manage the flow of subjects to the treating physician 24 hours a day must be in place after the required 14-day hospitalization

period. If the emergency department is to be utilized instead of a direct bypass to the dedicated triage center, that department and their staff must be trained to triage subjects directly to the bb2121 study staff for immediate management of signs and symptoms suggestive of CRS or neurotoxicity. Each site will implement and provide a detailed expedited CRS management plan and train all study staff for their respective roles regarding CRS or neurotoxicity detection and management.

Refer to Appendix C for Management Guidelines for Cytokine Release Syndrome and Neurologic Toxicities.

7.2.2.3.1. Dose for Subjects for Whom the Targeted Dose Cannot be Manufactured

bb2121 is manufactured 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. Subjects who have product manufactured with a dose of less than 150 x 10^6 CAR+ T cells may proceed to a 2nd leukapheresis procedure for a second attempt at bb2121 manufacturing. The administered bb2121 dose may be composed of more than one manufactured product from the same subject.

7.2.3. Retreatment

Retreatment with bb2121, including a second course of LD chemotherapy with or without bridging therapy, may be considered. There is no drug class restriction for bridging therapy used prior to retreatment, but bridging therapy should be completed at least 14 days prior to the start of LD chemotherapy. Subjects will be eligible to receive a second infusion of bb2121 if there is sufficient cryopreserved bb2121 drug product available and if the following criteria are met:

1. At least 8 weeks since first bb2121 infusion.
2. Best response to initial bb2121 was stable disease or better based on standard response criteria according to the IMWG Uniform Response Criteria for Multiple Myeloma (Kumar, 2016).
3. Evidence of disease progression according to IMWG criteria.
4. No history of Grade 4 CRS or neurotoxicity with prior bb2121 treatment.
5. Eligibility criteria for enrollment continues to be met (except for the exclusion of #1 subjects with known CNS involvement with myeloma, exclusion of #8 inadequate bone marrow function, and exclusion of #12 subjects who have received treatment with any gene therapy-based therapeutic for cancer or investigational cellular therapy or BCMA targeted therapy). Refer to Section 4.2 and Section 4.3 for eligibility criteria and Table 4 for select baseline evaluations required for retreatment.
6. Eligibility criteria for starting LD chemotherapy needs be met (refer to Section 6.2.1).
7. Subjects with progression of myeloma within the CNS that requires whole brain or directed cerebral radiotherapy (excluding palliative focal, minimally penetrating, radiotherapy to scalp or skull lesions), should not receive bb2121 re-treatment infusion until a gap of at least 8 weeks from last radiotherapy treatment has been observed.

Subjects who are retreated:

- Will receive a repeat course of LD chemotherapy before the second infusion of bb2121.
- May receive bridging therapy prior to LD chemotherapy according to Section 6.1.2
- Must have cryopreserved bb2121 drug product available (eg, remanufacture of bb2121 from cryopreserved PBMC and repeat leukapheresis are not allowed).

Retreated subjects will follow the Table of Events (refer to Table 4) starting with the baseline visit prior to the second infusion and will be followed on study until documented disease progression or for a minimum of 6 months following the last bb2121 infusion, whichever is longer.

7.3. Packaging and Labeling

The identity of the investigational product will be checked and verified at each critical step of cell processing as part of the chain of identity (COI). Procedures will be in place to address product tracking requirements and will encompass all process steps including collection of the leukapheresis product, receipt of the leukapheresis product, bb2121 manufacturing and testing, in-process labeling, and bb2121 labeling and packaging for shipment.

The label(s) for IP will include, but may not be limited to, sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations

7.3.1. Cell Product Supply and Storage

Detailed instructions on the storage, handling, serology testing, and preparation of bb2121 cell product will be provided in the bb2121 Product Receipt, Preparation, and Administration Manual.

7.4. Investigational Product Accountability and Disposal

7.4.1. Accountability Procedures

An inventory must be performed and a product receipt log filled out and signed by the person accepting the shipment of bb2121 cell product.

7.4.2. Drug Disposal and Destruction

The Sponsor (or designee) will review with the Investigator and relevant site personnel the process for investigational disposal, and/or destruction including responsibilities for the site versus sponsor (or designee) according to local and/or national biosafety guidelines.

7.5. Investigational Product Compliance

The administered bb2121 dosage will be recorded in the source documents. The investigator(s) or designee is responsible for taking an inventory of each shipment of investigational product received and comparing it with the accompanying shipping order/packaging slip.

At the study site, investigational product will be stored in a locked, safe area to prevent unauthorized access and should be stored as directed on the product label.

An accurate accounting of the dispensing and return of investigational product for each study subject will be maintained in source documents on an ongoing basis by a member of the study site staff. Additionally, if any investigational product is lost or damaged, this information should be documented in the study subject's electronic case report form (eCRF) and source documents.

The Sponsor will instruct the investigator on the disposal, and/or destruction of unused investigational product.

7.6. Overdose

Overdose, as defined for this protocol, refers to fludarabine (IV), cyclophosphamide (IV) or bb2121 (IV). On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose assigned to a given patient, regardless of any associated adverse events or sequelae:

- IV 10% over the protocol-specified dose for fludarabine and cyclophosphamide
- IV 20% over the protocol-specified dose for bb2121

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF. Refer to Section 10.1 for the reporting of adverse events associated with overdose.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

8.1. Permitted Concomitant Medications and Procedures

Medications taken by the subject at the time of an AE related to protocol-mandated procedures will be recorded from informed consent until initiation of LD chemotherapy. All medications will be recorded from the time of LD chemotherapy until 6 months after the last infusion of bb2121. From Month 7 post-last infusion of bb2121 until Month 24/EOS visit, concomitant medications associated with all Grade ≥ 3 AEs, all SAEs and all AESIs will be recorded. From Month 25 post-last infusion of bb2121 to end of study participation, only concomitant medications associated with possibly related Grade ≥ 3 AEs, possibly related SAEs and possibly related AESIs will be recorded. Subjects should be discouraged from use of illicit drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

If necessary, anti-myeloma treatment is allowed as bridging therapy while bb2121 is being manufactured, for disease control (refer to Section 6.1.2). Details on the bridging therapy including dose, schedule and dates of administration will be captured in the eCRF.

8.2. Prohibited Concomitant Medications and Procedures

The following medications are prohibited:

- Systemic steroids: dexamethasone, prednisone or other corticosteroids are not allowed unless used for the treatment of CRS or neurotoxicity, or as described below.

  If steroids are to be administered, it should be discussed with the medical monitor unless in the setting of acute clinical requirements (eg, Grade 3 or 4 CRS). Generally, the only setting for administration of systemic corticosteroids will be CRS management or severe neurotoxicity, following the guidelines in Section 10.7.1.

- Therapeutic doses of steroids may be used in life-threatening situations and for other medical conditions when indicated, or after loss of detectable bb2121 cells. Pre-treatment containing steroids may be given for necessary medications (eg, IVIG or in the setting of radiologic contrast allergy) after discussion with the sponsor. Premedication with steroids for bb2121 infusion is not allowed. Physiologic replacement dosing of steroids (≤ 12 mg/m^2/day hydrocortisone or equivalent [≤ 3 mg/m^2/day prednisone or ≤ 0.45 mg/m^2/day dexamethasone]) is allowed. Topical steroids, inhaled or intranasal steroids are permitted.

- Any systemic MM therapy within 14 days prior to leukapheresis.

- Any experimental agents for the treatment of MM from time of leukapheresis to LD chemotherapy, from LD chemotherapy to bb2121 infusion and from bb2121 infusion until documented PD

- Bridging myeloma therapies between leukapheresis and LD chemotherapy other than those described in Section 6.1.2

- Any systemic MM therapy, including experimental agents, within 14 days of lymphodepleting chemotherapy

- Any concurrent chemotherapy, immunotherapy, biologic, experimental or hormonal therapy following bb2121 infusion (follow-up period) for treatment of MM prior to documentation of PD. Palliative radiotherapy for treatment of symptomatic bone or soft tissue lesions is allowed
- Live vaccines during and for 3 months following fludarabine treatment

The following medications should be used with caution during the study. The sponsor must be notified if a subject receives any of these during the study.

- Any concurrent chemotherapy, radiation therapy, immunotherapy, biologic or hormonal therapy for cancer treatment (including treatment of MM beyond PD or other cancer);
- Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable;
- Herbal and natural remedies are to be avoided;
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers unless used for the management of sCRS or neurotoxicity.

8.3. Required Concomitant Medications and Procedures

8.3.1. Lymphodepleting Chemotherapy

Lymphodepleting regimens accompany bb2121 administration and utilize cyclophosphamide and fludarabine. Refer to Section 7.2.1.1 for administration and dose modification guidelines and local prescribing information.

8.3.2. Cytokine Release Syndrome Management

In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe cytokine release syndrome. Tocilizumab must be available at the site prior to infusion of the subject. Please refer to currently approved Summary of Product Characteristics. The preferred dose to intervene in subjects with sCRS is 8 mg/kg.

Refer to Section 10.7.1 and Appendix C for detailed management guidelines for CRS.

8.3.3. Other Medications

- It is recommended that subjects with serum IgG level less than 400 mg/dL should receive intravenous immunoglobulin replacement as needed to maintain an IgG level above 400 mg/dL, unless there is a contraindication.
- Antiviral therapy with appropriate antiviral agent for HBV is recommended in subjects with positive hepatitis B surface antigen, HBcAB, and/or measurable viral load. Appropriate first line agents include entecavir, tenofovir, and lamivudine (note that lamivudine has higher resistance rates).

- Subjects with a CD4 T cell count of < 200 μL should be maintained on pneumocystis prophylaxis with trimethoprim-sulfamethoxazole 1 double-strength tablet every Monday-Wednesday-Friday. If subjects cannot tolerate trimethoprim sulfamethoxazole, an alternative pneumocystis prophylaxis should be used.
- Neutropenia should be managed with myeloid growth factors according to local institutional guidelines.
- Fevers in the presence of neutropenia should be managed according to local institutional guidelines with regards to broad spectrum antibiotics and management.
- Transfusion support of platelets and packed RBCs may be used at the discretion of the treating investigator. Leukocyte filters are encouraged for all platelet and packed RBC transfusions.
- Subjects with history of seizures should consider use of levetiracetam or alternative anti-seizure medication as seizure prophylaxis.
- Ongoing treatment with bisphosphonates as prophylaxis or treatment for myeloma bone disease is allowed.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is an open-label, single arm, multi-center Phase 2 study to determine the efficacy and safety of bb2121 in subjects with RRMM.

Summaries of continuous variables will present the number of subjects included in the analysis (N), the mean and standard deviation (SDev) of the mean, the median, the minimum, and the maximum statistics. Counts and percentages will be presented in summaries of categorical variables. The denominator for each percentage will be the number of subjects in the population unless otherwise specified. In general, missing data will not be imputed unless otherwise specified.

All statistical analyses specified in this protocol will be conducted using SAS® Version 9.2 or higher unless otherwise specified.

9.2. Study Population Definitions

In this study, the following analysis populations will be defined for the analysis and presentation of the data.

9.2.1. Screened Population

The Screened population will include all subjects who have signed informed consent.

9.2.2. Enrolled Population

The Enrolled population will include all subjects in the Screened population who undergo leukapheresis.

9.2.3. bb2121 Treated Population

The bb2121-treated population will include all subjects in the Enrolled population who have received bb2121 infusion.

The bb2121-treated population will be used for the primary analysis for efficacy and safety.

9.2.4. Efficacy Evaluable Population

The Efficacy Evaluable (EE) population will include all subjects in the bb2121-treated population who have had a baseline and at least one post baseline (ie, post-bb2121 infusion) efficacy assessment.

9.2.5. Pharmacokinetic Analysis Population

The Pharmacokinetic (PK) Analysis population includes subjects who received at least one bb2121 infusion and have evaluable CAR T (ie, at least one measurable time point). The retreatment PK analysis population includes subjects who received the bb2121 retreatment dose and have evaluable CAR T data (ie, at least one measurable time point post dose) for the retreatment period.

9.2.6. Patient Reported Outcome Analysis Population

The PRO Analysis population will include all subjects who complete their baseline PRO questionnaires and have at least one post-baseline measurement in the bb2121-treated population.

9.3. Sample Size and Power Considerations

For the primary efficacy endpoint, overall response rate (ORR), the sample size is based on one-sample binomial test with normal approximation. The null hypothesis to be tested is that the ORR (defined as the proportion of subjects with at least a partial response (PR) based on all bb2121 treated subjects) is ≤ 50%; the alternative hypothesis is that the ORR is > 50%, with a target ORR of 70%. With these hypotheses, a sample size of 119 bb2121 treated subjects would provide > 99% power at a one-sided 0.025 alpha level. This criterion requires that the lower limit of the 95% confidence intervals for the ORR is greater than 50%. Assuming a dropout rate of 15% between the time of study enrollment and bb2121 infusion, a total number of up to 140 subjects will be enrolled.

