EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2021
EMA/409800/20212021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abecma

International non-proprietary name: idecabtagene vicleucel

Procedure No. EMEA/H/C/004662/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ADA	Antidrug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AMT	Antimyeloma therapy
AR	Assessment report
ASCT	Autologous stem cell transplant
AUC0-28days	Area under the curve of the transgene level from time of dose to 28 days postinfusion
bb2121	Idecabtagene vicleucel; ide-cel
BCMA	B-cell maturation antigen
BM	Bone marrow
B/R	Benefit/risk
CAR	Chimeric antigen receptor
CAR T	Chimeric antigen receptor-modified T (cells)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum transgene level or peak concentration, depending on context
CNS	Central nervous system
CR	Complete response
CRP	C-reactive protein
CRR	Complete response rate
CRS	Cytokine release syndrome
CSF	Colony-stimulating factor
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Cy	Cyclophosphamide
DCO	Data cut-off
DMSO	Dimethyl sulfoxide
DoR	Duration of response
EE	Efficacy evaluable

ECOG	Eastern Cooperative Oncology Group
ESS	Effective sample size
EMA	European Medicines Agency
EMP	Extramedullary plasmacytoma
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life-5 Dimensions health state classifier to 5 levels
ER	Exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FLC	Free light chain
Flu	Fludarabine
GCP	Good clinical practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICF	Informed consent form
Ide-cel	Idecabtagene vicleucel
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
INR	International normalized ratio
IPTW	Inverse probability of treatment weights
IRC	Independent Response Committee
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan–Meier
LDC	Lymphodepleting chemotherapy
LTFU	Long term follow-up
LVV	Lentiviral vector
MA	Marketing authorisation
MAA	Marketing authorisation application

mAB	Monoclonal antibody
MAIC	Matching-adjusted indirect comparisons
MM	Multiple myeloma
MR	Minimal response
MRD	Minimal residual disease
MTD	Maximum tolerated dose
NE	Not estimable
NGS	Next generation sequencing
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
Pd	Pomalidomide and dexamethasone
PD	Pharmacodynamic
PD	Progressive disease
PFS	Progression-free survival
PI	Proteasome inhibitor
PIP	Paediatric investigation plan
PK	Pharmacokinetic
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	Partial response
PRIME	Priority medicines
PRO	Patient reported outcome
PS	Performance status
PS	Propensity score
PTT	Partial thromboplastin time
QoL	Quality of life
RCT	Randomised controlled trial
R-ISS	Revised international staging system
RP2D	Recommended Phase 2 dose
RRMM	Relapsed and refractory multiple myeloma
RW	Real-world
RWS	Real-world study

sBCMA	Soluble B-cell maturation antigen
sCR	Stringent complete response
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SLR	Systematic literature review
SRC	Safety review committee
T0	Timepoint when patients met the criteria of progression
TTP	Time to progression
TTR	Time to response
ULN	Upper limit normal
US	United states
VGPR	Very good partial response

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celgene Europe BV submitted on 30 April 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Abecma, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 9 November 2017.

Abecma, was designated as an orphan medicinal product EU/3/17/1863 on 20 April 2017 in the following condition: treatment of multiple myeloma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Abecma as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/abecma.

Abecma was granted eligibility to PRIME on 10 November 2017 in the following indication: treatment of relapsed and refractory multiple myeloma.

Eligibility to PRIME was granted at the time in view of the following:

Based on the claims, the justification for such claims and the description of the available data provided by the applicant, the CHMP is of the view that:

- Despite available treatments, there is still a need for new options in the intended initial indication for the treatment of relapsed and refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody. The unmet medical need is agreed.
- *In vitro* studies were conducted using human tumour cell lines, primary cells, and tumour biopsies to demonstrate BCMA (target) expression, bb2121 anti-BCMA CAR (effector) expression, specificity, activity, and potency, as well as CAR-to-target binding. *In vivo* studies used animal models of human MM using immunodeficient mice with human tumour cell line xenografts. Overall, data suggest potential therapeutic activity and are supportive of the proof of principle.
- The applicant provided data from Study CRB-401, an ongoing non-randomised, open-label, phase 1 study and particularly, data from the dose escalation part of the study. The subjects enrolled in Study CRB-401were heavily pre-treated including 71.4% of patients who received prior daratumumab in addition to PI and IMID.
- Preliminary results show a high overall response rate (ORR), across all dose cohorts of 86% (18/21). This includes several patients with CR, sCR, VGPR and PR that had been previously treated with PI, IMID and daratumumab.
- Although follow-up is limited in some patients, responses appear durable, with median DOR for 15 subjects treated with >50 x 106 CAR+ T cells with at least 3 months follow-up not yet reached (range of follow-up: 4.3-14.9 months).
- Overall, the high ORR reported suggest the product has the potential to bring a major therapeutic advantage to relapsed/refractory MM patients that have received prior lines of therapies included IMID, PI and daratumumab.

Access to support through the PRIME scheme was therefore confirmed.

The applicant applied for the following indication: *Abecma is indicated for the treatment of adult*

patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that idecabtagene vicleucel was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0387/2019 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's requests for consideration

Conditional marketing authorisation and Accelerated assessment

The Applicant applied for a full marketing authorisation, but during the assessment, in response to CAT and CHMP concerns on the comprehensiveness of the data, requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance idecabtagene vicleucel contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union

Scientific recommendation on Classification

The developer, Bluebird bio France, submitted on 17 August 2017 an application for Scientific recommendation on Classification to the European Medicines Agency (EMA) for Abecma, which was designated as an Advanced Therapy Medicinal Product in accordance with Regulation (EC) No 1394/2007 on 13 October 2016. Abecma was classified as a gene therapy medicinal product.

PRIME support

Upon granting of eligibility to PRIME, Helga Haugom Olsen was appointed by the CHMP as rapporteur. Subsequently the Rapporteur was changed to Rune Kjeken.

A kick-off meeting was held on 14 March 2018. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

- The Rapporteur and EMA confirmed that Vector Copy Number (VCN) was a topic of ongoing discussion with CAR T therapies and encouraged the Applicant to seek Scientific Advice on this topic.
- Comparability package and justification for not including clinical data using the commercial LVV and drug product manufacturing sites in the pivotal study would need justification and recommendation for seeking Scientific Advice on the proposed approach was given
- Pivotal study: the applicant was suggested to further explore aspects of the MAA package and the use of external controls as follow:
    - The Rapporteur and EMA stated that a follow-up of 9-12 months may be more appropriate to assess longer term outcome data such as PFS and durability of response.
    - The Rapporteur had concerns that the proposed population of BB2121-MM-001 had not exhausted all treatment options as patients were not specifically required to have received various marketed regimens available in the EU. The Applicant will need to justify this at the time of the MAA.
    - the Rapporteur and EMA had concerns around the Applicant's intention to provide a literature review summary but not an external control containing patient level data. This approach not to include an external control may result in difficulties quantifying the magnitude of the benefit. Specifically, how the activity of bb2121 in the post-daratumumab patient population would compare to established MM treatment regimens in this setting may be challenging to demonstrate. Scientific Advice was recommended on this topic.
    - The Applicant acknowledged that DPd is not a currently approved regimen in the EU and explained that Scientific Advice on this study was not currently considered. The Rapporteur acknowledged this position and recommended that Scientific Advice be sought for the study, especially due to the choice of comparator arm given the multiple regimens available for the treatment of multiple myeloma in the EU. A more appropriate choice of comparator may be to allow a limited number of options (investigator's choice).
    - Due to the number of products approved, the Applicant was advised to consider an external control group for demonstration of significant benefit as lack of control arm poses a challenge with establishment of significant clinical benefit based on a single arm trial. The Applicant highlighted that this presents a difficulty in a post daratumumab population due to the current lack of data and obtaining this through retrospective literature review or prospective collection in a registry is not without challenges and limitations. One option may be to compare the clinical outcome of the treatment regimen received immediately prior to bb2121 in the MM-001 trial to the patient's response to bb2121. It was acknowledged that this approach had been acceptable for other MAAs although the EMA/Rapporteur were not able confirm whether this would be suitable in this specific case. Protocol Assistance on the topic of demonstrating Significant Benefit was advised.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
20 July 2017	EMA/CHMP/SAWP/431939/2017	*Dr Mair Powell, Dr Rune Kjeken*
26 April 2018	EMA/CHMP/SAWP/230494/2018	*Dr Odoardo Olimpieri, Dr Rune Kjeken*
28 February 2019	EMA/CHMP/SAWP/129829/2019	*Dr Paolo Foggi, Dr Rune Kjeken*
28 March 2019	EMA/CHMP/SAWP/175764/2019	*Prof. Flora Musuamba Tshinanu, Dr Olli Tenhunen*
27 June 2019	EMA/CHMP/SAWP/339654/2019	*Dr Rune Kjeken, Dr Olli Tenhunen*

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Proposed release and stability specifications, including the proposed tests for potency, sterility, mycoplasma and replication-competent lentivirus, and the comparability strategy to support manufacturing changes during development;
- The new commercial and clinical facility that is being constructed for bb2121; the process qualification of process validation for bb2121 drug product; the viral risk management strategy for human AB serum raw material;
- The strategy to demonstrate comparability between bb2121 pivotal trial lots and commercial bb2121 lots for MAA (analytical comparability assessment for the lentiviral vector and for the bb2121 drug product); the adequacy of the functional potency assay (IFNγ) to support release of the commercial LVV; the need to test for replication competent lentivirus (RCL) at bb2121 commercial drug product release.
- Non-clinical programme to support registration in subjects with RRMM;
- Study design and study population of the proposed Phase 2 registration study, bb2121-MM-001, to support registration in subjects with RRMM;
- The clinical pharmacology package, in particular the non-compartmental pharmacokinetic (PK) analyses for the clinical study reports (CSR) and the planned PK characterisation and exposure-response (ER) analyses to support a Marketing Authorisation Application.
- the adequacy of the *in vitro* characterisation data package to be included in the MAA for the assessment of the risk of insertional mutagenesis leading to oncogenesis.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

CAT Rapporteur: Rune Kjeken

CAT Co-Rapporteur: Olli Tenhunen/Heli Suila

CHMP Coordinator (Rapporteur): Bjørg Bolstad

CHMP Coordinator (Co-Rapporteur): Johanna Lähteenvuo

The application was received by the EMA on	30 April 2020
Accelerated Assessment procedure was agreed-upon by CAT and CHMP on	26 March 2020
The procedure started on	21 May 2020
The Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	11 August 2020
The Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	10 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CAT/CHMP during the meeting on	04 September 2020
The CAT agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	11 September 2020
The applicant submitted the responses to the CAT consolidated List of Questions on	04 November 2020
The Rapporteurs circulated the CAT/PRAC Joint Assessment Report on the responses to the List of Questions to all CAT and CHMP members on	20 November 2020
The CAT agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on In this occasion the accelerated procedure was reverted to the standard Timetable	04 December 2020
The applicant submitted the responses to the CAT List of Outstanding Issues on	20 January 2021
The Rapporteurs circulated the CAT/PRAC Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	04 February 2021
The CAT agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 February 2021
The following GMP inspection were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at Celgene corporation, 556 Morris Avenue, Summit, New Jersey, NJ 07901 United States has been conducted	04 May 2021

16th April 2021. The outcome of the inspection carried out was issued on.	
The applicant submitted the responses to the CAT List of Outstanding Issues on	19 May 2021
The Rapporteurs circulated the CAT/PRAC Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	03 June 2021
The CAT and CHMP adopted a report on similarity of Abecma against Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro and Blenrep on	18 June 2021
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Abecma on	18 June 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Abecma on	24 June 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The present application concerns the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

2.1.2. Epidemiology

Multiple myeloma (MM) accounts for about 10% to 18% of hematologic malignancies (Moreau, 2017) and primarily affects older individuals (Howlader, 2019). In Europe, the median age at onset of MM is 72 years (Moreau, 2017). MM is very rare in patients younger than 40 years old (Howlader, 2019). Overall, the estimated prevalence of MM in the EU in 2018 ranged from 1.79 to 3.61 in 10,000 persons. In Europe, 48,297 new cases of MM and 30,860 deaths due to MM were estimated in 2018 (International Agency for Research on Cancer [IARC], 2019). The course of MM is characterised by a period of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapy (Moreau, 2017). According to CancerMPact®, approximately 27% of patients in Western Europe who have received 3 prior lines of antimyeloma therapy (AMT) will receive a fourth line of systemic AMT (Kantar, 2019).

