SYNOPSIS

Closeout Clinical Study Report for Study BB2121-MM-007

TITLE OF STUDY: An exploratory Phase 1/2 trial to determine recommended phase 2 dose (RP2D), safety and preliminary efficacy of BB2121 (ide-cel) combinations in subjects with relapsed/refractory multiple myeloma (KarMMa-7)

PURPOSE: Study MM-007 was an open-label, multi-arm, multi-cohort, multicenter, phase 1/2 study to determine the safety, tolerability, efficacy, pharmacokinetics (PK) of bb2121 (idecabtagene vicleucel; hereafter referred as ide-cel) in combination with other therapies in adult subjects with RRMM.

The study consisted of 2 parts: dose finding (Phase 1) and dose expansion (Phase 2). During Phase 1, 3 different arms were planned to test ide-cel combinations. Within each arm, different doses and schedules could be tested in several cohorts and subcohorts.

During the Phase 2 part of the study, expansion of one or more combination therapies would be evaluated, using schedules and doses that were shown to be safe in Phase 1. Phase 2 was never reached; the trial was terminated based on an internal business decision by the Sponsor while the study was in Phase 1.

The study included a variety of combinations. Ultimately, only Arm A and B were opened for enrollment and details of treatments within these 2 Arms and subcohorts explored as well as the planned Arm C are as follows:

- Arm A tested ide-cel in combination with iberdomide (CC-220) (± low-dose dexamethasone). Of note, not all subcohorts in Arm A enrolled subjects as the trial was terminated.
  - Cohort 1 (≥ 3 prior anti-MM regimens)
    - **Arm A, Cohort 1a:** subjects received ide-cel infusion on D1 and iberdomide maintenance therapy starting M3D1 until PD.
  - Cohort 2 (1-3 prior anti-MM regimens)
    - **Arm A, Cohort 2a:** subjects received ide-cel infusion on D1 and iberdomide maintenance therapy starting M3D1 until PD.
    - **Arm A, Cohort 2a^{dex}:** subjects received ide-cel infusion on D1 and iberdomide and dexamethasone maintenance therapy starting M3D1 for 3 cycles (1 cycle = 28 day month). After 3 cycles, iberdomide maintenance was continued at a lower dose from M6D1 until PD.
- Arm B (≥ 3 prior anti-MM regimens) tested ide-cel in combination with BMS-986405 (JSMD194), which is a small molecule gamma secretase inhibitor (GSI) shown to efficiently block shedding of surface BCMA. Arm B was closed to further enrollment as of Protocol Amendment 2.0.
- Arm C tested ide-cel in combination with one of the following standard triplet regimens: daratumumab (DARA) in combination with pomalidomide (POM) and low-dose dexamethasone (DPd) OR pomalidomide (POM) in combination with bortezomib (BTZ) and low-dose dexamethasone (PVd). No subjects were enrolled on Arm C, and it was removed as of Protocol Amendment 2.0 due to an internal business decision.

This closeout clinical study report for study BB2121-MM-007 is presented in synoptic format, because the study was terminated based on an internal business decision made by the Sponsor during the dose finding (Phase 1) part of the study. Dose expansion (Phase 2) had not been initiated and RP2D was not determined. The decision to terminate the study was not related to any observed, expected, or perceived safety or efficacy findings in this study. The last patient, last visit (LPLV) occurred on 25-Apr-2025, with a final database lock (DBL) of 30-May-2025.

NUMBER OF SUBJECTS: Approximately 415 subjects with RRMM were planned to be enrolled, with approximately 312 subjects planned to receive the combination therapy (ide-cel + combination agents); 21 subjects were screened and underwent leukapheresis. Of the 21 subjects, 17 were treated with ide-cel. This study was terminated based on an internal decision by the Sponsor. The decision to terminate the study was not related to any observed, expected, or perceived safety or efficacy findings in this study.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

A total of 21 subjects were enrolled in the study. Of the enrolled subjects, 17 (81%) received ide-cel infusion. Participants were treated with ide-cel across 2 arms (Arms A and B) and within Arm A, in 3 subcohorts (Cohorts 1a, 2a, 2a^{dex}). A majority (16 [76.2%] subjects) discontinued treatment (Table 1); the most common reason for discontinuation was progressive disease. The median age of subjects in the enrolled population (N=21) was 62.0 years (range: 41, 74) and more than half (61.9%) of these subjects were < 65 years of age. Most subjects enrolled in the study were male (61.9%). The presence of bone lesions and extramedullary soft-tissue plasmacytomas at screening were seen in 13 (61.9%) and 9 (42.9%) subjects, respectively.