The selection of a null hypothesis of 50% ORR is based on the observed clinical activity of the best available single agent therapy in a heavily pretreated RRMM patient population. Daratumumab demonstrated a response rate ranging from 29% to 36% in RRMM patients who had received at least 3 prior lines of therapy including an IMiD drug and a proteasome inhibitor or who were double refractory (Dimopoulos, 2015; Richardson, 2014; San Miguel, 2013). A null hypothesis of 50% ORR represents an approximately 50% improvement over daratumumab (Daralex, 2017). The target ORR of 70% is based on the preliminary efficacy observed with bb2121 in the Phase 1 study, including an ORR of 81% in 36 evaluable patients receiving b2121 doses of 150 - 800 x 10^6 CAR+ T cells (Raje, 2018). A target ORR of 70% is considered achievable based on the existing clinical efficacy data with bb2121 and also represents an approximately 100% improvement over daratumumab.

If the ORR is tested positive, CR rate will be tested using a stepdown approach to control the overall alpha level, which will remain at the one-sided 0.025 level. For CR rate, the null hypothesis is ≤ 10%, with a target CR rate of 20%. With these hypotheses, also using one-sample binomial test, the same sample size of 119 bb2121 treated subjects would provide approximately 89% power at a one-sided 0.025 alpha level. This criterion requires that the lower limit of the two-sided 95% confidence intervals for the CR rate is greater than 10%.

9.4. Baseline and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations for both bb2121-treated population and Enrolled population.

Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for both the bb2121-treated population and Enrolled population.

9.5. Disposition

Subjects that are screened but not enrolled will be summarized by reason for screen failure.

Reasons for discontinuation will be summarized for the pre-treatment (post-screening), treatment, and post- treatment follow-up phases for the Enrolled population and for the bb2121-treated population, as appropriate.

9.6. Study Drug Exposure

Dosing information for cyclophosphamide and fludarabine will be summarized for the Enrolled population. Study drug administration and dosing information, will be summarized for the bb2121-treated population.

9.7. Efficacy Analysis

Efficacy analysis will be performed on the Enrolled population, bb2121-treated population and EE population. The primary efficacy analysis will be based on response assessments adjudicated by IRC according to the new IMWG criteria (Kumar, 2016) in the bb2121-treated population.

A responder will be any subject who shows at least a partial response (PR). The overall response rate (ORR) will be defined as the percentage of responders. The complete response (CR) rate will be defined as the percentage of subjects with at least a CR or sCR. ORR and CR rates with 95% confidence intervals will be provided for the overall population as well as for relevant subgroups including: dosing subgroups within the 150 to 450 x 10^6 CAR+ T cell dose range, high risk cytogenetics [t(4;14), t(14;16), or del17p], high risk MM (R-ISS III), tumor BCMA expression (≥ versus < 50% BCMA+) and others as relevant.

For responders, time to response and response duration will be analyzed. Time to response is the time from the date of bb2121 infusion to the first documentation of response of PR or better. Time to response will be summarized for responders using summary statistics.

Duration of response is the time from date of first documentation of response of PR or better to the first documentation of disease progression or death from any cause, whichever is first.

Progression-free survival is time from the date of bb2121 infusion to the first documented disease progression or death, whichever is earlier. Subjects who have not progressed and are still alive will be censored at the date of last adequate response assessment.

Time to progression is time from the date of bb2121 infusion to the first documented disease progression. Subjects who died prior to disease progression will be censored at the date of last adequate response assessment.

Overall survival is time from the date of bb2121 infusion to the date of death due to any cause. Subjects who are still alive will be censored at the date last known alive or the data cut-off date (if applicable), whichever is earlier.

Kaplan-Meier procedures will be used to characterize the time-to-event curves (PFS, TTP, OS, and duration of response).

9.7.1. Assessment of MRD

A secondary efficacy endpoint will consist of an analysis of clinical and imaging responses (per IMWG 2016 criteria) to study treatment in MRD negative and positive subpopulations. Clinical and imaging responses will be assessed for potential relationship to MRD status. The MRD status will be assessed in all subjects at baseline, M1, M3, M6, M12, M18 and M24. If PD

occurs after M24, assessments will be performed every 12 months thereafter for up to 5 years or until documented PD. MRD assessments will be performed at all bone marrow assessment time points through M12 independent of IMWG response. Thereafter, MRD assessments will only be performed in subjects with responses of VGPR or better and in those with MRD negative status at their last prior assessment. MRD will be evaluated using EuroFlow and NGS separately. The proportion of subjects who achieve MRD negative status using each method in the bb2121-treated population will be summarized. In addition, the proportion of subjects who are MRD negative after achieving CR or stringent Complete Response (sCR) will be evaluated.

MRD negative rates in the bb2121-treated population with 95% confidence intervals will be provided. For MRD negative rate using NGS, one-sample binomial test will be performed as descriptive analysis. The null hypothesis is MRD negative rate $\leq 10\%$, and the target is $\geq 20\%$. With these assumptions, also using the same sample size of 119 bb2121 treated subjects would provide approximately 89% nominal power at a one-sided 0.025 nominal alpha level. This criterion requires that the lower limit of the two-sided 95% confidence intervals for the MRD negative rate is greater than 10%.

9.8. Safety Analysis

Adverse events that occur between enrollment (ie, start of leukapheresis) and bb2121 infusion will be summarized for all subjects in the Enrolled population.

All subjects in the bb2121-treated population, will be included in the safety analyses between enrollment and bb2121 infusion and post-bb2121 treatment follow-up period. Adverse events, vital sign measurements, clinical laboratory information, and concomitant medications will be summarized as appropriate. Frequency and percentage of all AEs (including serious, Grade 3/4, AESI, and treatment-related) will be summarized by system organ class and preferred term.

Death will also be summarized.

All other measurements will be summarized using descriptive measures.

9.9. Pharmacokinetic Analysis

Noncompartmental PK parameters may be calculated using the cellular kinetics-PK over time data. Parameters such as Tmax, Cmax, AUC, and Tmin may be calculated. Additional parameters may be calculated if deemed appropriate. Descriptive statistics will be provided for all CAR+ T cell PK parameters.

The pharmacokinetic assessment may be explored by evaluating the PK versus response and PK versus adverse events.

9.10. Biomarker Analysis

Planned biomarker analyses will include:

- Immunophenotype of bb2121 CAR T and endogenous T cells in the blood, bone marrow and/or tumor tissue
- Cytokine/chemokine induction in the blood of subjects after infusion of bb2121

- Evaluate the percentage of B-cell maturation antigen (BCMA)-expressing (BCMA+) cells and levels of BCMA expression in bone marrow, and the level of circulating soluble BCMA
- Mechanisms of tumor sensitivity/resistance to bb2121
- Development of an anti-CAR immune response

A potential immune response to bb2121 will be evaluated for both humoral response as well as cell mediated responses. Serum samples collected from subjects post-infusion will be evaluated for a humoral response, for the formation of anti-CAR antibodies, using an immunoassay designed and validated to detect antibodies to the extracellular CAR domain. Cell mediated immune responses will be evaluated using an Interferon-gamma ELISPOT assay that will be performed on PBMCs derived from subjects. The subject's PBMC samples will be stimulated ex vivo using peptides that span the extracellular domain of the CAR construct. An antigen specific cellular immune response and the resulting production of interferon gamma will then be detected by ELISPOT.

Blood will be collected from subjects for these two evaluations (refer to Table 3). Sample processing and handling procedures will be described in a separate Sample Handling Manual.

Descriptive analysis summaries will be provided for biomarker endpoints.

9.11. Patient Reported Outcome Analysis

The Health Related Quality of Life instruments EORTC-QLQ-C30, EQ-5D-5L and EORTC-QLQ-MY20 values as well as change from baseline will be summarized descriptively at each planned timepoint.

Data on Hospital Resource Utilization will be summarized descriptively.

9.12. Timing of Analysis

There will be no planned interim analysis. Primary analysis will be performed after all subjects in the bb2121-treated population have been followed for sufficient amount of time for analysis (eg, at least 10 months after the last subject has received bb2121 infusion).

Analyses may be performed at other time points as needed, in addition to the primary analysis. Updated analyses will be performed at 24-months after the last subject has received bb2121 infusion.

9.13. Study Committees

9.13.1. Data Safety Monitoring Board

An external and independent DSMB with multidisciplinary representation will be established to monitor the safety and efficacy data regularly.

The DSMB chairman may convene formal DSMB meetings if there are any unusual safety or efficacy concerns. The Sponsor can also request a DSMB review of the safety data if unexpected safety concerns arise during the conduct of the trial. The DSMB responsibilities, authorities, and procedures will be detailed in the DSMB charter.

9.13.2. Independent Response Committee

An IRC will review all data for response assessment. The IRC will determine the response to therapy based on the IMWG Uniform Response Criteria (refer to Appendix B) for each subject.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF (refer to Section 7.6 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for bb2121 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

Adverse events will be collected during specific study periods as described below:

- All procedure-related AEs and all SAEs will be recorded by the Investigator from the time the subject signs ICF through the initiation of LD chemotherapy
- All adverse events regardless of grade or relationship to study treatment will be recorded from first dose of LD chemotherapy through 6 months post-bb2121 infusion
- All Grade ≥ 3 AEs, all SAEs and AESIs regardless of grade or relationship to study treatment (see Section 10.2.1), will be recorded from Month 7 continuously post-bb2121 until Month 24/EOS visit
- Possibly related Grade ≥ 3 AEs, possibly related SAEs and possibly related AESIs will be recorded from Month 25 post-last infusion of bb2121 to end of study participation

AEs, AESI and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the

Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

Upon discontinuation from this study, subjects will participate in a separate LTFU study, to be monitored for potential delayed toxicities of gene therapy for up to 15 years from last bb2121 infusion.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes 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. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Adverse events of special interest:

- For the purpose of this study, any new malignancy or new diagnosis of autoimmune-like, rheumatologic, or new diagnosis of hematologic disorder will be considered as a medically important AESI and, therefore immediately reportable to the Sponsor even if the events do not meet SAE criteria.
- Grade ≥ 3 adverse events of CRS, MAS, neurologic toxicity and infection will be considered as medically important AESIs and, therefore immediately reportable to the Sponsor, even if the events do not meet SAE criteria.

All AESIs will be reported to the Sponsor within 24 hours of the Investigator's first knowledge of the event. All AESIs should be communicated to the Sponsor on the SAE report form as described in the SAE reporting section.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to bb2121, action taken regarding bb2121, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03).

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of LD chemotherapy or bb2121 and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to LD chemotherapy or bb2121 administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of LD chemotherapy or bb2121 caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between LD chemotherapy or bb2121 and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to ancillary or additional medication that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with bb2121 as a result of an AE or SAE, as applicable and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality (if applicable):

- results in discontinuation from the study;
- requires treatment, modification/ interruption of bb2121 dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring at any time after receipt of bb2121, in either a female subject of childbearing potential or partner of childbearing potential of a male subject, are immediately reportable events.

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state), of a female subject occurring at any time after infusion of bb2121, are immediately reportable events. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity, or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent 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 for 1 year. SAEs experienced by newborn within 1 year is required to be immediately reported (ie, within 24 hours) on the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject that received bb2121 becomes pregnant, the male subject that received bb2121 should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to bb2121) that occur during the study (from the time the subject signs informed consent through 6 months after the last infusion of bb2121). In addition, all ≥ Grade 3 AEs, all SAEs and all AESIs will be recorded from Month 7 post-bb2121 infusion until Month 24/EOS. From Month 25 through to end of study participation (for up to 5 years until documented PD), possibly related Grade ≥ 3 AEs, possibly related SAEs and possibly related AESIs to bb2121 therapy are to be recorded.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Any sign, symptom, or manifestation of progressive disease that meet any of the seriousness criteria and result in death will be reported as individual SAEs. Any other AEs leading to death from the time the subject provides informed consent through 90 days after the bb2121 infusion should be reported as an SAE.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to bb2121 based on the current bb2121 Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The Sponsor will notify the appropriate regulatory/government agency(ies)/ of adverse events of special interest in accordance with local requirements.

In Canada, all serious unexpected adverse drug reactions (SUSARs) will be reported in an expedited manner in accordance with Division 5 of the Food and Drugs Act and Regulations, C.05.014:

1. During the course of a clinical trial, Celgene will inform the Minister of any **serious unexpected adverse drug reaction** in respect of the drug that has occurred inside or outside Canada as follows:
    a. if it is neither fatal nor life threatening, within 15 days after becoming aware of the information; and
    b. if it is fatal or life threatening, within seven days after becoming aware of the information.
2. Celgene, within eight days after having informed the Minister under paragraph (1)(b), will submit to the Minister a complete report in respect of that information that includes an assessment of the importance and implication of any findings made.