2.1.3. Biologic features, aetiology and pathogenesis

Multiple myeloma (MM) is an incurable blood cancer characterised by the clonal proliferation of malignant plasma cells both within the bone marrow (BM) and at localised extramedullary sites termed plasmacytomas. B-cell maturation antigen (BCMA) was selected as a therapeutic target, because BCMA is consistently expressed on plasma cells and myeloma cells from patients with MM, where the expression of BCMA is thought to support tumour cell survival in the BM niche (Carpenter, 2013). Normal, nonhematopoietic tissues do not express BCMA (Carpenter, 2013). In contrast, benign and malignant plasma cells contain high levels of BCMA messenger ribonucleic acid, and concentrations of soluble BCMA (sBCMA) within serum correlate with disease status (ie, disease burden), response to therapy, and overall survival (OS) (Sanchez, 2012).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

In MM, the malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein (M-protein) in the serum and urine and may result in BM failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcaemia, bone pain, and pathologic fractures (Munshi, 2012).

The criteria for diagnosis of MM as defined by the International Myeloma Working Group (IMWG), requires 10% clonal BM plasma cells or biopsy proven bony or extra-medullary plasmacytoma and evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, or biomarkers of malignancy (60% clonal BM plasma cells or involved/uninvolved serum-free light chain ratio >100 or > 1 focal lesion on magnetic resonance imaging studies).

The Revised International Staging System (R-ISS) is a widely accepted classification used for prognostic evaluation. It relies on the combination of serum levels of b2-microglobulin and albumin, cytogenetics by fluorescence in situ hybridisation and lactate dehydrogenase.

Despite progress in its current treatment and management, MM remains incurable. Although autologous stem cell transplant (ASCT) has extended survival in newly diagnosed MM, practically all patients eventually relapse. Historical data report an OS of 8 to 13 months in studies of relapsed/refractory MM patients who received $\geq$ 3 prior lines of therapy and were refractory to an immunomodulatory agent and a proteasome inhibitor (PI) (Kumar, 2017).

2.1.5. Management

Many factors influence the choice of therapy in the relapsed/refractory MM setting, including age, performance status (PS), comorbidities, the type, efficacy, and tolerability of the prior AMT, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (clinical versus biochemical) (Moreau, 2017).

The treatment landscape for relapsed/refractory MM has changed in recent years. Since the beginning of 2015, 8 relapsed/refractory MM indications (all for regimens evaluated in second or third line) have been approved for 6 products (including panobinostat, carfilzomib, ixazomib, daratumumab, pomalidomide, and elotuzumab) through the centralised procedure. In addition, two marketing authorisations have recently been granted one for Blenrep and one for Nexpovio both in the 5th line RRMM indication.

For relapsed/refractory MM patients with second or subsequent relapses, European Society for Medical Oncology (ESMO)-recommended options are a triplet regimen based on a backbone of pomalidomide

and dexamethasone (Pd) (plus bortezomib, cyclophosphamide, daratumumab, elotuzumab, or ixazomib), daratumumab (single agent or in combination), or enrolment in a clinical trial. For relapsed/refractory MM patients who cannot be considered for initiation of treatment with a 3-drug regimen, a 2-drug regimen, with a third drug added once performance improves, may be an option (NCCN-MM, 2020).

As most patients receive frontline therapy with a backbone of an immunomodulatory agent and/or a PI, the development of disease that is refractory to both of these classes represents a major therapeutic challenge. Furthermore, the progressive incorporation of daratumumab-based therapy, has led to a subset of patients being exposed to these 3 AMT classes. Relapsed/refractory MM, particularly in patients exposed to multiple prior AMTs, those exposed to an anti-CD38 antibody, or those refractory to major classes of AMT, is life threatening and is associated with low response rates, short duration of response (DoR), and poor survival. Thus, there is an unmet medical need for more treatment options capable of achieving deep and durable responses that afford the opportunity for treatment-free intervals and improved quality of life (QoL) for patients with relapsed/refractory MM who have received $\geq$ 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody.

About the product

Idecabtagene vicleucel (ide-cel) is a gene therapy product consisting of modified autologous T cells transduced with an anti-BCMA02 chimeric antigen receptor (CAR) lentiviral vector (LVV). The autologous T cells transduced ex vivo with the anti-BCMA02 CAR LVV express the anti-BCMA CAR on the T cell surface. Antigen-specific activation of ide-cel results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Ide-cel is provided as a single dose for intravenous (IV) infusion containing a dispersion of CAR+ T cells in one or more infusion bags. The proposed target dose is 420 x 10^6 anti-BCMA CAR+ viable T cells, within a range of 260 to 500 x 10^6 anti-BCMA CAR+ viable T cells.

The development programme/compliance with CHMP guidance/scientific advice

The clinical development programme for ide-cel consists of one Phase 1 dose-finding study (CRB-401), three ongoing, uncontrolled Phase 2 studies (MM-001, MM-001 - Japan and MM-002), one Phase 3 randomised controlled trial (RCT) (MM-003) and two long-term safety follow up studies (GC-LTFU-001 and LTF-305).

The primary data for this marketing authorisation application come from the Phase 2 study, MM-001. Supportive efficacy data are provided from Study CRB-401. In the remaining ongoing studies (MM-001-Japan, MM-002, and MM-003) a small number of subjects with limited follow-up time have been treated with ide-cel. These studies provide supportive data for the safety assessment only.

Ide-cel has been the subject of one prime kick-off meeting (March 2018), four scientific advices concerning quality and two scientific advices concerning the clinical efficacy of the product development.

The applicant did not amend the clinical development programme based on the concerns raised over the single arm trial approach and the limited duration of follow up. Furthermore, advice concerning the use of the ITT population as the primary efficacy population was not followed. However, results for both the enrolled (ITT) and infused (mITT) analyses set were generally presented in the marketing authorisation application (MAA).

Type of Application and aspects on development

Accelerated Assessment

The CHMP and CAT agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the fact that currently patients with relapse/refractory multiple myeloma have only limited treatment options with insufficient clinical outcome. An unmet medical need was substantiated by the applicant and was acknowledged. Data were presented to support that Ide-cell may address that unmet need. Though limited clinical data were submitted in support of the accelerated assessment request, the promising ORR and CR rate observed, and the possibility for long-term disease control suggested that Ide-cell might indeed represent a major therapeutic advantage over existing therapies. As such Ide-cell was considered to be of major interest from the point of view of public health. However, during the assessment a GMP inspection and provision of a GMP certificate were considered necessary which did not allow maintenance of the accelerated assessment timetable.

Conditional Marketing Authorisation

In light of the concerns raised during assessment on the comprehensiveness of the data set, the applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive in a patient population consistent with the MM-001 study population.
- It is likely that the applicant will be able to provide comprehensive data. In the ongoing randomised study (MM-003), ide-cel is compared to SOC triplet regimens in an overlapping patient population i.e. relapsed and refractory MM with 2-4 prior therapies and this study is considered to be suitable as a specific obligation to the MA. As of 06 Jan 2021, 261 subjects have been randomised, and patient enrolment is currently targeted to be completed by Q2 2021. Thus, a CMA granted in 2021 would most probably not interfere with the completion of this phase 3 study and data can be expected to be available within an appropriate timeframe. The data from study MM003 are estimated to be received by Q2 2023. In addition, updated efficacy and safety data (24 months after the last subject has received ide-cel) from the ongoing Study BB2121-MM-001 will be provided as a SOB to the CMA. These data will be provided by December 2021
- Unmet medical needs will be addressed, as Abecma would provide a new treatment option with a new MoA for these patients. In patients who have received at least 3 prior therapies and are refractory to at least one immunomodulatory drug, one proteasome inhibitor, and one anti-CD-38 antibody, and whose disease has progressed on the last therapy, available treatment options offer limited clinical benefit, and the unmet medical need can be agreed. In the setting where patients are not triple refractory, the greater availability and efficacy of SOC treatment options introduces higher uncertainty as to the true magnitude of the effect. Nevertheless, the response rates achieved with ide-cel in this less refractory population seem compelling. In addition ide-cel may provide a major contribution to patient care, acting through a different mechanism of action and thus providing a treatment alternative addressing the unmet need. More comprehensive and robust data in patients with less advanced disease (Study MM-003) will be a part of the obligations for the CMA.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Ide-cel has a unique mechanism of action leveraging the

patient's modified T cells to kill myeloma cells targeting a uniformly expressed plasma cell antigen. To date, there is no approved BCMA-targeting CAR T cell therapy available for the treatment of patients with relapsed and refractory MM. In addition, ide-cel as a 1-time therapy offers the opportunity for treatment-free intervals and improved quality of life as the need for frequent visits is reduced compared with standard treatments given continuously.
The clinically meaningful efficacy observed including frequent, deep, and durable clinical responses together with a manageable and well-characterised safety profile, confirm the positive benefit-risk assessment for ide-cel, which, represents a major therapeutic advantage. This positive benefit-risk assessment supports the fact that the immediate availability of ide-cel to MM patients in need of alternative AMTs outweighs the risks related to the requirement for additional confirmatory data.

2.2. Quality aspects

2.2.1. Introduction

Abecma (Idecabtagene vicleucel (ide-cel, bb2121)) is a genetically modified autologous T cell immunotherapy product consisting of T cells transduced with an anti-BCMA chimeric antigen receptor (CAR) lentiviral vector (LVV). The autologous T cells transduced *ex vivo* with the anti-BCMA CAR LVV to express the anti-BCMA CAR on the T cell surface. The B cell maturation antigen (BCMA) is a transmembrane protein selectively expressed in both normal and malignant plasma cells and blasts. Binding of ide-cel to BCMA-expressing target cells results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Ide-cel finished product (FP) is formulated as a single dose cell suspension (dispersion for infusion) for intravenous administration contained in ethylene vinyl acetate (EVA) cryopreservation bag(s).