Table 1: Subject Disposition - Enrolled Population

	Arm A			Arm B (N=1)	Total (N=21)[a]
	Cohort 1a (N=12)	Cohort 2a (N=2)	Cohort 2a^{dex} (N=2)		
Ongoing Treatment[b]	0	0	0	0	0
Completed Treatment[b] - n (%)	1 (8.3)	0	0	0	1 (4.8)
Discontinued Treatment[b] - n (%)	11 (91.7)	2 (100)	2 (100)	1 (100)	16 (76.2)
Reason for Discontinuation of Treatment[b]					
Completed	0	0	0	0	0
Death	0	0	0	1 (100)	1 (4.8)
Adverse Event	3 (25.0)	0	1 (50.0)	0	4 (19.0)
Progressive Disease	3 (25.0)	2 (100)	1 (50.0)	0	6 (28.6)
Physician Decision	2 (16.7)	0	0	0	2 (9.5)
Other	3 (25.0)	0	0	0	3 (14.3)
Ongoing Study	0	0	0	0	0
Discontinued Study	7 (58.3)	1 (50.0)	2 (100)	1 (100)	11 (52.4)
Reason for Discontinuation of Study					
Death	5 (41.7)	0	1 (50.0)	1 (100)	7 (33.3)
Study Terminated By Sponsor	0	1 (50.0)	0	0	1 (4.8)
Withdrawal By Subject	2 (16.7)	0	1 (50.0)	0	3 (14.3)
Bb2121 Discontinued Due to Adverse Event	0	0	0	0	0
Not Treated Subjects[a]	0	0	0	0	4 (19.0)
Reason for Not Treated					
Adverse Event	0	0	0	0	1 (4.8)
Death	0	0	0	0	2 (9.5)

Table 1: Subject Disposition - Enrolled Population

	Arm A			Arm B (N=1)	Total (N=21)[a]
	Cohort 1a (N=12)	Cohort 2a (N=2)	Cohort 2a^{dex} (N=2)		
Failure to Meet Treatment Criteria	0	0	0	0	1 (4.8)

Note: Survival follow-up is 15 months post bb2121 infusion. Subjects classified as 'Not treated' were enrolled in the study but did not receive any infusion.

[a] Of the 21 enrolled subjects, 4 subjects were not treated for the following reasons: 2 subjects died (progressive disease and abdominal pain), 1 subject experienced AEs (Grade 3 diplopia, Grade 2 invasive fungal infection, Grade 2 bacterial infection), and 1 subject failed to meet treatment criteria at pre-treatment.

[b] Treatment refers to both ide-cel infusion + combination agent

SUMMARY OF SAFETY RESULTS:

The primary objective of Study BB2121-MM-007 was to evaluate the safety and to determine the RP2D and schedule of combination agents administered with ide-cel in subjects with relapsed/refractory multiple myeloma (RRMM).

The overall safety profile of ide-cel in the Study BB2121-MM-007 population was consistent with the known safety profile of ide-cel. No new safety concerns or new clinically relevant types of AEs were reported. Due to limited number of subjects enrolled in the trial, the summary of safety results provided below includes all subjects treated in the trial across Arms A and B.

- In the DLT evaluable population, 1 subject in Arm B experienced 2 dose-limiting toxicities (DLTs) (Grade 3 neurotoxicity that progressed to Grade 4 and a Grade 3 cytokine release syndrome [CRS] that progressed to a maximum grade of Grade 5). One subject in Arm A, Cohort 1a who experienced Grade 3 septic shock but did not receive 75% of the planned dose of iberdomide and was not considered DLT evaluable. No other subjects experienced DLTs.
- On or after ide-cel infusion, any grade AEs and Grade 3 or 4 AEs were reported in all subjects (Table 2).
- On or after combination therapy , any grade AEs were reported in all subjects. Grade 3 or 4 AEs were reported in 11 (91.7%) subjects (Table 2).
- On or after ide-cel infusion, any grade SAE were reported in 13 (76.5%) subjects, and 10 (58.8%) subjects reported with Grade 3 or 4 SAEs (Table 2).
- On or after combination therapy, any grade SAE were reported in 8 (66.7%) subjects, and 7 (58.3%) subjects reported with Grade 3 or 4 SAEs (Table 2).
- On or after ide-cel infusion, any grade AESI and Grade 3 or 4 AESI were reported in all subjects. (Table 2).
- In the treated population, 12 (70.6%) subjects experienced at least 1 CRS event (Table 3). The median time to first onset was 1.5 days (range 1-3 days) post ide-cel infusion and median duration was 2.0 days (range 1-10 days). Eleven (64.7%) subjects received tocilizumab and one (5.9%) subject received steroids for treatment.
- In the treated population, 3 (17.6%) subjects experienced at least 1 iiNT event (Table 3). The iiNT events were of varying grades (Grade 1, Grade 2, and Grade 4), with similar onset time (Days 6 - 8 post ide-cel infusion) and duration (2 resolved in under 5 days, while 1 remained unresolved).
- There were 7 deaths within the treated population with 1 occurring within 30 days of ide-cel infusion. The other 6 deaths occurred ≥ 30 days after ide-cel infusion (range: 58 days to 519 days post ide-cel infusion).