Celgene or its authorized representative shall notify the Investigators of the following information:

- Any AE suspected of being related to the use of bb2121 in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC (refer to Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

10.7. Potential Risks and Management of Treatment Toxicities

A summary of potential risks and management of treatment toxicity is provided below. See the Investigator's Brochure for a complete discussion of potential risks associated with bb2121.

10.7.1. Cytokine Release Syndrome

Administration of CAR T cells is associated with cytokine release syndrome (CRS) and CRS has been reported frequently following treatment with bb2121. CRS is a potentially serious disorder associated with uncontrolled activation and proliferation of CAR T cells and associated cytokine secretion. CRS is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, anorexia, and neurologic abnormalities (eg, altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity). Laboratory abnormalities may include cytopenias, coagulopathy, electrolyte, renal and liver function abnormalities as well as c-reactive protein, ferritin and cytokine elevations. Organ dysfunction, in particular, cardiac, pulmonary and neurologic dysfunction, can be observed as part of CRS.

Refer to Appendix C for detailed information on diagnosis, grading and clinical management of CRS.

10.7.2. Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a potentially serious disorder associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages. MAS is typically characterized by high-grade, non-remitting fever, cytopenias, and hepatosplenomegaly. Laboratory abnormalities found in MAS include elevated inflammatory cytokine levels, serum ferritin, soluble IL-2 receptor (sCD25), triglycerides, and decreased circulating NK cells. Other findings include variable levels of transaminases, signs of acute liver failure, coagulopathy, and disseminated intravascular coagulopathy. There are no definitive diagnostic criteria for MAS; it is typically diagnosed using published criteria for hemophagocytic lymphohistiocytosis (Schulert, 2015). While there is considerable overlap in clinical manifestations and laboratory findings between MAS and CRS, other distinguishing MAS physical findings such as hepatosplenomegaly and lymphadenopathy are not common in adult subjects treated with activated T cell therapies.

Refer to Appendix C for detailed information on diagnosis, grading and clinical management of CRS and related MAS.

10.7.3. Fever

The possibility of CRS should be considered for all subjects with fever (≥ 38°C/≥100.4°F) following bb2121 infusion. Subjects should be monitored closely for hemodynamic instability and changing neurologic status. Febrile subjects, neutropenic or otherwise, should be evaluated promptly for infection and managed per institutional or standard clinical practice.

10.7.3.1. Temperature Self-monitoring

Once bb2121 infusion has completed and subject is discharged from the hospital, subjects are required to take their temperature, every 6 to 8 hours (while awake) through M1 post-bb2121 infusion and record the temperature information in the provided diary. They must contact their treating investigator for any fever ≥ 38°C/ ≥100.4°F. Site staff should review the temperature self-monitoring diary at each study visit through Month 1. 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 by clinic staff. At the discretion of individual investigators, subjects may remain hospitalized for AE monitoring if preferred.

10.7.4. Neurologic Toxicities

CAR T cell therapy is associated with potentially serious neurologic toxicities and life-threatening neurotoxicity has been reported with bb2121. The etiology and optimal management of neurologic toxicities remains unclear. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity, and can accompany CRS (precede or follow other CRS symptoms) or can occur in isolation. Neurologic symptoms may begin 2 to 14 days (can be later) after CAR T cell infusion and in severe cases may require admission to the ICU for frequent monitoring, respiratory support, or intubation for airway protection. Any signs or symptoms of neurotoxicity (other than headache) should prompt hospitalization.

Refer to Appendix C for detailed information on diagnosis, grading and clinical management of neurologic toxicities.

10.7.5. Infusion Reactions

Administration of bb2121 may cause infusion reactions, such as fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea.

To minimize the risk of infusion reactions, all subjects should receive premedication prior to bb2121 infusion. Pre-medication should occur approximately 30 minutes prior to the infusion and should include acetaminophen 650 mg orally (or according to institutional standards) and diphenhydramine 12.5 mg IV or 25 to 50 mg orally (or equivalent). Mild infusion reactions should be managed expectantly with antipyretics, antihistamines, and anti-emetics. Corticosteroids should be avoided because of the potential impact on efficacy of infused bb2121. Rigors may be treated with meperidine (pethidine).

The following guidelines should be followed for infusion reactions:

- Grade 1: administer symptomatic treatment; continue bb2121 infusion at the same dose and rate
- Grade 2: administer symptomatic treatment; continue bb2121 with a reduced rate of administration
- Grade 3: stop administration of bb2121, administer symptomatic treatment, and resume at a reduced rate of administration only after symptoms resolve. If Grade 3 reaction recurs, discontinue bb2121 infusion.
- Grade 4: discontinue administration of bb2121 and administer symptomatic treatment as necessary; no further bb2121 should be administered.

10.7.6. Tumor Lysis Syndrome

Both LD chemotherapy and bb2121 may cause tumor lysis syndrome (TLS) in subjects with high disease burden. Subjects should be closely monitored for laboratory evidence of TLS, and subjects at high risk should receive prophylactic treatment per standard clinical practice. Treatment of TLS should be administered per institutional standards. In severe cases hemodialysis may be required.

10.7.7. Plasma Cell Aplasia and Hypogammaglobulinemia

Plasma cell aplasia is an expected off-tumor, on-target toxicity of bb2121 and was observed in the phase 1 bb2121 clinical trial. The expected duration of plasma cell aplasia is unknown, but may persist as long as bb2121 CAR+ T cells remain in the body. Prolonged plasma cell aplasia is expected to result in hypogammaglobulinemia which can also be observed as a manifestation of myeloma itself. Hypogammaglobulinemia may increase the risk of bacterial and other infections including opportunistic infections and viral reactivation. Serum immunoglobulin levels will be obtained from all subjects prior to and at regular time points following bb2121 treatment. It is recommended that subjects with serum IgG levels less than 400 mg/dL receive intravenous immunoglobulin replacement as needed to maintain an IgG level above 400 mg/dL, unless there is a contraindication to such therapy. A decision to stop IVIG therapy should be made on a case-by-case basis, preferably in consultation with the Sponsor. The use of prophylactic antibiotics may also be considered.

10.7.8. Replication-Competent Lentivirus, Clonality and Insertional Oncogenesis

Lentiviral vectors used in gene transfer are engineered to be replication-defective; however, generation of RCL during manufacturing is still a possibility. Modern vector production systems have been improved to reduce the risk of RCL generation. To date, there have been no reports of RCL generated during lentiviral vector manufacturing, which may be due, at least in part, to the use of self-inactivating vectors such as the lentiviral vector used in the production of bb2121 (Rothe, 2013).

Concern for possible neoplastic transformation due to the location of the vector integration into the host genome has arisen due to preclinical studies that have shown retrovirus-mediated malignant transformation in mice (Li, 2002; Modlich, 2005) and monkeys (Donahue, 1992) and a single clinical study reporting development of leukemia in subjects with X-linked severe

combined immunodeficiency (SCID) who received retroviral-modified CD34+ hematopoietic stem cells (Hacein-Bey-Abina, 2003), including one subject who died (Couzin, 2005). Of note, no instances of RCL generation during production or lentivirus-mediated malignant transformation in animals or subjects treated in trials of gene-modified T cells have been reported to date.

Data has recently been published on the integration sites of retroviral and lentiviral vectors used for T cell modification in clinical trials (McGarrity, 2013; Scholler, 2012; Wang, 2009). No clonality of integration sites was observed. In addition, there did not appear to be enrichment of integration sites near genes involved in clonal expansion or persistence.

10.7.9. New Malignancies and Other Potential Late Toxicities of Gene Therapy

New malignancies represent AESIs and must be reported as SAEs and includes any second primary malignancy, (refer to Section 10.2.1). All new malignancies will be recorded from informed consent through to Month 24/EOS (for subject who had PD). From Month 25 through to end of study participation, for up to 5 years until documented PD, only new malignancies possibly related to bb2121 therapy are to be recorded. These events must also be documented in the appropriate page(s) of the eCRF and subject's source documents. Documentation on the diagnosis of the new malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc).

Other potential late toxicities of genetically modified T cells include neurologic disorders, hematologic disorders, rheumatic and autoimmune disorders or exacerbation of one of these pre-existing conditions. Monitoring for these AESI will be performed in this study as well as the planned LTFU study.

10.8. Risks Associated with Lymphodepleting Chemotherapy

Subjects will receive fludarabine and cyclophosphamide prior to treatment with bb2121 to facilitate LD chemotherapy and CAR T cell engraftment. Common side effects of fludarabine and cyclophosphamide include bone marrow cytopenias and immune suppression which increase the risk of bleeding and infection and may be exacerbated by bb2121 treatment. Refer to the summary of product characteristics for specific details surrounding the risks of fludarabine and cyclophosphamide.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the IP:

- Failure to manufacture product
- Adverse event
- Subject fails to meet eligibility criteria for LD chemotherapy
- Withdrawal by subject
- Death
- Lost to follow-up
- Progressive disease
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

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.

11.2. Study Discontinuation

The following events are considered possible reasons for discontinuing a subject:

- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Progressive Disease
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, bb2121 will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

bb2121 can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.

14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of eCRFs and of documentation of corrections for all subjects;
- bb2121 accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 13 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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APPENDIX A. TABLE OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BCMA	B-cell maturation antigen
BM	Bone marrow
BMA	Bone marrow aspirate
BNP	Brain natriuretic protein
BUN	Blood urea nitrogen
CR	Complete response
CAR	Chimeric antigen receptor
CBC	Complete blood count
CrCL	Creatinine clearance
C_{max}	Maximum plasma concentration of drug
CNS	Central nervous system
COI	Chain of identity
CR	Complete response
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DOR	Duration of response

Abbreviation or Specialist Term	Explanation
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMP	Extramedullary plasmacytoma
EOS	End of study
FCBP	Females of child bearing potential
FDA	Food and Drug Administration
FISH	Fluorescence in-situ hybridization
FLC	Free light chain
GCP	Good Clinical Practice
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCV	Hepatitis C virus
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICF	Informed consent form
ICH	International Conference for Harmonisation
ICU	Intensive care unit
IFE	Immunofixation
IFN-γ	Interferon gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IMWG	International Myeloma Working Group

Abbreviation or Specialist Term	Explanation
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRC	Independent Response Committee
IV	Intravenous
IVIG	Intravenous immunoglobulins
LD	Lymphodepleting
LDH	Lactate dehydrogenase
LTFU	Long term follow-up
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MMSE	Mini mental state examination
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next generation sequencing
NSAID	Non-steroidal anti-inflammatory drug
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed cell death protein 1
PFS	Progression-free survival
PICC	Peripherally inserted central catheter
PK	Pharmacokinetics
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes

Abbreviation or Specialist Term	Explanation
PRO	Patient reported outcomes
qPCR	Quantitative polymerase chain reaction
RBC	Red blood cell count
RCL	Replication competent lentivirus
RCP	Reunion de Concertation Pluridisciplinaire
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RR	Relapsed refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
sPEP	Serum protein electrophoresis
SUSAR	Suspected unexpected serious adverse reaction
TLS	Tumor lysis syndrome
Tmax	Time to maximum concentration
TTR	Time to response
TTP	Time to progression
ULN	Upper limit of normal
uPEP	Urine protein electrophoresis
VGPR	Very good partial response
Vss	Volume of distribution
WBC	White blood cell count

APPENDIX B. INTERNATIONAL MYELOMA WORKING GROUP RESPONSE CRITERIA

Response Category	Response Criteria*
Standard IMWG response criteria	
Stringent Complete Response (sCR)	Complete response (CR) as defined below, *plus* Normal serum free light chain (FLC) ratio** *and* Absence of clonal plasma cells by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete Response (CR)	Negative immunofixation of serum and urine *and* Disappearance of any soft tissue plasmacytomas *and* < 5% plasma cells in bone marrow aspirates In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis *or* 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours In patients in whom the only measurable disease is by serum FLC levels: VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.
Partial Response (PR)	≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are not measurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and the serum free light chain assay is also unmeasurable, a ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to these criteria, if present at baseline, a ≥50% reduction in the size measured by sum of the products (SPD) §§ of the maximal perpendicular diameters of soft tissue plasmacytomas is also required
Stable Disease (SD)	Not meeting criteria for CR, VGPR, MR, PR, or progressive disease (PD)

Response Category	Response Criteria*
Progressive disease (PD) ¶¶ ‖‖	**Requires only one of the following:** Increase of 25% from lowest response value in any of the following: • Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or* • Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or* Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥ 10%) Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical Relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcaemia (>11 mg/dL); Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Minimal Response (MR)	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50%-89% In addition to the above criteria, if present at baseline, ≥50% reduction in the size (SPD) §§ of soft tissue plasmacytomas is also required

Refer to IMWG criteria for specific details (Kumar, 2016).
For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL

to avoid haemodilution. IMWG=International Myeloma Working Group. MRD=minimal residual disease. NGF=next-generation flow. NGS=next-generation sequencing. FLC=free light chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features=calcium elevation, renal failure, anaemia, lytic bone lesions. FCM=flow cytometry. SUVmax=maximum standardised uptake value. MFC=multiparameter flow cytometry. ^{18}F-FDG PET=^{18}F-fluorodeoxyglucose PET. ASCT=autologous stem cell transplantation.