The finished product is formulated and cryopreserved in a solution containing Plasma-Lyte A (sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, water for injections) and CryoStor CS10, resulting in a final dimethyl sulfoxide (DMSO) concentration of 5%.

A single dose of ide-cel contains a cell suspension of 260 to 500 x 10^6 CAR+ viable T cells in one or more infusion bags of the same size and fill. The quantitative information regarding CAR+ T cells/mL and volume are presented in the release for infusion certificate accompanying the final product.

2.2.2. Active Substance

Idecabtagene vicleucel (ide-cel, bb2121) is produced from leukapheresis material obtained from individual patients, and therefore the product is unique to each patient. The patient's T cells are engineered *ex vivo* to express the anti-BCMA CAR on the T cell surface.

The section on the active substance is separated into two parts; part 1 for the anti-BCMA02 CAR lentiviral vector (LVV) and part 2 for the transduced cells resulting in the active substance Idecabtagene vicleucel.

2.2.2.1. Part 1: Anti-BCMA02 CAR lentiviral vector (LVV)

General Information (Anti-BCMA02 CAR LVV (LVV))

The anti-BCMA02 CAR LVV (LVV) is considered as a starting material for the manufacturing of ide-cel. The LVV is derived from the human immunodeficiency virus type 1 (HIV-1) and is replication incompetent and self-inactivating (SIN). It is manufactured using a third-generation vector design in which the necessary viral genes are expressed from four separate plasmids to minimise the risk of generating replication competent lentivirus (RCL).

Manufacture, process controls and characterisation (Anti-BCMA02 CAR LVV (LVV))

Manufacturing process (Anti-BCMA02 CAR LVV)

Manufacturing of the LVV starts with thawing of one vial of HEK293T producer cells, which are then expanded to multilayer cell cultures (MLCCs). This results in a crude vector harvest. The single crude harvest pool is purified and concentrated to final LVV product filled into vials, which is the definition of one lot of anti-BCMA02 CAR LVV. The final LVV pool is automatically filled to a target volume of 5 mL in 10 mL vials within a Grade A isolator environment. The vector is stored at -65°C.

The single steps of the LVV manufacturing process are sufficiently described. Acceptable ranges/action limits are defined for critical process parameters (CPPs) and in-process controls (IPCs) and listed for each unit operation. In addition to action limits and acceptance criteria, ongoing process verification (OPV) establishes and assesses internal control limits for process monitoring across multiple lots indicating that the manufacturing process is performing in a state of control. The OPV programme is acceptable. Process parameters are listed in the manufacturing process description. Assays used for IPCs and in process monitoring are sufficiently described.

The overall control strategy including in-process controls and testing of starting materials is adequate to control the process resulting in an LVV of consistent quality.

Control of materials (Anti-BCMA02 CAR LVV)

All raw materials and key consumables are listed. The materials of biological origin are accepted for use in the manufacture of anti-BCMA02 CAR LVV based on the Certificate of Analysis (CoA) from the supplier. Representative certificates of analysis for each materials of biological origin are provided.

The generation of the starting plasmids is sufficiently described, including full listing of all genetic elements. The testing performed to qualify each packaging plasmid is sufficiently documented. All results met acceptance criteria. Certificate of analysis of all plasmids are provided. The cell banks are sufficiently documented.

The origin and preparation of the cell banks have been set out in sufficient detail. Adequate information on the qualification of the current master cell bank (MCB) is presented, including a comprehensive adventitious agent testing programme in accordance with ICH Q5A, covering relevant human, porcine and bovine viruses.

Process validation (Anti-BCMA02 CAR LVV)

The LVV commercial manufacturing process was validated. All process validation acceptance criteria, including critical quality attributes (CQAs), critical process parameters (CPPs), and performance attributes were met for the PPQ batches. Additionally, all non-CPP proven acceptable ranges (PARs) were met, indicating that the LVV manufacturing process performs in a consistent manner. Deviations occurring during the execution of the PPQ runs were investigated, corrective and preventative actions determined, and their impact to PPQ are sufficiently addressed.

Following execution of the PPQ batches, the criticality of process parameters and IPCs was re-evaluated along with the corresponding acceptance criteria to define the commercial manufacturing control strategy. The re-evaluation of CPPs and IPCs are justified.

An OPV programme has been implemented for commercial production to provide evidence that the process and product quality remains in a validated state of control during routine commercial manufacturing by monitoring, at minimum, the CQAs, CPPs, and IPCs. The OPV plan includes the parameters and attributes to be monitored, their limits, and the frequency of reporting. The OPV programme is endorsed. The normal operation range (NOR) of the manufacturing process has been established and will be monitored and updated as appropriate as part of product life cycle management for subsequent commercial lots. Lists of CPPs with NORs in addition to the PARs are provided.

A buffer and media microbial hold time qualification study was executed to establish hold times for commercial manufacturing. The hold times suggestions for the applied media and buffers based on these studies seem reasonable. The temperature-controlled dry ice shipping systems used for shipping LVV were sufficiently validated.

Additional validation consisted of the validation of the sterility of the filling process with media fill simulations exceeding the maximum vial fills of standard batches, shipping validation for LVV and media storage time evaluation. All presented data show sufficient performance of the processes.

The provided risk assessment in respect of extractables and leachables concluded that the LVV manufacturing process does not pose additional risks to the product and is considered acceptable.

Manufacturing process development (Anti-BCMA02 CAR LVV)

An evaluation of product quality attributes for LVV was conducted following quality risk management principles. LVV quality attributes are categorised as CQAs and non-CQAs based on the predicted severity of impact to patient safety and finished product efficacy. The determination of quality attributes seems reasonable.

LVV manufacturing data are analysed through testing of in-process pools from LVV batches produced using the commercial process (Process IV). Average performance recovery data are presented for process steps indicating good performance. Likewise, impurity clearance summary levels are provided. Impurity concentration results indicate consistent ability of the process to meet IPC criteria.

In general, the PARs set during the process characterisation are reasonably justified.

Characterisation (Anti-BCMA02 CAR LVV)

The applicant conducted a comprehensive characterisation of the LVV with respect to structure and composition. The assays used were able to positively detect the presence of major species for all lots, as well as expression of viral proteins critical to the formation of functional LVV.

Impurities (Anti-BCMA02 CAR LVV)

A comprehensive description and characterisation data for all product and process related impurities has been provided.

Specification, analytical procedures, reference standards, batch analysis, and container closure (Anti-BCMA02 CAR LVV)

The release and stability specifications for anti-BCMA02 CAR LVV are provided. Overall, the tests conducted for LVV batch release and the specifications are considered adequate.

Analytical methods (Anti-BCMA02 CAR LVV)

Validation reports were presented for all analytical assays. The validation parameters were selected in accordance with ICH Q2(R1) based on the intended use of the method and were assessed to confirm the suitability of the method. Verification details for pharmacopeial procedures are also included.

The validation of the analytical methods in use for control of LVV is considered acceptable.

Batch analysis (Anti-BCMA02 CAR LVV)

Several batches of anti-BCMA-LVV have been manufactured. Overall, the batch data provided are considered sufficient and support LVV-consistency.

For LVV-batch release, an LVV-reference standard is used as internal control. This reference standard is qualified according to batch release tests and additional characterisation assays.

Container closure system (Anti-BCMA02 CAR LVV)

The LVV is filled in vials that are stoppered and capped with aluminium seals.

The vials, stoppers, and seals are supplied in a sterile, ready-to-use state to represent a primary packaging that complies with Ph. Eur. standards.

Stability (Anti-BCMA02 CAR LVV)

Several Anti-BCMA02 CAR LVV lots have been placed on stability at the intended long-term storage condition to demonstrate the biological and physical stability throughout the proposed shelf-life.

In addition, several stability lots were placed on stability at an accelerated storage condition to evaluate biological and physical stability during potential temperature excursions outside the intended long-term storage condition. In addition, freeze/thaw and thermal stress stability were also evaluated.

Based on the presented data and justifications, the proposed shelf life at the recommended storage condition is acceptable.

2.2.2.2. Part 2: Active substance (Idecabtagene vicleucel)

General Information

Idecabtagene vicleucel consists of T cells transduced with the anti-BCMA02 CAR LVV encoding a CAR that recognises BCMA. The CAR is comprised of a murine extracellular single-chain variable fragment (scFv) specific for recognising BCMA followed by a human CD8α hinge and transmembrane domain fused to the T cell cytoplasmic signalling domains of CD137 (4-1BB) and CD3ζ chain, in tandem. Antigen-specific activation induces signalling initiated by CD3ζ and 4-1BB domains and subsequent CAR+ T cell activation.

Details on the CAR protein construct within the transduced T cell together with a description of the different CAR domains and their main function have been provided. Information on the nucleotide and amino acid sequence of the CAR construct annotating the major components has been also presented.

Manufacture, process controls and characterisation

Manufacturers

The ide-cel active substance (AS) manufacturing process consists of two steps: PBMCs (intermediate) and cell culture. The cryopreserved PBMC is shipped to the ide-cel manufacturing and testing facility in USA, Celgene Corporation, Building S12, 556 Morris Avenue, Summit, New Jersey 07901, USA, which holds a valid EU GMP certificate.

Celgene Distribution B.V. in Utrecht in the Netherlands is responsible for importation and batch release of ide-cel product into EU/EEA and holds a valid EU GMP certificate and a valid manufacturing authorisation.

Manufacturing process and process controls

The manufacture of ide-cel is a continuous process from active substance (AS) to final product (FP). The patient's PBMCs are obtained via a standard leukapheresis procedure followed by a PBMC isolation. At the Celgene S12 manufacturing facility, the PBMC bags are thawed for cell culture expansion.

IPCs, critical and non-critical process parameters, and processing times are listed for each unit operation for the manufacturing process. Compositions of cell culture media and solutions have been provided.

Control of materials

Raw materials are purchased sterile from approved suppliers and are accepted based on suppliers' certification documentation and testing following approved specifications. The suppliers, grade and specifications for the raw materials are provided as well as representative certificates.

The applicant confirms that apheresis procurement and testing is controlled according to the requirements of the relevant European Commission Directives in each Member State, and that an apheresis centre qualification programme is in place to ensure proper oversight of the apheresis process and to initiate and maintain both chain of custody (COC) and chain of identity (COI).

Controls of critical steps and intermediates

Performance parameters for ide-cel manufacturing are classified as critical process parameter (CPP) or non-critical process parameter (nCPP) and are evaluated as controllable within PARs.

Microbial contamination control within the manufacturing process is ensured by using aseptic techniques and closed system manipulations, whenever possible. A mycoplasma release test at harvest day is performed. Manufacturing facilitates are designed to prevent microbial contamination, and microbial contamination controls are in place. Raw materials used are procured sterile or sterile filtered prior to use in manufacture.