Table 2: Overall Summary of Safety - Ide-cel Treated Population

Categories	On/after ide-cel infusion - Treated population					On/after Combination treatment - Combination Treated population				
	Arm A			Arm B	Total	Arm A			Arm B	Total
	Cohort 1a (N=12) n (%)	Cohort 2a (N=2) n (%)	Cohort 2a^{dex} (N=2) n (%)	(N=1) n (%)	(N=17) n (%)	Cohort 1a (N=7) n (%)	Cohort 2a (N=2) n (%)	Cohort 2a^{dex} (N=2) n (%)	(N=1) n (%)	(N=12) n (%)
Any Grade AE[a]	12 (100)	2 (100)	2 (100)	1 (100)	17 (100)	7 (100)	2 (100)	2 (100)	1 (100)	12 (100)
Grade 3 or 4 AE	12 (100)	2 (100)	2 (100)	1 (100)	17 (100)	7 (100)	1 (50.0)	2 (100)	1 (100)	11 (91.7)
SAEs[a]	10 (83.3)	1 (50.0)	1 (50.0)	1 (100)	13 (76.5)	5 (71.4)	1 (50.0)	1 (50.0)	1 (100)	8 (66.7)
Grade 3 or 4 SAE	8 (66.7)	1 (50.0)	0	1 (100)	10 (58.8)	5 (71.4)	1 (50.0)	0	1 (100)	7 (58.3)
AESI/selected AEs[b]	12 (100)	2 (100)	2 (100)	1 (100)	17 (100)	-	-	-	-	-
Grade 3 or 4 AESI/Selected AE	12 (100)	2 (100)	2 (100)	1 (100)	17 (100)	7 (100)	1 (50.0)	2 (100)	1 (100)	11 (91.7)

[a] Coded using MedDRA version 27.1. A subject is counted only once for multiple events within preferred term/system organ class.

[b] AESI/Selected AEs categories used either MedDRA v27.1 SMQ or sub-SMQ or SOC or HLT or list of preferred terms. A subject is counted only once for multiple events within each AESI category.

Table 3: Summary of Cytokine Release Syndrome - Ide-cel Treated Population

	Arm A			Arm B	Overall
	Cohort 1a (N=12)	Cohort 2a (N=2)	Cohort 2a^{dex} (N=2)	(N=1)	(N=17)
Subjects with ≥ 1 CRS event - n (%)	9 (75.0)	1 (50.0)	1 (50.0)	1 (100)	12 (70.6)
Maximum Reported CRS Grade - n (%)					
1	8 (66.7)	1 (50.0)	1 (50.0)	0	10 (58.8)
2	1 (8.3)	0	0	0	1 (5.9)
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	1 (100)	1 (5.9)
Time to first onset of events (days)[a]					
n	9	1	1	1	12
Median (min, max)	1.0 (1, 3)	2.0 (2, 2)	2.0 (2, 2)	1.0 (1, 1)	1.5 (1, 3)
Total number of events, n	9	1	1	1	12
Number of events by length of duration (days), n (%)					
1-5	9 (100)	1 (100)	1 (100)	0	11 (91.7)
6-10	0	0	0	1 (100)	1 (8.3)
>10	0	0	0	0	0
Ongoing[b]	0	0	0	0	0
Duration per event (days)[c]					
Median (min, max)	2.0 (1, 4)	1.0 (1, 1)	2.0 (2, 2)	10.0 (10,10)	2.0 (1, 10)
Number of subjects received tocilizumab - n (%)	8 (66.7)	1 (50.0)	1 (50.0)	1 (100)	11 (64.7)
Number of subjects received siltuximab - n (%)	0	0	0	1 (100)	1 (5.9)
Number of subjects received anakinra - n (%)	0	0	0	1 (100)	1 (5.9)
Number of subjects received steroids - n (%)	1 (8.3)	0	0	1 (100)	2 (11.8)
Number of subjects with CRS symptoms any Grade - n (%)	9 (75.0)	1 (50.0)	1 (50.0)	1 (100)	12 (70.6)
Pyrexia	9 (75.0)	1 (50.0)	1 (50.0)	1 (100)	12 (70.6)