* All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

¶ Criteria used by Zamagni and colleagues,[85] and expert panel (IMPetUs; Italian Myeloma criteria for PET Use).[81,97] Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax=2·5 within osteolytic CT areas >1 cm in size, or SUVmax=1·5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

‖ Derived from international uniform response criteria for multiple myeloma.[11] Minor response definition and clarifications derived from Rajkumar and colleagues.[14] When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0·26 to 1·65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

** All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

†† Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

‡‡ Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody. §§Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

¶¶ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

|||| In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

APPENDIX C. GUIDELINES FOR MANAGEMENT OF COMMON TOXICITIES THAT OCCUR AFTER CAR T CELL INFUSIONS

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).

1.1. Pathophysiology of Cytokine Release Syndrome

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 fractalkine 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.

1.2. Clinical Presentation of Cytokine Release Syndrome

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 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 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 1: Clinical Signs and Symptoms Associated with Cytokine Release Syndrome

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 2).	

1.3. Clinical Management of Cytokine Release Syndrome

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 2 (Lee, 2014).

Table 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 ≥ 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 3.

Table 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]

Table 3: High Dose Vasopressors (all doses required for ≥ 3 hours) (continued)

Vasopressor	Dose
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).

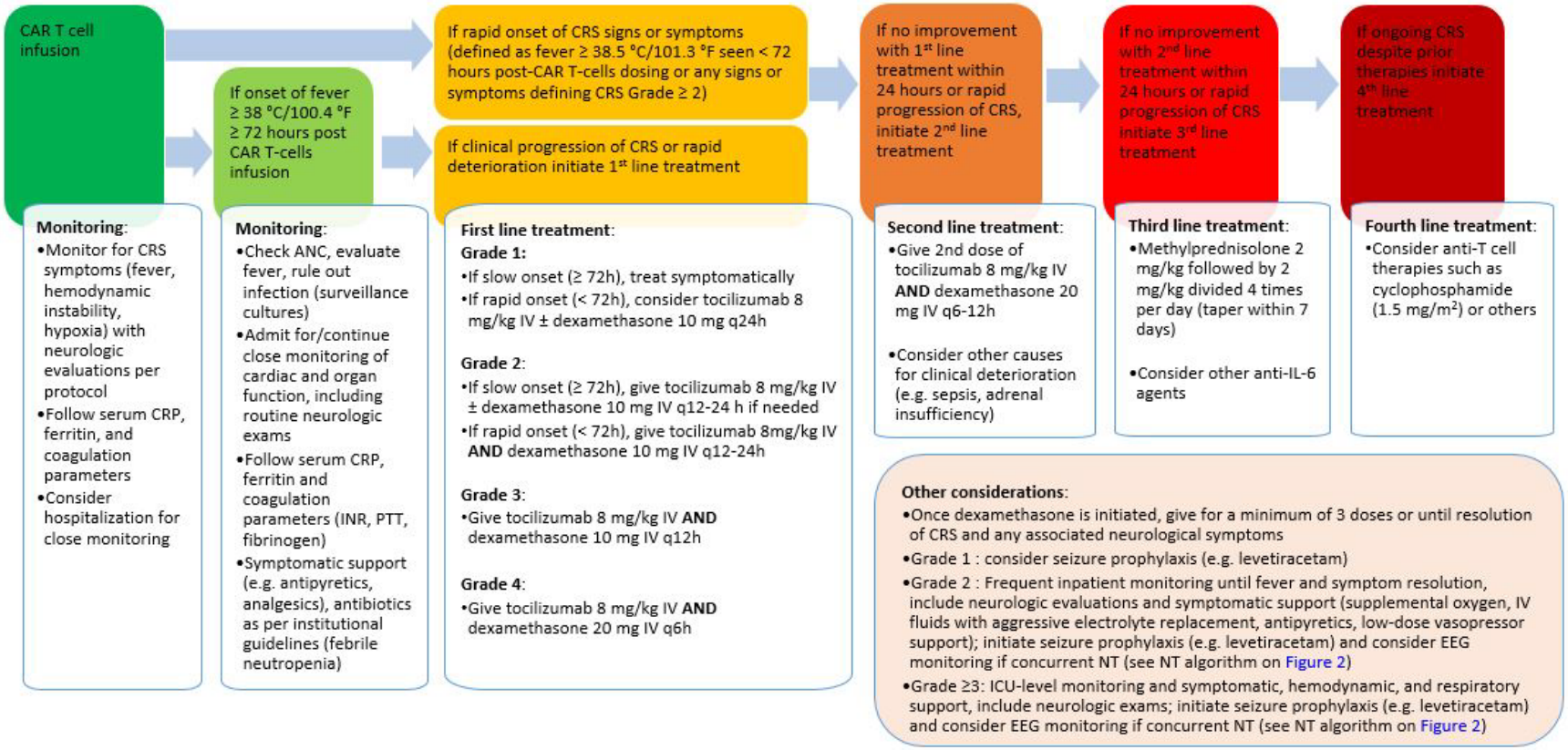
Detailed CRS management guidelines are shown in Figure 1. Treatment should be individualized for each subject's clinical needs. This guidance emphasizes the importance of early intervention for Grade 2 CRS, or in the setting of a rapid onset or rapid progression of CRS symptoms, to prevent the development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

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.

2.1. Pathophysiology of Neurologic 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).

2.2. Clinical Management of Neurologic 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).

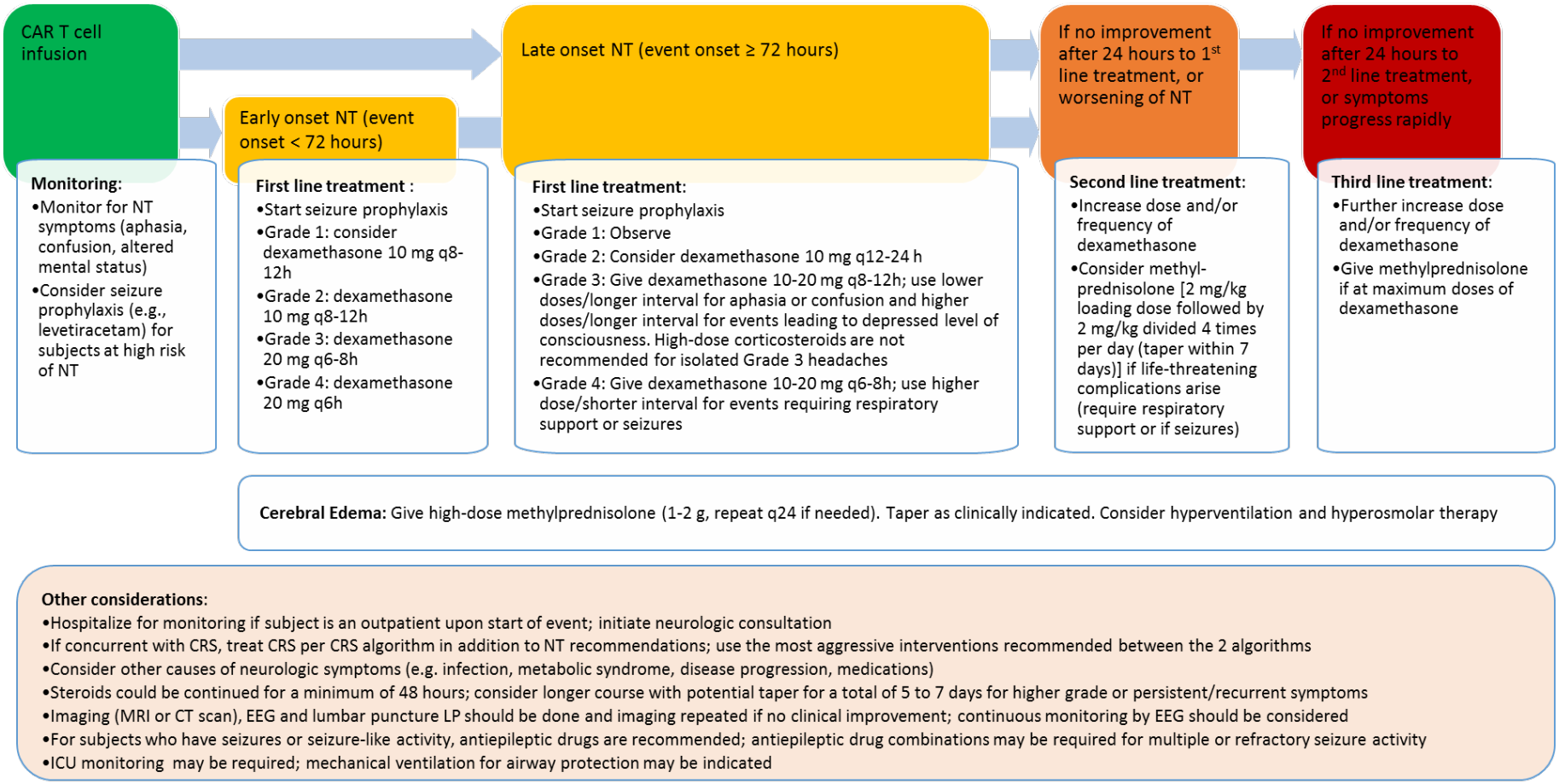
For subjects who have neurologic toxicity in the presence of CRS, the CRS should be managed following the guidelines provided in Figure 1.

Neurotoxicity should be evaluated following the guidelines provided in Figure 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 2.