Process validation

Process validation was based on site-specific and product-specific validation studies.

Validation of the manufacturing route intended for the EU/EEA market covered leukapheresis receipt to manufacturing of cryopreserved PBMCs followed by final product manufacturing at the Celgene S12 facility.

Manufacturing process development

Critical quality attributes were identified according to ICH Q8, Q9, and Q10 utilising a risk-based approach to assess and categorise product quality attributes. Justifications for each attribute's designation are provided.

Overall, adequate process parameters, process time and hold time studies were performed for different operations of the manufacturing process.

Overall, the manufacturing process development is considered satisfactory.

Characterisation

Characterisation of the ide-cel CAR, vector integration, mechanism of action and clinical finished product batches were performed.

The characterisation test methods are sufficiently described.

Impurities

Potential product-related impurities in ide-cel product are provided. Summaries of impurity characterisation analytical methods are provided, including the determined limit of quantification. Analytical methods were qualified to detect process-related impurity levels (in the required matrices) and demonstrated to be suitable for their intended use.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The ide-cel active substance immediately enters the finished product process, the transition from active substance to finished product does not include any hold steps. Therefore, there are no specifications, batch analyses or justification of specification or description of container closure systems for ide-cel active substance. Ide-cel is controlled at the level of the finished product. Considering the nature of the product, the applicant's approach is considered acceptable.

Stability

Due to the continuous manufacturing process, there are no stability data presented for ide-cel active substance. As no hold step is foreseen at active substance level before manufacturing of finished product, no stability studies have been performed at that level and this is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Ide-cel is formulated as a cell suspension (dispersion) for IV administration. The finished product is formulated and cryopreserved in a cryopreservation medium suitable for infusion containing Plasma-Lyte A and CryoStor® CS10.

Ide-cel is provided as a single-dose for infusion in one or more CryoStore freezing bags containing a total of 260 - 500 × 10^6 anti-BCMA CAR-positive viable T cells, at the target cell concentration of 10 × 10^6 cells/mL.

Ide-cel is stored in the vapour phase of liquid nitrogen at ≤ -130 °C. For any given batch, the same nominal fill volume is targeted in all bags filled. Each product bag remains housed within its metal cassette throughout cryopreservation, storage, and shipping.

Pharmaceutical development

The excipients used in the formulation of finished product are Plasma-Lyte A (sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, water for injections), which provides the source of electrolytes and CryoStor CS10, which is the cryopreservative agent. The formulation with a final DMSO concentration of 5% (v/v) was demonstrated to be suitable for the intended use. There are no novel excipients used. There has been no formulation change during ide-cel manufacturing development history.

Manufacture of the product and process controls

Manufacture

In general, the finished product manufacturing process is well described. Manufacturing for ide-cel is a continuous process.

Process validation

The process validation for the entire manufacturing process, from apheresis material to cryopreserved ide-cel, is adequately described.

Product specification, analytical procedures, batch analysis

Specification

The release and stability specifications for ide-cel finished product are provided. The potential presence of elemental impurities in the active substance and finished product has been assessed on a risk-based approach in line with the ICH Q3D guideline for elemental impurities. The risk of carryover of elemental impurities from reagents and materials used for manufacture is considered negligible and no additional control is required.

Based on a review of the manufacturing process, a risk analysis and the information received from both the raw material and the single use component suppliers, no actionable risk for the presence of nitrosamine impurities in ide-cel finished product was identified. The applicant will assess the risk for the presence of nitrosamines in the event of process and/or material changes and will initiate confirmatory testing as required if a risk is identified.

Analytical procedures and reference standards

The principle of each method and the most relevant information for performance of the methods used for finished product release are provided.

A summary of validation data for the non-compendial methods, as well as verification information for the compendial method are provided. In addition, full validation reports are also provided. History of analytical method development and finished product specification has been presented.

Analytical methods have been transferred. Assay transfer was monitored by testing several batches at both sites, respectively, and monitoring the results against predefined acceptance criteria.

The information provided is sufficient and adequate.

Batch analysis

Release data for ide-cel batches manufactured during clinical trials is included in the dossier and reveal no inconsistencies or safety concerns.

Container closure system

The primary container closure systems for distribution of ide-cel, are commercially available and designed for storage of blood and blood components and are made from ethylene vinyl acetate (EVA) film. Each infusion bag contains 10-30 mL (50 mL bag), 30-70 mL (250 mL bag) or 55-100 mL (500 mL bag) of cell dispersion for infusion. The secondary packaging is an aluminium cassette, designed to protect the product during storage, shipment, and handling. A vapour phase liquid-nitrogen shipping container is used to ship ide-cel to the treatment site. The suitability of the container closure system including discussion of extractables and leachables has been demonstrated.

Stability of the product

A 12 months shelf-life when stored at the recommended long-term storage condition in the vapour phase of liquid nitrogen (≤ -130°C) is claimed for the finished product.

The presented stability protocol reflects the commercial finished product release and stability specifications.

Based on the stability data presented the claimed shelf life for the finished product of 12 months when stored in the vapour phase of liquid nitrogen (≤ -130°C) is acceptable. Each bag must be infused within 1 hour from start of thaw. After thawing, the volume of the product intended for infusion should be kept at room temperature (20°C – 25°C). The product must not be refrozen following thaw.

Post approval change management protocol(s)

N/A

Adventitious agents

Virus safety

The virus safety of the ide-cel final product relies solely on the selection and quality of the raw materials, testing of starting materials and adherence to GMP.

The anti-BCMA02 lentiviral vector is produced by transient transfection of HEK293T cells. The cell line genealogy has been sufficiently described and tested sufficiently for adventitious viruses according to Ph. Eur. 5.2.3 and ICH Q5A. No viruses were found by any assay in any cell bank.

The autologous PBMCs are obtained from the patients by leukapheresis. Each patient/PBMC donor is tested at minimum according to Directive 2006/17/EC with CE-marked test kits.

No materials of direct animal origin are used in the manufacture of ide-cel. None of the excipients are of animal or human origin. Sufficient information on virus safety is provided for the other raw materials of biological origin and is supported by respective certificates. In summary, virus safety has been sufficiently assured.

TSE compliance

Raw materials of animal or human origin are used in the ide-cel manufacturing process. Valid certificates of suitability issued by the EDQM are provided. Compliance with the TSE guideline for all raw materials of direct animal origin and with EU Directives for human-derived materials has been demonstrated.

GMO

Environmental risk associated with ide-cel is considered to be negligible (see non-clinical section for further information).

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, adequate quality documentation is provided for the anti-BCMA02 LVV and ide-cel product.

All relevant manufacturing and testing sites hold valid manufacturing authorisations and/or valid EU GMP certificates.

The ide-cel manufacturing process is sufficiently described, and CPPs and intermediates are demonstrated to be overall adequately controlled. Starting and raw materials for ide-cel are also considered appropriately controlled.

The LVV commercial manufacturing process was sufficiently validated. The criticality of process parameters and IPCs was re-evaluated along with the corresponding acceptance criteria to define the commercial manufacturing control strategy. An OPV programme has been implemented for commercial production. The determination of quality attributes is reasonable. Average performance recovery data and impurities concentration are presented for several process steps and indicate good performance.

Process parameter risk assessment and process characterisation has been performed. Comprehensive validation reports were presented for all analytical assays. Critical quality attributes (CQAs) were identified utilising a risk-based approach, and justifications for each attribute's designation are provided. Both product-related as well as process-related impurities are demonstrated to be overall sufficiently controlled.

The final product composition preserves quality attributes throughout formulation, cryopreservation, thawing and administration, and is deemed suitable for the intended use. The production process for final product is considered validated and demonstrates that the manufacture of finished product is of acceptable quality.

Long-term stability data have been provided for a sufficient number of batches supporting the proposed shelf life of 12 months when stored at ≤ -130°C.

The TSE and virus safety of Abecma has been sufficiently shown.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Abecma is considered acceptable when used in accordance with the conditions as defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Abecma is considered approvable from the quality point of view.

The applicant agreed to the Recommendations as identified below.

The CHMP endorse the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT recommended several points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

Ide-cel is an autologous gene-engineered T cell therapy expressing BCMA-specific CAR. The principal mechanism of action is cytolysis of BCMA+ cells through specific recognition and binding to BCMA expressing cells, signalling through the CAR to activate the CAR+ T cells, release of cytokines such as IFN-γ, and stimulation of cell proliferation to increase the population of CD3+/CAR+ T cells and cytolysis of BCMA+ tumour cells.

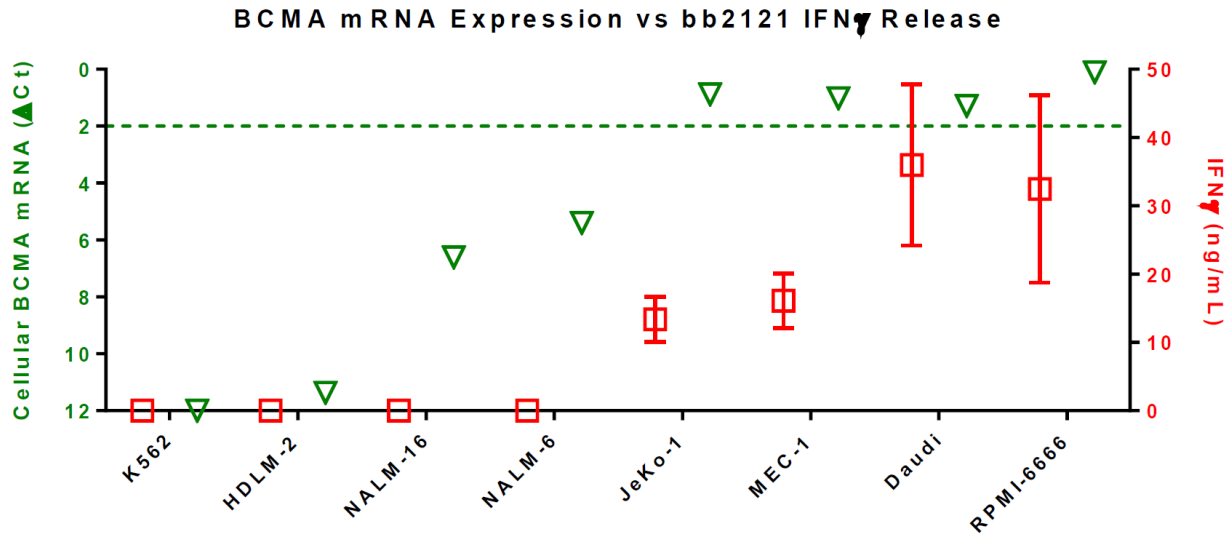
In vitro studies

The *in vitro* pharmacology studies used human tumour cell lines, primary cells, and tumour biopsies to determine BCMA expression, ide-cel anti-BCMA CAR expression, CAR-to-target binding, specificity, activity and potency.