Table 3: Summary of Cytokine Release Syndrome - Ide-cel Treated Population

	Arm A			Arm B (N=1)	Overall (N=17)
	Cohort 1a (N=12)	Cohort 2a (N=2)	Cohort 2a[dex] (N=2)		
Hypotension	2 (16.7)	0	0	1 (100)	3 (17.6)
Aspartate aminotransferase increased	1 (8.3)	0	0	1 (100)	2 (11.8)
Tachycardia	1 (8.3)	0	0	1 (100)	2 (11.8)
Acute kidney injury	0	0	0	1 (100)	1 (5.9)
Alanine aminotransferase increased	0	0	0	1 (100)	1 (5.9)
Asthenia	0	0	0	1 (100)	1 (5.9)
C-reactive protein increased	1 (8.3)	0	0	0	1 (5.9)
Chills	1 (8.3)	0	0	0	1 (5.9)
Circulatory collapse	0	0	0	1 (100)	1 (5.9)
Gamma-glutamyltransferase increased	0	0	0	1 (100)	1 (5.9)
Hypoxia	0	0	0	1 (100)	1 (5.9)
Oxygen saturation decreased	0	0	0	1 (100)	1 (5.9)
Number of Subjects with CRS Symptoms Grade 3 and 4 n (%)	1 (8.3)	0	0	1 (100)	2 (11.8)
Acute kidney injury	0	0	0	1 (100)	1 (5.9)
Circulatory collapse	0	0	0	1 (100)	1 (5.9)
Gamma-glutamyltransferase increased	0	0	0	1 (100)	1 (5.9)
Hypotension	1 (8.3)	0	0	0	1 (5.9)
Hypoxia	0	0	0	1 (100)	1 (5.9)
Oxygen saturation decreased	0	0	0	1 (100)	1 (5.9)

[a] Time to first onset of CRS: first start date of CRS - bb2121 infusion date + 1

[b] Ongoing CRS was excluded from calculation of duration of CRS.

[c] Algorithm for duration: if gap between two events ≤ 1 day, then these two events were considered as one event regardless grade change, drug relationship change or severity change.

Table 4: Summary of Investigator-Identified Neurotoxicity - Ide-cel Treated Population

	Arm A			Arm B (N=1)	Overall (N=17)
	Cohort 1a (N=12)	Cohort 2a (N=2)	Cohort 2a^{dex} (N=2)		
Subjects with ≥ 1 iiNT event - n (%)	2 (16.7)	0	0	1 (100)	3 (17.6)
Maximum Reported iiNT Grade - n (%)					
1	1 (8.3)	0	0	0	1 (5.9)
2	1 (8.3)	0	0	0	1 (5.9)
3	0	0	0	0	0
4	0	0	0	1 (100)	1 (5.9)
5	0	0	0	0	0
Time to first onset of events (days)[a]					
n	2	0	0	1	3
Median (min, max)	5.5 (5, 6)	-	-	7.0 (7, 7)	6.0 (5, 7)
Total number of events, n	2	0	0	1	3
Number of events by length of duration (days), n (%)					
1-5	2 (100)	0	0	0	2 (66.7)
6-10	0	0	0	0	0
>10	0	0	0	0	0
Ongoing[b]	0	0	0	1 (100)	1 (33.3)
Duration of iiNT per event (days)[c]					
Median (min, max)	1.5 (1, 2)	-	-	-	1.5 (1, 2)
Number of subjects received tocilizumab - n (%)	0	0	0	0	0
Number of subjects received siltuximab - n (%)	0	0	0	0	0
Number of subjects received anakinra - n (%)	0	0	0	0	0
Number of subjects received steroids - n (%)	0	0	0	0	0
Number of subjects with iiNT symptoms any Grade - n (%)	2 (16.7)	0	0	1 (100)	3 (17.6)

Table 4: Summary of Investigator-Identified Neurotoxicity - Ide-cel Treated Population

	Arm A			Arm B (N=1)	Overall (N=17)
	Cohort 1a (N=12)	Cohort 2a (N=2)	Cohort 2a[dex] (N=2)		
Depressed level of consciousness	1 (8.3)	0	0	1 (100)	2 (11.8)
Aphasia	1 (8.3)	0	0	0	1 (5.9)
Mobility decreased	0	0	0	1 (100)	1 (5.9)
Neurotoxicity	0	0	0	1 (100)	1 (5.9)
Unresponsive to stimuli	0	0	0	1 (100)	1 (5.9)
Number of Subjects with iiNT Symptoms Grade 3 and 4[d] n (%)	0	0	0	1 (100)	1 (5.9)
Depressed level of consciousness	0	0	0	1 (100)	1 (5.9)
Mobility decreased	0	0	0	1 (100)	1 (5.9)
Neurotoxicity	0	0	0	1 (100)	1 (5.9)
Unresponsive to stimuli	0	0	0	1 (100)	1 (5.9)

[a] Time to first onset of iiNT: first start date of iiNT - bb2121 infusion date + 1

[b] Ongoing iiNT was excluded from calculation of duration of iiNT.

[c] Algorithm for duration: if gap between two events ≤ 1 day, then these two events were considered as one event regardless grade change, drug relationship change or severity change.

[d] Subject may have signs or symptoms without meeting the MedDRA criteria for diagnosis.

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