Figure 2: Neurotoxicity Treatment Algorithm

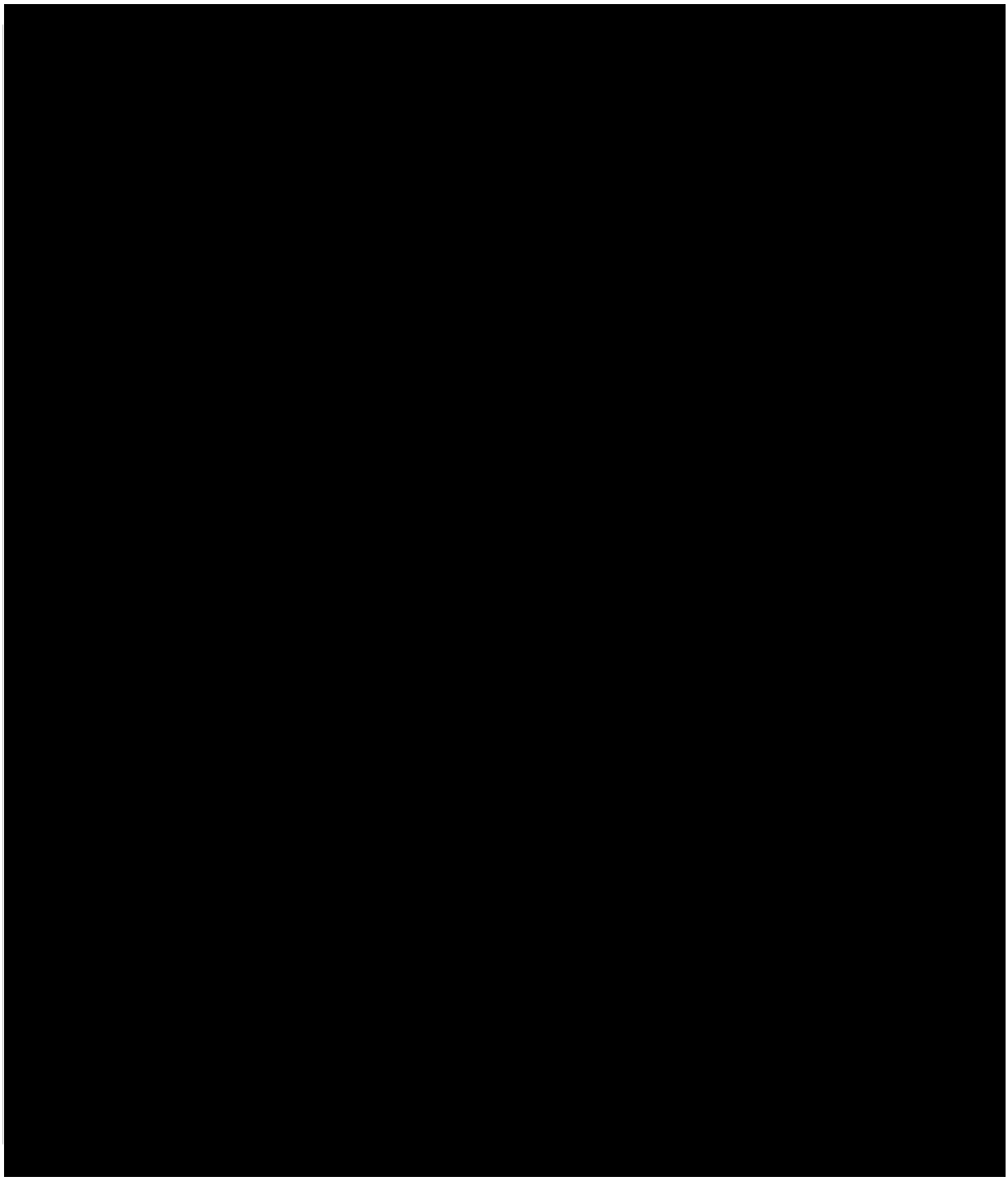


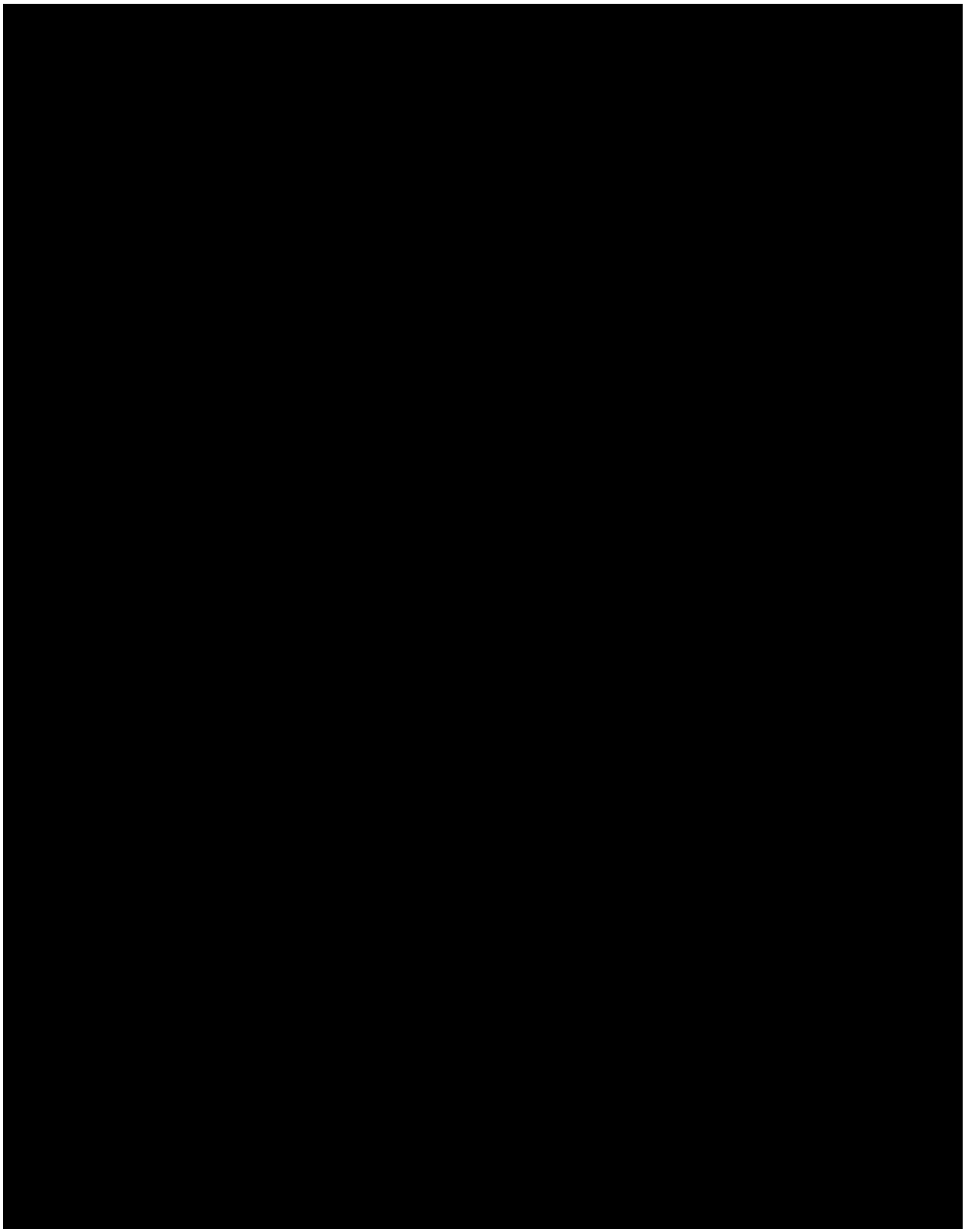
Abbreviations: CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CT = computed tomography; EEG = electroencephalogram; ICU = intensive care unit; LP = lumbar puncture; MRI = magnetic resonance imaging; NT = neurotoxicity; q = every.

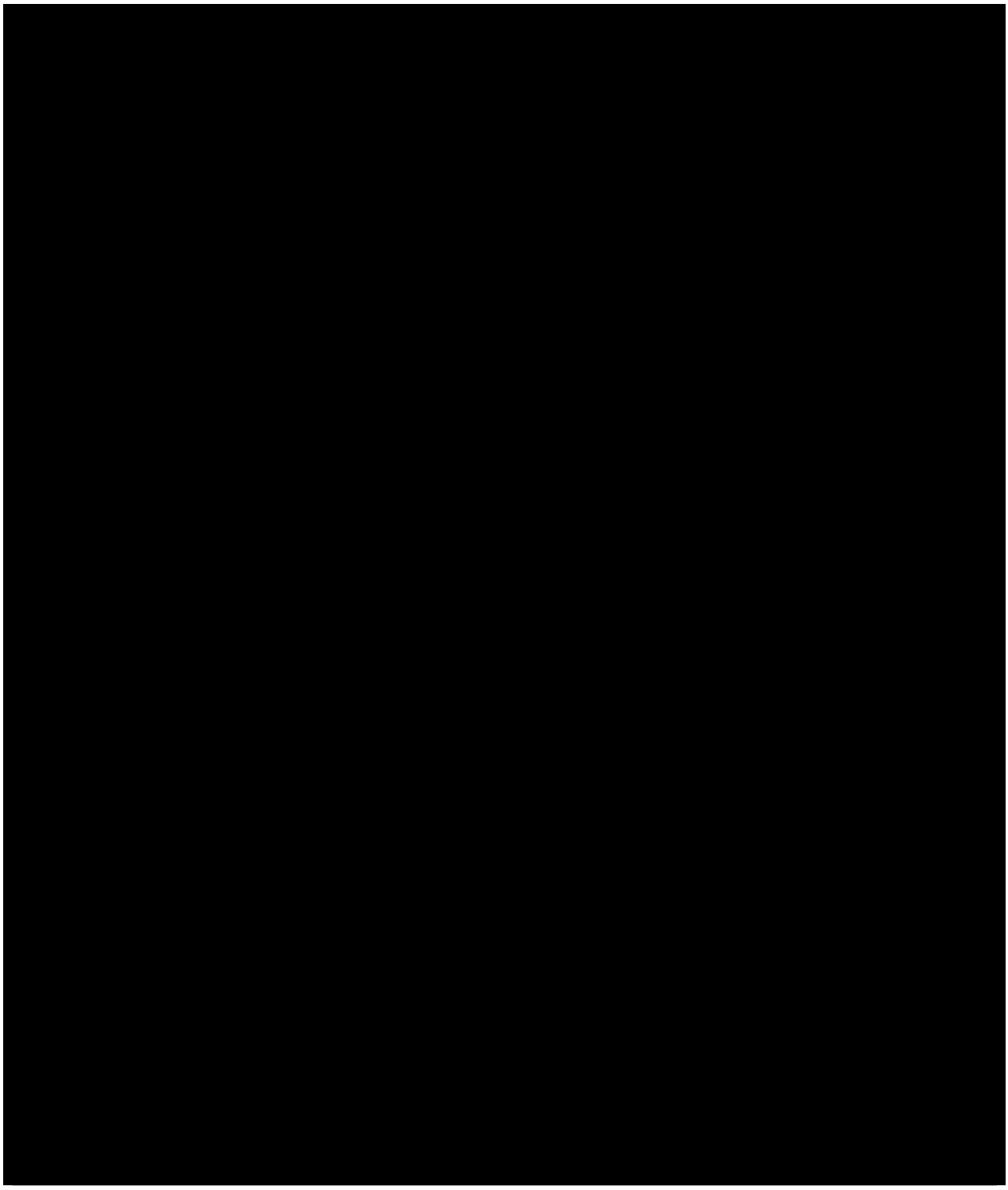
APPENDIX D. ECOG PERFORMANCE STATUS SCALE

Score	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX E. MINI MENTAL STATE EXAMINATION







APPENDIX F. LOCAL CLINICAL LABORATORY EVALUATIONS

Laboratory Panel	Analytes
Chemistry	Sodium, potassium, calcium, chloride, blood urea nitrogen, creatinine, glucose, albumin, alkaline phosphatase, total bilirubin, direct bilirubin (if total bilirubin abnormal), AST, ALT, lactate dehydrogenase, bicarbonate, corrected calcium level, BNP, creatinine clearance (CrCl)
Hematology	CBC with differential including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count (with differential) and platelet count
Lymphocyte subset panel	CD3, CD4, CD8, CD19/CD20
TLS/CRS	Magnesium, uric acid, phosphorus, ferritin, C-reactive protein, creatine phosphokinase
Coagulation	PTT, INR, fibrinogen, d-dimers
Viral serology	HIV, Hepatitis B (HBsAb, HBsAg and HBcAb), Hepatitis C (HCV antibody), syphilis and HTLV-1 antibody
Urinalysis	Appearance, pH, specific gravity, protein Glucose, ketones, RBCs, WBCs
Pregnancy	B-HCG (serum or urine)
Other non-laboratory local evaluations	ECHO/MUGA, ECG, Skeletal survey, PET/CT, CT or MRI

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ALP = alkaline phosphatase; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CBC = complete blood count; CrCl = creatinine clearance; CT = computed tomography; ECG = electrocardiogram; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV= human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell.

APPENDIX G. COCKCROFT-GAULT EQUATION FOR CALCULATING ESTIMATED CREATININE CLEARANCE

Serum creatinine units	Gender	Estimated Creatinine Clearance (mL/min)
mg/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)}}{72 \times \text{subject serum creatinine (mg/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 0.85}{72 \times \text{subject serum creatinine (mg/dL)}}$
µM/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.23}{\text{Subject serum creatinine (µM/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.04}{\text{Subject serum creatinine (µM/dL)}}$

– SUMMARY OF CHANGES –

AMENDMENT NO. 4.0

A PHASE 2, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF BB2121 IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

INVESTIGATIONAL PRODUCT (IP):	**bb2121**
PROTOCOL NUMBER:	**BB2121-MM-001**
ORIGINAL DATE:	**25 Aug 2017**
AMENDMENT No. 1.0 DATE:	**09 Nov 2017**
AMENDMENT No. 2.0 DATE:	**14 Jun 2018**
AMENDMENT No. 3.0 DATE:	**28 Sep 2018**
AMENDMENT No. 4.0 DATE:	**18 Jul 2019**
EudraCT NUMBER:	**2017-002245-29**
IND NUMBER:	**016664**

Contact Information:

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Title: [redacted]

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San Francisco, CA 94158

Phone: [redacted]

E-mail: [redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
[redacted]	
Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.	

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
[redacted]	
Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.	

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Moved minimal residual disease (MRD) assessment by EuroFlow to Exploratory Objectives and Exploratory Endpoints.**

  The primary purpose of this protocol amendment is to move the MRD assessment by EuroFlow from the Secondary Objectives and Secondary Endpoints to the Exploratory Objectives and Exploratory Endpoints.

  The draft guidance "Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry" recommends that the Sponsor prespecify the selected platform for MRD assessment. The initial protocol language included the potential use of both EuroFlow and next generation sequencing (NGS). The changes in the amendment make it clear that NGS is the selected methodology for analysis as the secondary endpoint, and the EuroFlow analysis will be conducted as an exploratory endpoint.

  - Revised Sections: Protocol Summary, Table 1: Study Objectives, and Table 2: Study Endpoints

- **Updated the term "vector copy number" (VCN).**

  To avoid confusion of the term VCN when discussing the manufacture of bb2121 and when discussing the characterization of chimeric antigen receptor (CAR) + T cell expansion in the peripheral blood or bone marrow postinfusion, VCN as related to CAR+ T cell expansion will now be referred to as cellular kinetics, pharmacokinetics (PK), CAR+ T cells, or CAR transgene.