In vitro correlation between BCMA expression, cell surface BCMA and CAR T cell activation

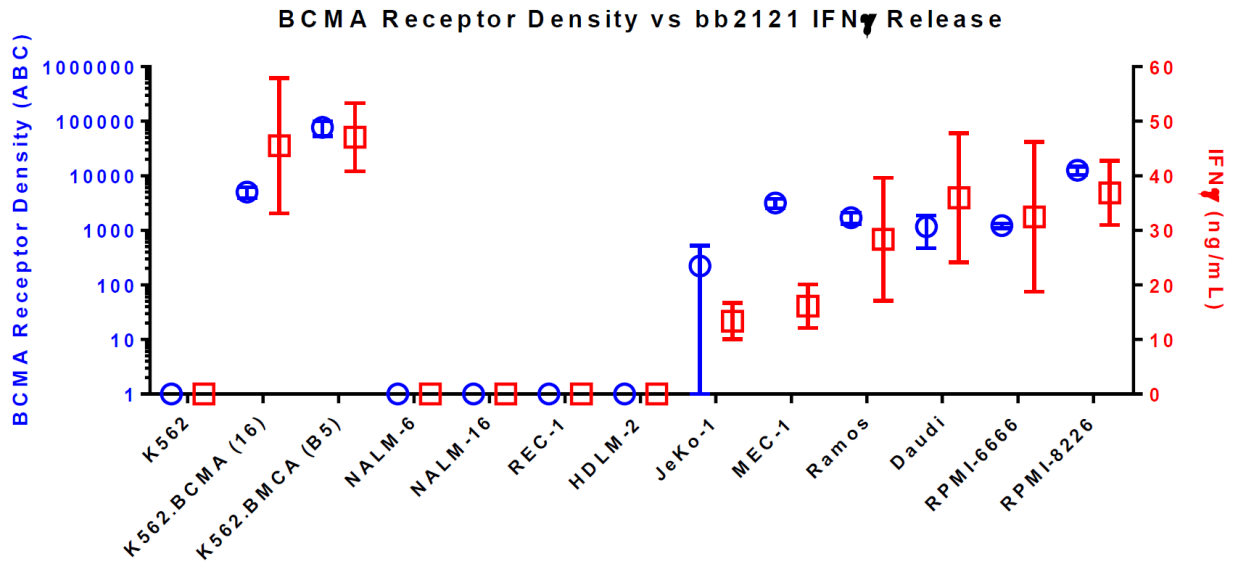
When correlating tumour cell line BCMA mRNA expression and IFN-γ release, it was shown (Figures 1 and 2) that there is a threshold for BCMA mRNA level above which the anti-BCMA CAR T cells are activated and start releasing IFN-γ. In particular, cell lines HDLM-2, NALM-6 and NALM-16 express BCMA but have mRNA levels below the threshold and do not produce detectable cell surface BCMA. Other tumour cell lines, such as MEC-1, Daudi and RPMI-6666, have BCMA mRNA levels above the threshold and sufficient cell surface BCMA receptor expression to activate the anti-BCMA CAR T cells. Similarly, when using biopsied primary human CLL tumour cells, only BCMA-positive tumour cells trigger activation of the anti-BCMA CAR T cells and start releasing IFN-γ (figure 3).

Figure 1: Ide-cel IFN-gamma release correlates with tumour cell line BCMA mRNA expression



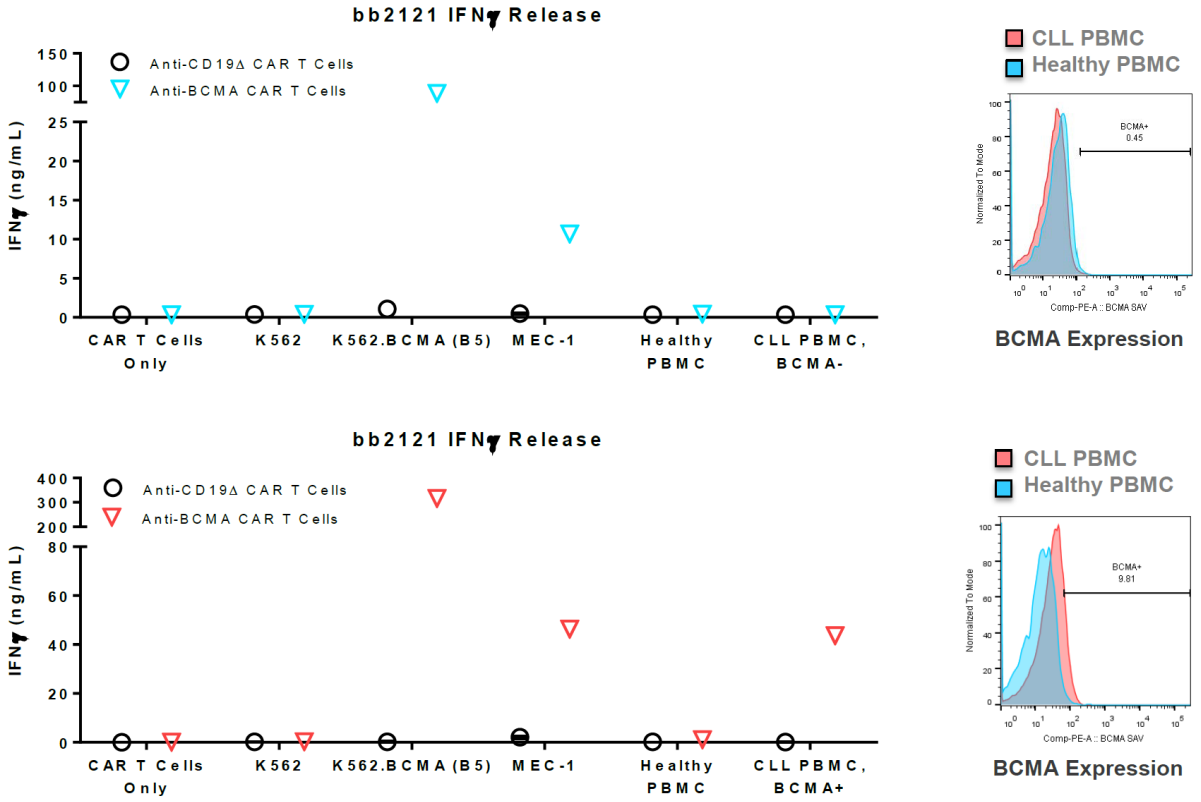
Anti-BCMA CAR T cell (ide-cel) activation and IFN-γ release correlates with BCMA mRNA expression in human B cell tumour cell lines. The relative BCMA mRNA expression (▽) was assessed by RT-qPCR assay, and expressed as the difference in amplification cycle times (ΔCt) relative to a "housekeeping" gene. ΔCt levels are inversely proportional to the amount of BCMA mRNA in the sample. The BCMA-negative (BCMA-) myelogenous leukaemia cell line K562 was used as a control. Control or tumour cell lines were co-cultured for 24 hours with anti-BCMA CAR T cells and IFN-γ release (□) was quantified by ELISA. No, or very little, IFN-γ was released upon co-culture with BCMA- tumour cell lines representing myelogenous (K562) or acute lymphoblastic (NALM-6 and NALM-16) leukaemia and Hodgkin's (HDLM-2) lymphoma. In contrast, substantial amounts of IFN-γ were released upon co-culture with BCMA+ tumour cell lines representing B cell chronic lymphoblastic (MEC-1) leukaemia and Mantle cell (JeKo-1), Hodgkin's (RPMI-6666) or Burkitt's (Daudi) lymphomas. BCMA mRNA expression correlated with BCMA receptor density. Substantial IFN-γ release was observed for tumour cell lines expressing BCMA mRNA at a threshold (- - -) of ΔCt ≤ 2.

Figure 2: ide-cel IFN-gamma release correlates with tumour cell line BCMA receptor density



Anti-BCMA CAR T cell (ide-cel) activation and IFN-γ release correlates with BCMA receptor density on human multiple myeloma and B cell tumour cell lines. Tumour cell surface BCMA expression (○) was determined by flow cytometric analysis using a mouse anti-human BCMA monoclonal antibody. The relative BCMA receptor density was assessed by correlating the fluorescence intensity to a known number of bound antibodies (antibody binding capacity, ABC). Controls included the BCMA- myelogenous leukaemia cell line K562, and K562 cells transduced to express BCMA at low (clone 16) or high (clone B5) densities. Control or tumour cell lines were co-cultured for 24 hours with anti-BCMA CAR T cells and release (□) was quantified by ELISA. No, or very little, IFN-γ was released upon co-culture with BCMA- tumour cell lines representing myelogenous (K562) or acute lymphoblastic (NALM-6 and NALM-16) leukaemia and Mantel cell (REC-1) or Hodgkin's (HDLM-2) lymphomas. In contrast, substantial amounts of IFN-γ were released upon co-culture with BCMA+ K562-BCMA transductants (clones 16 [moderate] and B5 [high]) and BCMA+ tumour cell lines representing B cell chronic lymphoblastic (MEC-1) leukaemia, Mantle cell (JeKo-1), Hodgkin's (RPMI-6666) or Burkitt's (Daudi, Ramos) lymphomas, and MM (RPMI-8226). IFN-γ release and BCMA receptor density correlated with tumour cell BCMA mRNA expression. Note: BCMA receptor density of '0' (not detectable) is shown as '1' on log scale.

Figure 3: ide-cel IFN-gamma release correlates with CLL BCMA receptor expression

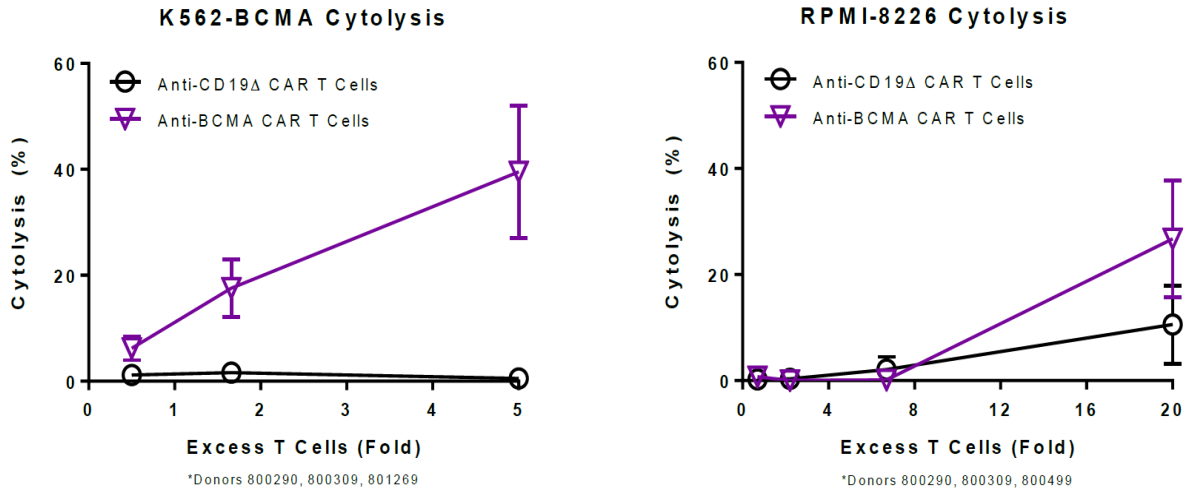


Anti-BCMA CAR T cell (ide-cel) activation and IFN-γ release correlates with specific recognition of BCMA on B cell CLL (MEC-1) tumour cell lines and primary CLL PBMCs. In two separate experiments, anti-CD19Δ (control, ○) or anti-BCMA CAR T cells (▽, ▽) were co-cultured with PBMCs from healthy donors or from patients with BCMA- (top) or BCMA+ (bottom) CLL, as determined flow cytometry. Additional controls included CAR T cells alone or co-cultured with BCMA- K562 cells, BCMA+ K562-BCMA transductants (clone B5), or the BCMA+ MEC-1 CLL cell line. As determined by ELISA, IFN-γ was released only by anti-BCMA CAR T cells co-cultured with the BCMA+ K562-BCMA transductants, CLL MEC-1 cells or CLL PBMCs. No IFN-γ was released spontaneously (CAR cells alone) or in the presence of healthy PBMCs or BCMA- CLL PBMCs

In vitro BCMA-specific cytolysis of tumour cells

Flow cytometry analysis showed that the anti-BCMA CAR T cells specifically killed the BCMA-positive cells while little or no cytolysis occurred upon co-culture with the negative control, anti-CD19Δ CAR T cells (figure 4).