  - Revised Sections: Protocol Summary, Table 1: Study Objectives, Table 3: Table of Events, Table 5: Table of Events – Evaluations for Disease Progression after Month 24, Section 6.1.1. Screening Evaluations (performed within 28 days prior to leukapheresis), Section 6.3.1. Post-bb2121 Infusion (Day 1 through Month 1), Section 6.3.2. Post-bb2121 Infusion (M1 through Month 24/EOS), Section 6.3.4. Post-bb2121 Infusion (Disease Progression/CR), Section 6.4.4.1. Vector Integration Site Analysis, Section 6.7. Pharmacokinetics, Section 7.2.2.3. bb2121 Infusion, and Section 9.9. Pharmacokinetic Analysis

- **Separated the secondary objective of characterization of the expansion of CAR+ T cells in the peripheral blood and bone marrow into two objectives. Evaluation of CAR+ T cells in the peripheral blood will remain as a secondary objective while evaluation in the bone marrow will be an exploratory objective. Evaluation in the bone marrow was also added as an exploratory endpoint.**

  As the characterization of CAR + T cell expansion in the peripheral blood and bone marrow are considered two distinct analyses, where one is serving as a PK measurement; this objective has been separated into two objectives. Qualification of the assay to perform the assessment of CAR+ T cells in the bone marrow was conducted to a level to support use as an exploratory objective and exploratory endpoint only.

  - Revised Sections: Protocol Summary, Table 1: Study Objectives, and Table 2: Study Endpoints

- **Removed the secondary objective and secondary endpoint, "Evaluate cytokine induction in the blood of subjects after infusion of bb2121", and removed cytokines as a key safety assessment.**

  This objective and endpoint was previously listed as both secondary and exploratory. Qualification of the assay was performed to support use as an exploratory objective and exploratory endpoint only.

  - Revised Sections: Protocol Summary, Table 1: Study Objectives, and Table 2: Study Endpoints

- **Moved the secondary objective and secondary endpoint, "Evaluate the percentage of B-cell maturation antigen (BCMA)-expressing (BCMA+) cells and levels of BCMA expression in bone marrow, and the level of circulating soluble BCMA" to exploratory objectives and exploratory endpoints.**

  Qualification of the assay was performed to support use as an exploratory objective and exploratory endpoint only.

  - Revised Sections: Protocol Summary, Table 1: Study Objectives, and Table 2: Study Endpoints

- **Clarified the definition of "cellular kinetics".**

  The cellular kinetic profile (PK) will be described by time course of transgene copies per microgram of genomic DNA as measured by quantitative polymerase chain reaction (qPCR) using CD3+ sorted T cells.

  - Revised Section: Section 6.7. Pharmacokinetics

- **Clarified the definition of the Pharmacokinetic (PK) Analysis Population.**

  Definition of the retreatment PK Analysis Population was added to differentiate the subjects in the population who were retreated (received a second bb2121 dose).

  - Revised Section: Section 9.2.5 Pharmacokinetic Analysis Population

- **Removed option to remanufacture bb2121 from cryopreserved peripheral blood mononuclear cells (PBMCs) for retreatment.**

  Subjects who progress after initial bb2121 infusion are at risk of rapid clinical deterioration while waiting for remanufacture of bb2121 from cryopreserved peripheral blood mononuclear cells (PBMCs). In order to avoid increased safety risk due to rapid progression and preserve bb2121 manufacturing slots for those subjects receiving an initial infusion, subjects must have cryopreserved bb2121 product available in order to be candidates for retreatment.

  - Revised Sections: Table 4: Table of Events – Retreatment Evaluations and Section 7.2.3. Retreatment

- **Updated guidance on type of bridging therapy that may be used prior to retreatment.**

  To allow flexibility of treatment options for subjects who have progressed after initial bb2121 infusion and are at risk of rapid disease progression, there is no longer a restriction of drug classes that may be used for bridging therapy prior to retreatment. The restriction of drug classes that may be used for bridging therapy prior to initial bb2121 infusion remains the same.

  - Revised Sections: Protocol Summary, Section 3.1. Study Design, and Section 7.2.3. Retreatment

- **Updated Inclusion Criteria #8.**

  Updated inclusion criteria #8 to align with the summary of product characteristics (SMPC) pregnancy guidance for cyclophosphamide. In addition, the update eliminates the exemption from using contraception, abstaining from breastfeeding, and refraining from tissue donation based on testing for absence of residual bb2121 CAR T cell persistence. There is no assay commercially available to support patient management for this clinical application, and so it has been removed from this guidance. Clarified that there are insufficient exposure data to provide any recommendation concerning duration of contraception, abstaining from breastfeeding, and refraining from tissue donation following treatment with bb2121. Clarified the highly effective contraception methods: "tubal ligation" to "bilateral tubal ligation" and "partner's vasectomy" to "successful vasectomy".

  - Revised Section: Section 4.2 Inclusion Criteria

- **Added footnote "hh" in Table 3 to clarify that an additional Unscheduled visit may be required proximate to the primary analysis.**

  For the completeness of key efficacy data at the time of data cutoff for the primary analysis, efficacy assessments according to the International Myeloma Working Group (IMWG) and survival sweep may be conducted in between scheduled visits and before the primary analysis data cut-off date.

  - Revised Section: Table 3: Table of Events

- **Removed requirement of sample collection for peripheral blood for immunophenotyping by flow cytometry at Months 12, 18, 24, 30, and 36+.**

  CAR+ T cells are not detectable in sufficient numbers by this method to enable interpretable immunophenotyping measurements in most patients at these later timepoints.

  - Revised Section: Table 3: Table of Events and Table 5: Table of Events – Evaluations for Disease Progression after Month 24

- **Added an optional extramedullary plasmacytoma (EMP) biopsy.**

  Added the optional EMP biopsy to Table 3 and Table 5 to distinguish the plasmacytoma biopsy from the tumor biopsy for second primary malignancies that was added in this amendment.

  - Revised Section: Table 3: Table of Events and Table 5: Table of Events – Evaluations for Disease Progression after Month 24

- **Added tumor biopsy sample collection for second primary malignancies.**

  Per FDA guidance, evaluation of potential CAR transgene involvement in the generation of second or new malignancies is suggested.

  - Revised Section: Table 3: Table of Events, Table 5: Table of Events – Evaluations for Disease Progression after Month 24, and added new Section 6.3.7. Assessment at Time of Second Malignancy

- **Updated timing of the primary analysis from "6 months" to "10 months" after bb2121 infusion.**

  The primary analysis will be performed 9 months following the first response assessment at Month 1 (eg, at 10 months) based on Health Authority interactions.

  - Revised Sections: Protocol Summary, Section 2. Study Objectives and Endpoints, Section 6.5.5.2. Independent Response Committee (IRC) Assessment, and Section 9.12. Timing of Analysis

- **Updated Section 9.7.1. Assessment of MRD.**

  Removed, "a flow MRD negative response, a sequencing MRD negative response, a sustained MRD negative response and an imaging plus MRD negative response, per IMWG Uniform Response Criteria will be summarized (Kumar, 2016)." These categories of MRD response are not being adjudicated by the IRC and thus, will not be considered verified IMWG response categories. However, assessment of MRD negative response and summarization of MRD negative rates for the bb2121-treated population and in subjects reaching select IMWG response categories will be performed.

  - Revised Section: Section 9.7.1. Assessment of MRD

- **Removed the sentence, "Response assessments will be made according to updated 2016 International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma (refer to Appendix B)."**

  MRD response will not be adjudicated.

  - Revised Section: 1.3.3. Rationale for Pharmacodynamics and Potential Predictive Biomarkers and Section 6.5.4. Bone Marrow Aspiration and/or Biopsy

- **Updated that the IRC will not adjudicate time of response.**

  The IRC will adjudicate response; however, the date of response or date of progression will be programmatically derived.

  - Revised Sections: Protocol Summary, Section 3.1. Study Design, Section 6.5.5.2. Independent Response Committee (IRC) Assessment, and Section 9.13.2. Independent Response Committee

- **Updated that any pregnancy after bb2121 infusion is a reportable event.**

  The update eliminates the exemption for pregnancy reporting based on testing for absence of residual bb2121 CAR T cell persistence. There is no assay commercially available to support patient management for this clinical application and so it has been removed from this guidance. All pregnancies occurring at any time after bb2121 infusion will be considered reportable events.

  - Revised Section: Section 10.4.1. Females of Childbearing Potential

The amendment also includes other minor corrections:

- Updated Medical Monitor contacts.
- Clarified description of minimal residual disease (MRD) in Table 2: Study Endpoints.
- Clarified duration of follow up after retreatment in Section 3.3. Study Duration for Subjects.
- Clarified description of PK in Table 2: Study Endpoints.
- Clarified laboratory tests included in the chemistry panel in Section 6.1.1. Screening Evaluations (performed within 28 days prior to leukapheresis) and Section 6.4.2. Laboratory Assessments for Safety Parameters.
- Clarified the sample types in Table 7: Biomarkers sampling.
- Clarified periods in which concomitant medications are recorded in the electronic data capture (EDC) system in Section 8.1. Permitted Concomitant Medications and Procedures.
- Clarified periods in which adverse events are recorded in the EDC system in Table 5: Table of Events – Evaluations for Disease Progression after Month 24, Section 6.3.2. Post-bb2121 Infusion (M1 through Month 24/EOS), and Section 10.1. Monitoring, Recording and Reporting of Adverse Events.
- Clarified in Table 5: Table of Events – Evaluations for Disease Progression after Month 24 that from Month 25 post-last infusion of bb2121 to end of study participation, only possibly related adverse events (AEs), possibly related serious adverse events (SAEs), and possibly related adverse events of special interest (AESIs) are collected. This table now aligns with Sections 8.1 and 10.1.
- Updated language to clarify that analyses may be performed at other time points as needed (ie, either prior to or after the primary analysis) in Section 9.12. Timing of Analysis.
- Updated possible reasons for treatment discontinuation or study discontinuation in Section 11.1. Treatment Discontinuation and Section 11.2. Study Discontinuation to include “Progressive Disease”.
- Removed MRD response criteria from Appendix B. International Myeloma Working Group Response Criteria.
- Typographical corrections.

– SUMMARY OF CHANGES –

AMENDMENT NO. 3.0

A PHASE 2, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF BB2121 IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

INVESTIGATIONAL PRODUCT (IP):	**bb2121**
PROTOCOL NUMBER:	**BB2121-MM-001**
ORIGINAL DATE:	**25 Aug 2017**
AMENDMENT No. 1.0 DATE:	**09 Nov 2017**
AMENDMENT No. 2.0 DATE:	**14 Jun 2018**
AMENDMENT No. 3.0 DATE:	**28 Sep 2018**
EudraCT NUMBER:	**2017-002245-29**
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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.	

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By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.	

1. JUSTIFICATION FOR AMENDMENT

The current protocol requires that subjects should complete baseline assessments within 72 hours or on the same day of lymphodepleting chemotherapy (Section 6.1.3) and specifically requires that eligibility criteria are met prior to start of lymphodepleting chemotherapy and that no intercurrent illness or toxicity that places the subject at undue risk of proceeding to lymphodepleting chemotherapy and bb2121 infusion (Section 6.2.1).

This amendment provides further guidance on intercurrent illness or toxicity that is considered to place the subject at undue risk of proceeding to bb2121 infusion and for which bb2121 infusion should be delayed.

Revised section: Section 6.2.2, bb2121 Infusion

The amendment also includes a minor update:

- Change of Celgene Therapeutic Area Head

– SUMMARY OF CHANGES –

AMENDMENT NO. 2.0

A PHASE 2, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF BB2121 IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

INVESTIGATIONAL PRODUCT (IP):	**bb2121**
PROTOCOL NUMBER:	**BB2121-MM-001**
ORIGINAL DATE:	**August 25, 2017**
AMENDMENT No. 1.0 DATE:	**November 9, 2017**
AMENDMENT No. 2.0 DATE:	**June 14, 2018**
EudraCT NUMBER:	**2017-002245-29**
IND NUMBER:	**016664**

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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment include: 1) increase of the upper bound of the bb2121 dose range to 450 x 10^6 CAR+ T cells, 2) increase of the sample size to enroll up to 140 subjects with up to 119 subjects treated with bb2121, 3) modification of the bb2121 overdose definition, and 4) incorporation of feedback from health authorities.

bb2121 Dose Range Modification

The upper bound of the dose range is expanded from 300 x 10^6 to 450 x 10^6 CAR+ T cells. The rationale for this change to the dose range is based on the preliminary safety and efficacy data in the phase 1 study, CRB-401 (n=43 subjects treated across the dose range of 50 - 800 x 10^6 CAR+ T cells) and preliminary safety data in this study (n=32 subjects treated across the dose range of 150 - 300 x 10^6 CAR+ T cells).