Figure 4: BCMA-specific cytolysis of tumour cells by ide-cel



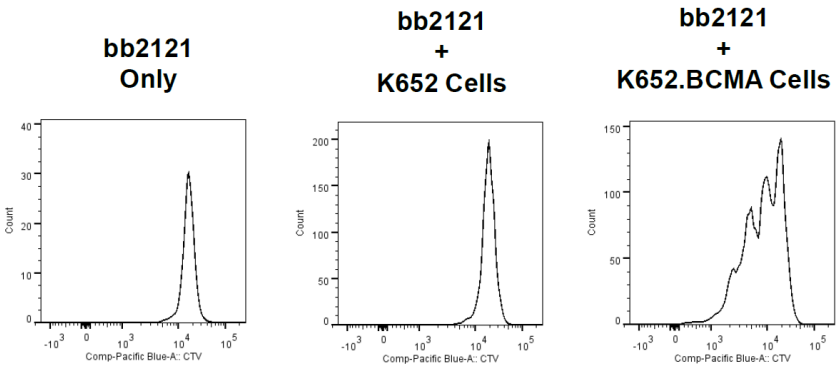
Anti-BCMA CAR T cells (ide-cel) specifically kill BCMA+ tumour cells. BCMA- K562 and BCMA+ K562-BCMA transductants were each labelled with unique florescent dyes and mixed in equal numbers, prior to co-culture for 4 hours in the presence of anti-CD19Δ (control, ○) or anti-BCMA CAR T cells (▽) that were added to achieve different effector cell-to-target cell ratios (fold excess T cells). After incubation, the numbers of BCMA+ and BCMA- tumour cells surviving were determined by flow cytometry. The percentage (%) of BCMA+ tumour cells undergoing cytotoxicity was calculated as 100% minus the number of surviving BCMA+ tumour cells divided by the number of surviving BCMA- tumour cells, after correcting for spontaneous cytolysis. Anti-BCMA, but not anti-CD19Δ, CAR T cells, induced specific cytolysis of BCMA+ K562-BCMA transductants, but not BCMA- K562 cells (left). Ide-cel, but not bb612 anti-CD19Δ, CAR T cells induced specific cytolysis of BCMA+ MM RPMI-8226 cells (right).

In vitro BCMA-specific proliferation of ide-cel CAR T cells

T cells are activated and proliferate when adequately stimulated by professional antigen presenting cells (APCs). Similar, CAR T cells activate and proliferate when appropriately triggered by target cells, but without the need for APCs. As expected, the anti-BCMA CAR T cells proliferated only when the target cells expressed BCMA (Figure 5).

Figure 5: BCMA-specific proliferation of ide-cel CAR+ T cells

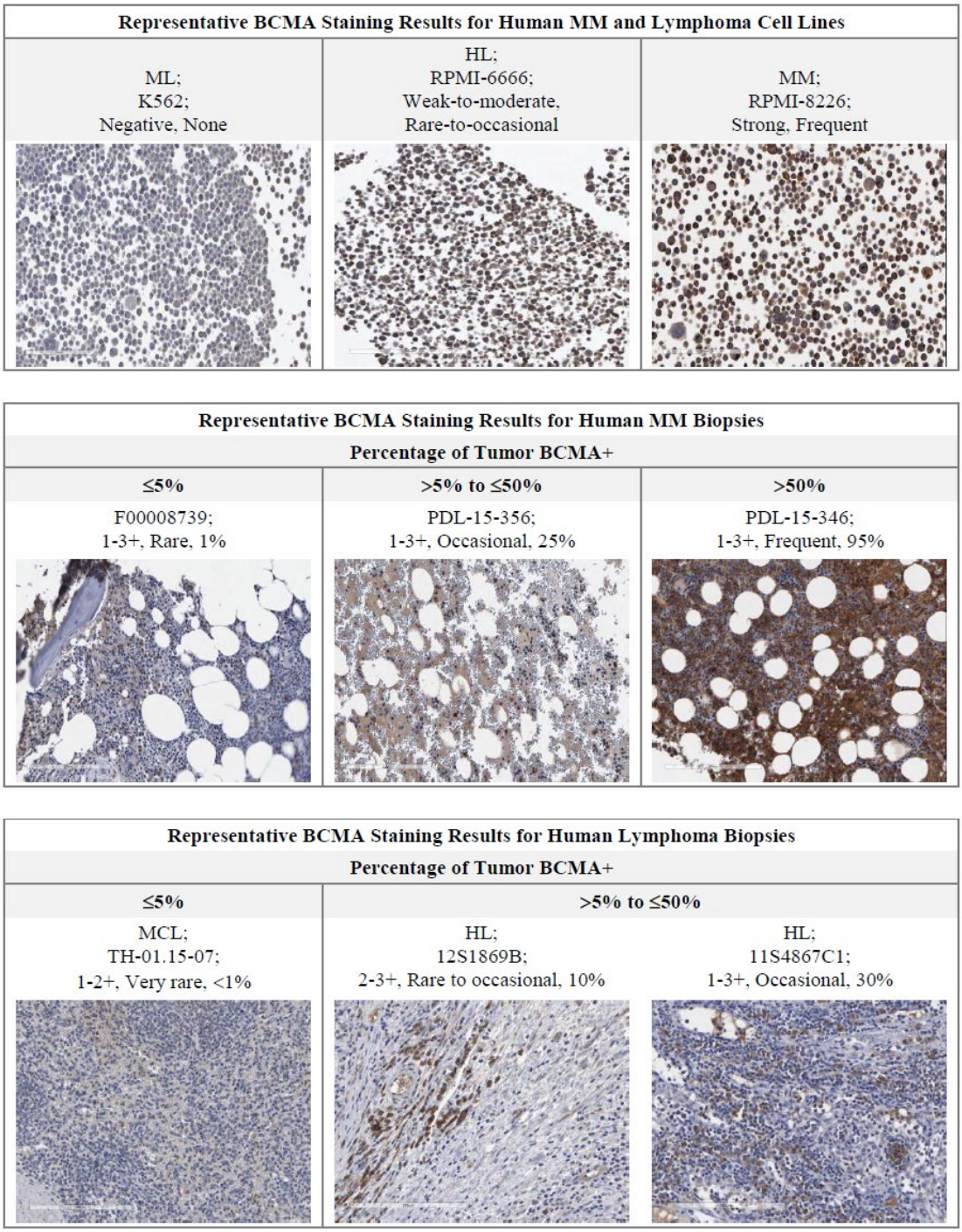
Anti-BCMA CAR T cells (bb2121) specifically proliferate in response to recognition of and activation by BCMA+ tumor cells. Anti-BCMA CAR T cells were labeled with a cytoplasmic dye prior to culture alone (left) or in the presence of BCMA- K562 cells (middle) or BCMA+ K562-BCMA transductants (right). Proliferation, evident as multiple fluorescence peaks of diminishing intensity, occurs only when anti-BCMA CAR T cells encounter BCMA+ tumor cells.



In vitro - BCMA mRNA and receptor expression on tumour cell lines and primary human tissues

Most of the lymphomas with substantial BCMA mRNA expression were non-Hodgkin's lymphomas (NHL), while only a few of the Hodgkin's lymphomas expressed a significant amount of BCMA mRNA. Some non-lymphoma tissues, such as spleen and samples from patients with ulcerative colitis, had significant expression of BCMA mRNA. These tissues are enriched with normal mature B-lymphocytes, which are known to express BCMA. In the current MAA for Abecma (ide-cel), only treatment of multiple myeloma (MM) is applied for. Notably, BCMA mRNA levels in MM tumours were not investigated. However, BCMA receptor expression on human MM was investigated using immunohistochemistry (IHC). IHC staining of BCMA were performed on human MM and lymphoma tumour cell lines, and on primary human MM and lymphoma biopsies. BCMA staining was less prevalent within human lymphoma biopsies than in MM biopsies. BCMA+ cells represented ≥50% of the tumour tissue in 41% of the MM biopsies evaluated, while no lymphoma biopsy displayed > 30% BCMA+ cells (figure 6).