CRB-401: Summary of Clinical Safety Data

Updated information, based on a data-cut-off of 29 March 2018, is available on 43 subjects enrolled in the dose escalation and expansion phases of the Phase 1 study, CRB-401. bb2121 doses administered included: 50 (N = 3), 150 (N = 18), 200 (N = 1), 450 (N = 18) and 800 (N = 3) x 10^6 CAR+ T cells. CRS of any grade was observed in 27 of 43 (63%) subjects with grade 3 CRS events reported in 2 of 43 subjects (4.6%). These included 1 reversible grade 3 CRS event at a dose of 450 and 800 x 10^6 CAR+ T cells, respectively. No grade 4 CRS events were reported. The median time to onset of CRS was 2 days and median duration was 6 days. The overall frequency of CRS across the dose range of 150 to 450 x 10^6 CAR+ T cells was 60%, including 39% at a dose of 150 x 10^6 CAR+ T cells and 83% at a dose of 450 x 10^6 CAR+ T cells. All cases of CRS were reversible. Neurotoxicity of any grade was observed in 14 of 43 (33%) subjects including one reversible grade 4 event (2.3%) and no grade 3 events. The overall frequency of neurotoxicity across the dose range of 150 to 450 x 10^6 CAR+ T cells was 30% with a grade ≥ 3 frequency of 2.7%. This includes an overall frequency of 11% at a dose of 150 x 10^6 CAR+ T cells (with no grade ≥ 3 events) and 50% at a dose of 450 x 10^6 CAR+ T cells (with one grade ≥ 3 events, 5.6%). Nine subjects (21%) were treated with tocilizumab for grade 1 to 3 CRS. Of these, four subjects (9%) received corticosteroids for management of CRS or neurotoxicity. All cases of neurotoxicity were reversible. For this analysis of neurotoxicity, a broad inclusion of observed events within the neurologic System-Organ-Class (SOC) were included (preferred terms including dizziness, bradyphrenia, somnolence, confusional state, nystagmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination). Most neurologic events were grade 1/2 and likely multifactorial in nature, while only one grade ≥ 3 event clearly attributable to CAR T cell associated encephalopathy was reported. To address the grade ≥ 3 neurotoxicity event observed in CRB-401, the CRB-401 and BB2121-MM-001 protocols were modified to update the eligibility criteria to exclude patients with history or presence of clinically relevant central nervous system (CNS) pathology and the protocol safety monitoring plan, including a mandatory 14-day hospitalization, twice weekly outpatient visits in weeks 3 and 4 and a detailed CAR T toxicity management guideline to ensure adequate safety oversight. To date no additional grade 3/4 events have been observed.

BB2121-MM-001: Summary of Clinical Safety Data

As of 17 May 2018, 32 subjects have been infused in BB2121-MM-001. Preliminary safety data (unaudited data) are available for 32 subjects in BB2121-MM-001 infused with the dose range 150 to 300 x 10^6 CAR+ T cells. Of these 32 subjects, 28 were dosed at the upper end of the dose range (300 x 10^6 CAR+ T cells). Cytokine release syndrome was observed in 20 of 32 (63%) across the dose range. At the upper end of the dose range (300 x 10^6 CAR+ T cells) in BB2121-MM-001, the frequency of CRS is 64% (n= 18 of 28). Only one reversible grade 3 CRS event was observed at the upper end of the dose range (300 x 10^6 CAR+ T cells dose). No grade 4 CRS events were reported. Neurotoxicity was observed in 4 of 32 subjects (13%), all dosed at the upper end of the dose range (14%, n=4 of 28), with no grade 3 or 4 events reported. Grade 1/2 neurotoxicity event terms included short term memory loss, hallucinations, hand writing changes, spelling difficulty and right sided weakness. Ten subjects were treated with tocilizumab for grade 1 to 3 CRS. Of these, one subject received a single dose of dexamethasone for management of grade 3 CRS and grade 1 neurotoxicity. All CRS and neurotoxicity events were reversible. These frequencies observed to date in this study, are between the frequencies observed in subjects infused in CRB-401 at a dose of 150 x 10^6 CAR+ T cells (CRS: n=7 of 18, 39%; neurotoxicity event: n=2 of 18, 11%) and at a dose of 450 x 10^6 CAR+ T cells; (CRS: n=15 of 18, 83%; neurotoxicity event: n=9 of 18, 50%).

CRB-401: Summary of Clinical Efficacy Data

Preliminary efficacy data from CRB-401 are summarized in the table below:

	CRB-401 (29 Mar 2018 data cut-off)	
Response[1]	**150 x 10^6 CAR+ T cells**	**450 x 10^6 CAR+ T cells**
N	14	19[1]
ORR, n (%)	8 (57)	18 (95)
CR, n (%)	6 (43)	9 (47)

CR, complete response; ORR, objective response rate
[1] Includes one subject treated with 200 x 10^6 CAR+ T cells

Based on a data cut-off of 29 March 2018 in CRB-401, efficacy data is available from 39 evaluable subjects with at least 2 months of tumor response assessments or with disease progression within 2 months. Of these, 33 were treated across the dose range of 150 to 450 x 10^6 CAR+ T cells. The reported overall tumor response rate (ORR) at doses of 150 to 450 x 10^6 CAR+ T cells in the 33 evaluable subjects was 79% with a median duration of response of 10.8 months. A dose response was observed across the 150 to 450 x 10^6 CAR+ T cell dose range with an ORR of 57% at the 150 x 10^6 CAR+ T cell dose and 95% at the 450 x 10^6 CAR+ T cell dose. Within the active dose cohorts (150 to 800 x 10^6 CAR+ T cells) tumor response was more frequent in patients with CRS than without CRS (ORR 92% vs 55%, respectively).

These interim safety data from this study and from CRB-401 support a manageable safety profile for bb2121 at doses up to 800 x 10^6 CAR+ T cells. Furthermore, these data demonstrate a more favorable benefit:risk relationship at the higher end of the dose range and provide justification for the expansion of the dose range to include 450 x 10^6 CAR+ T cells.

Modification to Protocol Sample Size and Statistical Assumptions

The sample size is modified to allow up to 140 subjects to be enrolled with up to 119 subjects treated with bb2121. The rationale for this change includes an increase in statistical power for the primary and key secondary endpoint based on a composite analysis across the 150 to 450 x 10^6 CAR+ T cell dose range as well as increased nominal power for subgroup analyses of safety and efficacy within this revised dose range.

With this increase in sample size to include up to 119 bb2121 treated subjects, the statistical power for the key secondary endpoint of complete response (CR) rate (defined as the proportion of subjects with at least a complete response) will be increased from 78% (in the original protocol) to approximately 89%, with the null hypothesis of CR rate ≤ 10% and target CR rate ≥ 20% at a one-sided 0.025 alpha level.

For the primary endpoint of overall response rate (ORR) (defined as the proportion of subjects with at least a partial response), with the same null hypothesis of ORR ≤ 50% and the target ORR ≥ 70% as in the original protocol, a sample size of 119 bb2121 treated subjects would provide >99% power at a one-sided 0.025 alpha.

Modification of the bb2121 overdose definition

The protocol definition of overdose (Section 7.6) for bb2121 is changed from > 10% to > 20% of the protocol specified dose to allow for the final product to be filled across the full protocol-specified dose range of 150 – 450 x 10^6 CAR+ T cells and delivered without the need for further manipulation at the clinical site post thaw prior to infusion.

Given the expected variability of +/- 20% between estimated CAR+ cell count (on which product bags are filled) and final CAR+ cell count (on which administered CAR+ cell dose is calculated), extension of the definition of overdose to > 20% will allow reliable delivery of the filled product bags containing bb2121 cells with less need for post-thaw manipulation at the clinical site resulting in greater quality control. The safety profile of bb2121, including doses administered up to 800 x 10^6 CAR+ T cells in the phase 1 CRB-401 trial without establishment of a maximum tolerated dose, supports the safety of extending the definition of overdose to > 20%.

Incorporation of feedback from Health Authorities

The Sponsor is incorporating feedback received from health authorities in order to: 1) clarify selected screening exclusion and lymphodepleting chemotherapy criteria, 2) add live vaccines to the list of prohibited medications, 3) align pregnancy monitoring with clinical trials facilitation group (CTFG) guidelines, and 4) remove the option for repeat leukapheresis for those re-treated with bb2121.

Changes included in this amendment are summarized below:

Changes to the sample size and dose range

- Protocol Summary and Section 4.1 Number of Subjects have been updated to reflect the modified sample size and dose range.

Changes to rationale for study design

- Section 1.3.1.2 Rationale for the study design has been updated to include more recent safety and efficacy information from the dose escalation study, CRB-401.

Changes to rationale for dose, schedule and regimen selection

- Section 1.3.2 Rationale for dose, schedule and regimen selection has been updated with up to date data to support the selected dose range.

Changes to existing inclusion criteria

- Section 4.2 criterion #8 Females of childbearing potential and male subjects on how long a subject must practice abstinence have been updated to be consistent across bb2121 programs.
- Added a list of highly effective methods of birth control

Changes to existing screening exclusion criteria

- Section 4.3 criterion #3 updated to clarify that subjects with active or history of plasma cell leukemia are excluded.
- Section 4.3 criterion #19 updated to clarify that subjects with hypersensitivity to cyclophosphamide, fludarabine or tocilizumab are excluded.
- Section 4.3 criterion #21 updated to clarify that active uncontrolled infections or the need for ongoing intravenous antimicrobials to control infections are excluded.

Changes to criteria for proceeding with lymphodepleting chemotherapy

- Section 6.2.1 updated to add "no active urinary outflow obstruction" as a criterion to proceed with lymphodepleting (LD) chemotherapy as these subjects cannot safely receive cyclophosphamide chemotherapy.

Changes to prohibited concomitant medications and procedures

- Section 8.2 updated to add live vaccines during and for 3 months following fludarabine treatment to the prohibited concomitant medication list based on risk of active infection following live vaccine administration in patients treated with fludarabine lymphotoxic chemotherapy.
- Section 6.1.2 and 8.2 changed to not allow systemic MM therapy within 14 days prior to leukapheresis instead of 7 days. The rationale for changing this criterion is to align with the original Phase 1 protocol (CRB-401) and to help mitigate the risk of manufacturing lots not yielding the minimum 150 million CAR+ T cell dose due to low CD3+ T cell counts in the leukapheresis material.
- Section 6.1.2 and 8.2 changed to remove restriction on experimental agents within 4 weeks of leukapheresis. Experimental agents are covered under the revised 14-day washout period for systemic MM therapy.

Changes to pregnancy monitoring

- Section 5, Table of Events, and Section 6.3.2 updated to include serum/urine pregnancy tests at Month 3 and Month 12 to align with CTFG guidelines.

Removal of the option of repeat leukapheresis for those re-treated with bb2121

- The option for repeat leukapheresis in Section 7.23 will be removed due to the risk of repeat transduction of bb2121 CAR+ T cells in the manufacture of bb2121 product from a repeat leukapheresis for subjects considering re-treatment with bb2121.

Subjects will continue to be allowed to undergo re-treatment with existing frozen drug product or drug product manufactured from frozen PBMCs from the initial pre-treatment leukapheresis material.

- Section 7.2.3 updated to include clarification that remaining drug product of cryopreserved peripheral blood mononuclear cells (PBMC) may be used to initiate remanufacture of drug product and bridging therapy allowed prior to receiving bb2121.
- Section 7.2.3 added language that subjects with progressive disease within the CNS that requires whole brain or directed cerebral radiotherapy (excluding palliative focal, minimally penetrating, radiotherapy to scalp or skull lesions), should not receive bb2121 re-treatment infusion until a gap of at least 8 weeks from last radiotherapy treatment has been observed. Rationale is to minimize risk of neurotoxicity in subjects re-treated who have CNS myeloma involvement.

Addition of optional plasmacytoma biopsies

- Collection of tumor tissue biopsies added as optional (Sections 6.1.1, 6.3.2, 6.3.4 and 6.8.1) in order to explore mechanisms of response and progression in these tissues, including B-cell maturation antigen (BCMA) expression on tumor cells, immune microenvironment markers and other translational assays.

Clarification of expedited adverse event reporting language

- The expedited reporting of Grade 4 or greater cytokine release syndrome, neurologic toxicities, infections and deaths within 28 days post bb2121 infusion was removed and replaced with "according to local authorities" in Section 10.6. This wording will accommodate differences in reporting requests that may come from different local authorities.

Changes to the statistical assumptions

- Sections 9.3 and 9.7 have been updated to reflect the modified sample size and statistical assumptions and additional plan for dosing subgroup analyses.

Administrative and/or minor clarifications

1. Section 5, Table of Events (Table 3):
   - Temperature monitoring clarified to every 6 – 8 hours D0 – D14 while the subject is hospitalized.
   - Added serum and PBMC immunogenicity collection to baseline visit if subject is retreated
   - Clarification of Viral serology testing requirements
2. Section 6.4.3 corrected collection of brain natriuretic peptide (BNP) to within 72 hours of LD chemotherapy
3. Clarify throughout protocol oxygen saturation performed at screening, within 3 days of leukapheresis, baseline, Day 0, M1, M2 and M3 only.

4. Clarify language regarding mandatory 14-day hospitalization to reflect that subjects can be discharged on day 14 after safety evaluations completed.
5. Clarify language frequency of vital sign monitoring during the first 4 hours following bb2121 infusion.
6. Clarify language if a subject has disease progression after M24, subject is evaluable for retreatment.
7. Table 6 – Patient interviews, a 7-day window was added to each assessment post bb2121 infusion to allow for patient compliance.
8. Additional clarifications made throughout protocol.

– SUMMARY OF CHANGES –

AMENDMENT NO. 1.0

A PHASE 2, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF BB2121 IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

INVESTIGATIONAL PRODUCT (IP):	**bb2121**
PROTOCOL NUMBER:	**BB2121-MM-001**
ORIGINAL DATE:	**August 25, 2017**
AMENDMENT No. 1.0 DATE:	**November 9, 2017**
EudraCT NUMBER:	**2017-002245-29**
IND NUMBER:	**016664**

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
Printed Name of Celgene Therapeutic Area Head and Title By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.	

1. JUSTIFICATION FOR AMENDMENT

The primary justification for this amendment to the bb2121-MM-001 protocol is to modify the overall safety management plans in response to a recent serious adverse event in the Phase 1 bb2121-CRB-401 trial.

In study CRB-401 a case of Grade 4 neurotoxicity occurring on Day 12 post bb2121 infusion in the context of Grade 3 tumor lysis syndrome (TLS) and Grade 1 cytokine release syndrome (CRS) has been reported. The subject experienced rapid onset of neurotoxicity associated with cerebral edema and subarachnoid hemorrhage, rising C-reactive protein associated with CRS, and mixed respiratory and metabolic acidosis, and acute kidney injury associated with TLS. Management including mechanical ventilation, hemodialysis, tocilizumab and methylprednisolone. The event was reversible with complete resolution of neurotoxicity, TLS and CRS.

Based on this case, the bb121-MM-001 protocol will be amended to include additional safety mitigation and management.

In addition, updates to the background information on the CRB-401 trial data and rationale for the proposed dose range are included and several additional corrections and clarifications are made throughout the protocol.

Significant changes included in this amendment are summarized below:

- **Rationale for study design section modified to include updated CRB-401 trial data as well as the recent Grade 4 neurotoxicity event and updated rationale for bb2121 dose.**

Data from the Phase 1 CRB-401 trial was updated to reflect a 14 July 2017 data cutoff including outcome data on 18 subjects treated at doses above 5 x 10^7 CAR+ T cells and additional MRD data on a total of 9 subjects.

One serious adverse event of reversible Grade 4 neurotoxicity associated with tumor lysis syndrome and CRS has been reported in the expansion cohort since the 14 July 2017 safety data cutoff date and is included as relevant background information.

The rationale for the selected bb2121 dose has been modified to include reference to the Grade 4 neurotoxicity event and to further justify the selected dose range of 15 to 30 x 10^7 CAR+ T cells.

Revised Section: Section 1.3.1.2 Rationale for the Study Design, Section 1.3.2 Rationale for Dose, Schedule and Regimen Selection

- **Inclusion/Exclusion criteria updated**

The exclusion criteria have been updated to exclude subjects with previous history of subarachnoid hemorrhage or other central nervous system (CNS) bleed and to exclude subjects on therapeutic anticoagulation due to the increased risk of coagulopathy and bleeding associated with CRS and neurotoxicity.

In addition, subjects with Waldenstroms, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin change) or clinically significant amyloidosis will also be excluded to enhance the homogeneity of the bb2121 treated population.

The exclusion criteria for defining adequate bone marrow function at screening is modified to absolute neutrophil count (ANC) <1000 cells/mm^3 and platelet count <50,000 mm^3, and the requirement that these counts be achieved in the absence of growth factor or transfusion support. Specific time frames are added for no prior growth factors (within 7 days of screening for filgrastim and 14 days for peg-filgrastim) and platelet transfusions (within 7 days of screening).

Revised Section: Section 4.3 Exclusion Criteria, Section 6.2.1 Lymphodepleting Chemotherapy

- **Updated overall safety monitoring plan, including required 14-day hospitalization and twice weekly visits in Weeks 3 and 4. More specific criteria for hospital discharge and re-hospitalization and updated neurotoxicity management guidelines are included.**

Additional safety data from the on-going Phase 1 trial support the following additional safety measures. Subjects treated on the MM-001 protocol must be admitted for inpatient safety monitoring with daily local safety assessments, including physical exam with neurologic exam, weight, Mini Mental State Examination (MMSE), chemistry, hematology, coagulation, and TLS/CRS laboratory assessments, from Day 0 through Day 14 post bb2121 infusion; subjects may receive bb2121 as an outpatient, and then be hospitalized following the infusion on Day 0. Additional laboratory safety assessments have also been added including: electrocardiogram (ECG) at screening and baseline and brain natriuretic peptide (BNP) at baseline to provide additional baseline assessments of cardiac function, and D-dimers as part of the coagulation panel based on recent data showing this may be a key parameter associated with neurotoxicity and coagulopathy in subjects treated with CAR T cells. Timing of MMSE assessments have been modified for consistency to every other day while an inpatient.

After Day 14, subjects must be afebrile for 24 hours, signs and symptoms of CRS and neurotoxicity must have resolved, and CRP should be declining, if elevated from baseline, or stable and not rising to consider the subject suitable for discharge to outpatient care. Once the subject is discharged, any signs of fever (≥38°C/100.4°F), signs or symptoms suggestive of CRS or neurotoxicity, will require re-hospitalization.

Two additional study visits have been added on Days 17 and 24 to provide additional monitoring for late onset CRS or neurotoxicity. Local safety assessments including physical exam with neurologic exam, weight, MMSE, chemistry, hematology, coagulation, and TLS/CRS laboratory assessments will be performed at these visits.

Management guidelines for CAR T cell toxicities have been updated, specifically providing additional guidance on monitoring, diagnostic studies and treatment guidelines for neurotoxicity based on recent publications. More specific guidance is included on corticosteroid dosing for Grade 4 neurotoxicity with cerebral edema.

Revised Sections: Protocol Summary, Section 3.1 Study Design, Section 5 Table 3 Table of Events, Section 6.1.1 Screening Evaluations, Section 6.1.3 Baseline Evaluations, Section 6.2.2 bb2121 Infusion, Section 6.3.1 Post bb2121 Infusion (Days 1 through Day 24), Section 6.4.2 Laboratory Assessments for Safety Parameters, Section 6.4.3 Cardiac Assessments, Section 7.2.2.3 bb2121 Infusion, and Appendix C

The amendment also includes several other clarifications and corrections:

- Clarified that retreated subjects will follow Table 3 starting with baseline evaluations; all subjects will be followed for survival in the current study until LSLV – Protocol Summary, Section 3.1 Study Design, Section 3.4 Figure 3 Study Schematic
- Clarified criteria for pausing or stopping the study as follows: 1) Clarified that these criteria refer to serious adverse events. 2) Removed study pausing criteria "Life threatening (Grade 4) toxicity to vital organs in 2 or more subjects". The deleted bullet would unnecessarily impose a study pause for expected hematologic toxicities following lymphodepleting chemotherapy and Grade 4 transaminitis associated with Grade 3 CRS; Criteria for pausing or stopping the study are adequately covered in the remaining two bullets addressing unexpected and unmanageable life threatening (Grade 4) toxicities not related to bridging or lymphodepleting chemotherapy and any death within 28 days. 3) Clarified that expected toxicities, including observed and potential toxicities, associated with bb2121 and/or lymphodepleting chemotherapy are described in protocol Section 10.7, Section 10.8 and the IB – Section 3.2.1 Criteria for Pausing or Stopping the Study
- Corrected the 80 subjects enrolled will be the bb2121 treated population – Section 4.1 Number of Subjects, Section 4.2 Inclusion Criteria
- Updated inclusion criterion #4 Serum M-protein ≥ 1.0 g/L (previously 0.5 g/L) and removal of "bone marrow plasma cells > 30%" as criteria for measurable disease to be consistent with the IMWG 2016 criterion; added a footnote to provide a definition of female of child bearing potential FCBP – Section 4.2 Inclusion Criteria
- Updated exclusion criterion #4 to add non-secretory myeloma is not allowed; updated exclusion #5 to clarify that total bilirubin (not direct bilirubin) > 1.5 x upper limit of normal (ULN) is the relevant exclusion (unless due to Gilbert's syndrome and direct bilirubin is ≤ 1.5 x ULN); updated exclusion criterion #16 to remove stroke (redundancy with exclusion criterion #2); updated exclusion #3 to exclude Waldenstrom's macroglobulinemia, POEMS syndrome and clinically significant amyloidosis – Section 4.3. Exclusion Criteria, Section 6.2.1 Lymphodepleting Chemotherapy
- Clarified that cytokine assessments will be performed daily on Days 1 through 6; added Day 9 vector copy number (VCN) collection to be consistent with Table 3 – Section 5 Table 3 Table of Events, Section 6.3.1 Post bb2121 Infusion (Day 1 through Day 24)
- Added an additional immunogenicity assessment prior to leukapheresis in subjects undergoing retreatment if a second leukapheresis is performed - Section 5 Table 4
- Clarified viral serology testing applicable for US and Canadian sites during screening and viral serology testing applicable for EU sites prior to leukapheresis – Section 6.1.1 Screening Evaluations, Section 6.1.2 Leukapheresis
- Modified one of the criteria for leukapheresis; removed "and at least 3 half-lives have relapsed prior to leukapheresis" as this is unrealistic for antibody therapies with prolonged half-lives– Section 6.1.2 Leukapheresis (approximately 4-5 weeks prior to planned bb2121 infusion
- Clarified that there will be no gap in AE collection between M24 and M27. Adverse Events

(AE) collection continues from M25 until end of study (EOS) – Section 5 Table 5 - Table of Events – Evaluations for Disease Progression after Month 24

- Clarified oxygen saturation no longer needs to be collected beyond the M3 study visit as this is most relevant during the early post bb2121 treatment period to monitor for CRS – Section 6.3.2 Post-bb2121 infusion (M1 through Month 24/EOS)
- Clarified AESI collection also includes CRS and macrophage activation syndrome starting at M7 – Section 6.3.2 Post-bb2121 infusion (M1 through Month 24/EOS), Section 6.3.4 Post-bb2121 Infusion (Disease Progression/CR)
- Added a new section and language to allow for autopsy sample collection at the time of death – Section 6.3.6 Assessment at Time of Death
- Added mental status as part of routine neurologic examination – Section 6.4.1 Physical Examination, Vital Signs, ECOG, Height and Weight, Routine Neurologic Examination, MMSE
- Added ECG assessment at screening and baseline, and BNP at baseline only – Section 6.4.2 Cardiac Assessments
- Updated retreatment criteria to include no history of Grade 4 CRS or neurotoxicity with prior bb2121 treatment and subject has adequate bone marrow function, to ensure subject will tolerate a 2nd infusion of bb2121 and minimize occurrence of toxicities – Section 7.2.3 Retreatment
- Added language to allow ongoing treatment with bisphosphonates for prophylaxis or treatment of myeloma bone disease – Section 8.3.3 Other Medications
- Updated the statistical section to indicate subjects screened but not eligible for enrollment will be summarized by screen failure; dosing information for LD chemotherapy will be summarized as part of the Enrolled population – Section 9.5 Disposition, Section 9.6 Study Drug Exposure
- Clarified language that from M7 until end of study, all ≥ Grade 3 AEs, SAEs and AESI will be collected – Section 10.5 Reporting Serious Adverse Events
- Added clarifying language that common side effects of fludarabine and cyclophosphamide include bone marrow cytopenias and immune suppression which increase the risk of bleeding and infection and may be exacerbated by bb2121 treatment – Section 10.8 Risks Associated with Lymphodepleting Chemotherapy
- Updated language to clarify temperature monitoring is required and will occur post hospital discharge and during waking hours – Section 10.7.3.1 Temperature Self-monitoring
- References are updated – Section 17 References and Appendix C
- Minor additional updates and clarifications are made throughout the protocol