Figure 6: Representative BCMA Staining Results for Human MM and Lymphoma Cell Lines and Biopsies



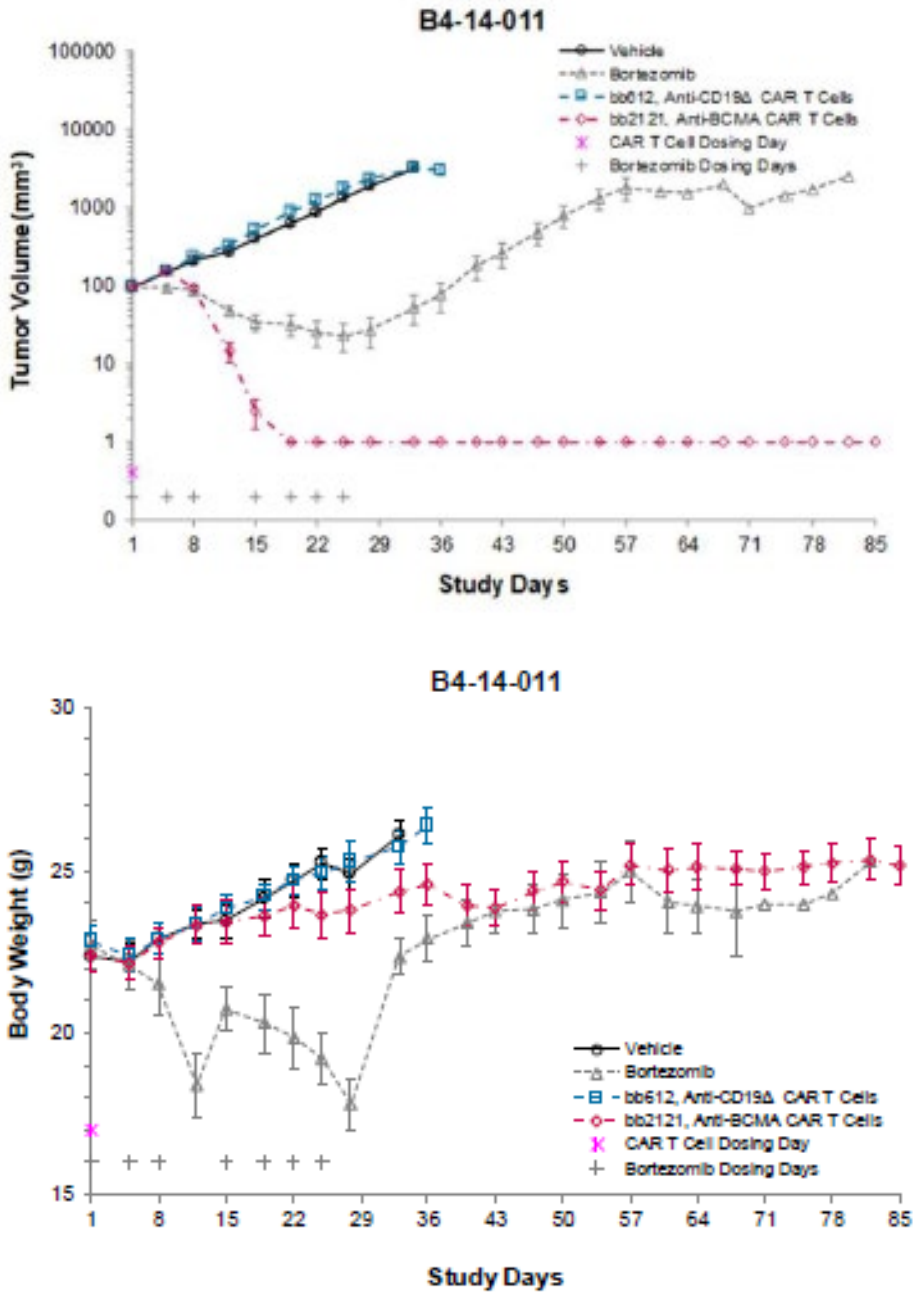
MCL=Mantle Cell Lymphoma; HL=Hodgkin Lymphoma; ML=Myelogenous Leukaemia; MM=Multiple Myeloma

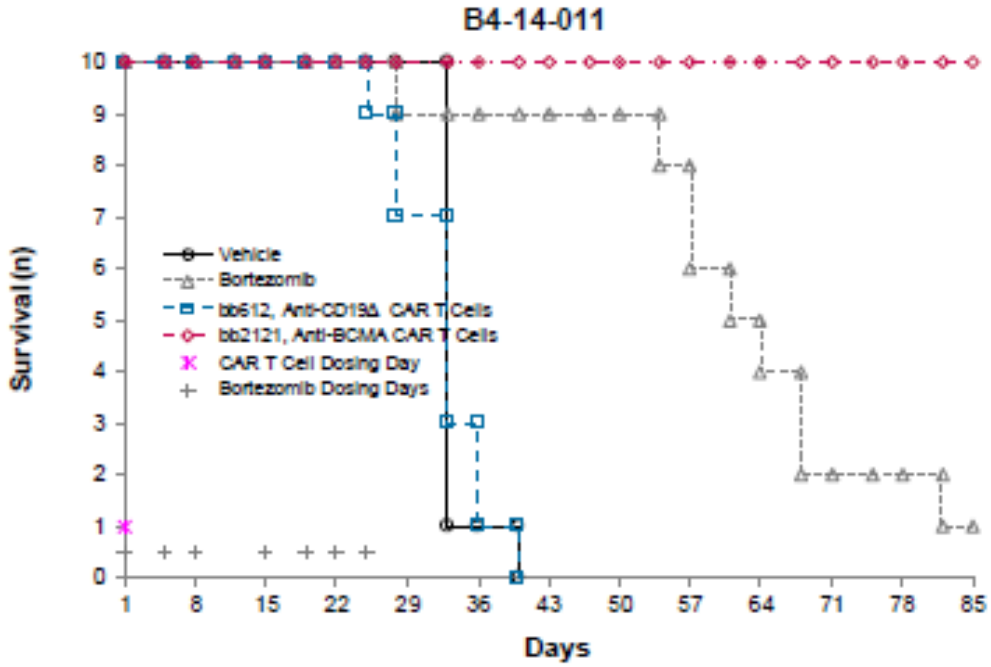
In vivo studies using BCMA+ RPMI-8226 human multiple myeloma xenografts

Studies were performed with BCMA+ RPMI-8226 multiple myeloma tumour cell line xenografts. RPMI-8226 multiple myeloma tumour cells with relatively high level of BCMA expression were subcutaneously injected into immunocompromised NSG mice, and ide-cel treatment was started at day 18 (study B4-14-011) or 39 (Study B4-14-043) post-tumour implantation. In both studies, an

additional group received 1 mg/kg bortezomib (Velcade® - positive control) IV twice weekly for 4 weeks starting at day 18 (study B4-14-011) or 1 mg/kg bortezomib (Velcade® - positive control) IV twice weekly for 2 weeks starting at day 49 (Study B4-14-043). In both settings, ide-cel treatment rapidly eliminated RPMI-8226 tumours. Treatment was well tolerated, and survival was 100% in the ide-cel groups, Figures 7 and 8.

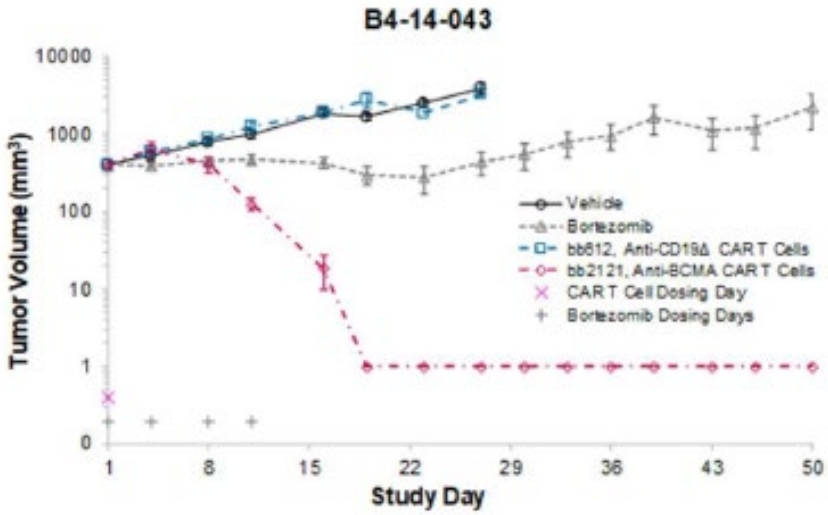
Figure 7: Ide-cel effect on survival and multiple myeloma tumour growth in mice

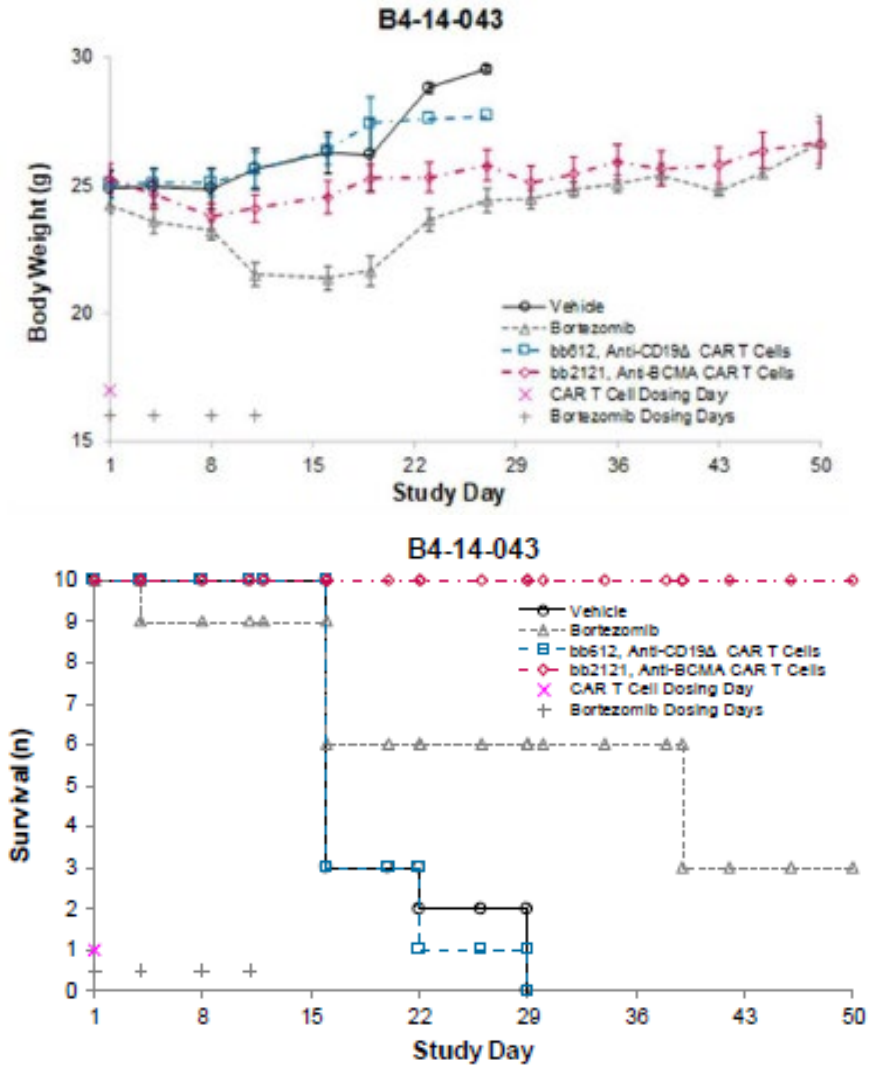




Day 1 = dosing (18 days after injection of tumour cells). Day 85 = in-life completed.

Figure 8: Ide-cel effect on tumour growth and survival of mice with large multiple myeloma tumors

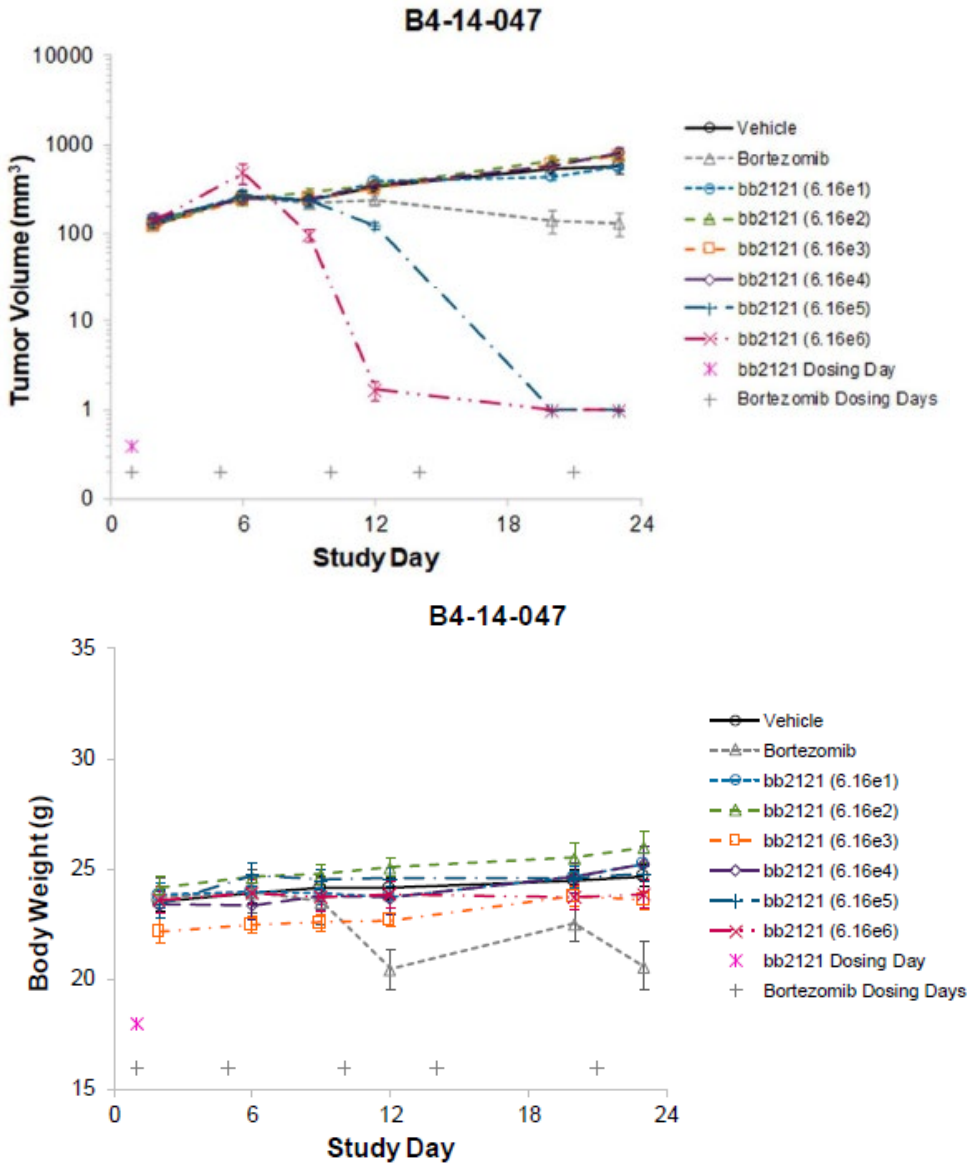




Day 1 = dosing (39 days after injection of tumour cells). Day 50 = in-life completed.

Pharmacological dose responses of ide-cel was investigated with BCMA+ RPMI-8226 human MM SC xenografts. A single IV administration of ide-cel at doses ≤6.16 x 10^4 CAR+ T cells had no effect on tumour growth, while doses ≥6.16 x 10^5 CAR+ T cells resulted in clearance of all tumours (Figure 9).

Figure 9: Dose response of Ide-cel on regression of multiple myeloma tumour xenografts in mice



Day 1 = dosing (20 days after injection of tumour cells). Day 23 = in-life completed.

These results indicate that treatment with ide-cel is either fully effective or not effective at all, and that the number of injected CAR+ T cells has to exceed a certain level for a successful outcome.

In vivo studies using BCMA+/CD19+ Daudi human Burkitt's lymphoma xenografts

In vivo studies were performed by intravenously injecting BCMA+/CD19+ Daudi human Burkitt's lymphoma tumour cells into NSG mice. The applied indication for ide-cel includes only treatment of multiple myeloma, and not lymphoma. However, the Daudi lymphoma cell line represents cells with lower BCMA expression than the RPMI-8226 multiple myeloma cell line, thus giving information about how a low surface level of BCMA affects treatment.

In the first study (Study B4-14-050), a single IV administration of 6.16 x 10^6 CAR+ ide-cel on Day 8 or 18 post-tumour injection was well tolerated, and resulted in inhibition of tumour growth, increasing

body weights and 100% survival at Day 51. Tumours were not totally eliminated, but mean tumour size was still decreasing at D51 when the study was terminated (data not shown).

The second study (Study B4-14-065) was conducted to investigate the dose-response relationship. Female NSG mice received IV injections of BCMA+/CD19+ Daudi BL FFLuc-transduced tumour cells to establish systemic xenografts. At 9 days post-tumour cell injection, mice received a single IV injection of either the vehicle alone (vehicle control) or total T cell doses of 1 x 103 to 1 x 107 ide-cel (test article). Because the percentage of CAR+ T cells in ide-cel was 70.1%, the respective CAR+ T cell doses were 7.0 x 102 to 7.0 x 106 CAR+ T cells. Ide-cel doses of ≥3.5 x 10^6 CAR+ T cells resulted in near elimination of BCMA+ tumours and 100% survival until the end of study, while doses of ≤7.0 x 10^4 CAR+ T cells had no effect on tumour growth or survival. Doses of ide-cel between these resulted only in temporary tumour reductions, since tumour size initially decreased and then increased 1-2 weeks after start of treatment (data not shown).

In vivo – pharmacologic activity, pharmacokinetics, pharmacodynamics, biodistribution and general safety

The pharmacologic activity, pharmacokinetics, pharmacodynamics, biodistribution, and general safety of ide-cel anti-BCMA CAR T cells were investigated in NSG mice with and without BCMA+ RPMI-8226 human multiple myeloma subcutaneous xenografts (Study B4-15-090 – Table 1). Female NOD-Cg-Prkdcscid IL2rgtm1Wjl/SzJ (NSG) mice received SC injections of 0.2 mL of a 5 x 10^7 cell/mL suspension containing 1 x 10^7 BCMA+ RPMI-8226 MM tumour cells to establish SC xenografts. At 25 days post-tumour implantation, one group each of mice with and without xenografts received a single intravenous (IV) injection of 0.2 mL of a cell suspension containing either the vehicle alone (vehicle control) or an identical CAR+ T cell dose of 3 x 10^6 CAR+ bb612 anti-CD19Δ CAR T cells (negative control) or 3 x 10^6 CAR+ ide-cel anti-BCMA CAR T cells (test article). Because the percentages of CAR+ T cells in bb612 and ide-cel were 38.2% and 60.4%, respectively, the respective total T cell doses were 7.9 x 106 and 5.0 x 106 CAR+ T cells for bb612 and ide-cel. bb612 anti-CD19Δ CAR T cells lack T cell signalling domains and are therefore an inactive CAR T cell control. The bb612 and ide-cel CAR T cells were manufactured from T cells from the same healthy human donor (Donor No. 800499) by transduction with lentiviral vector (LVV) Lot Nos. 11913 and 11213, respectively. Mice were monitored until Day 29.

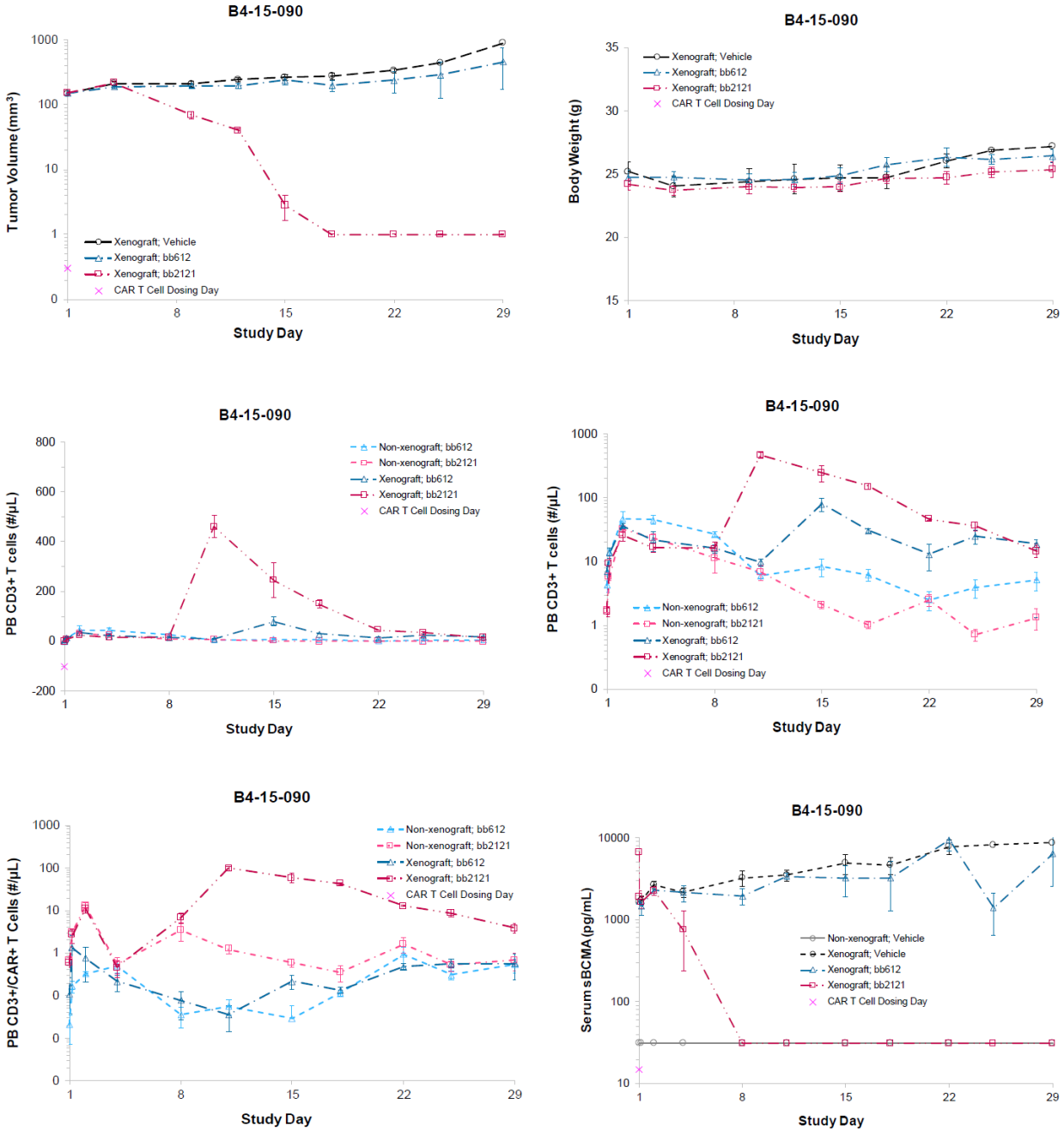
Table 1:**Study No. B4-15-090 Study Design**

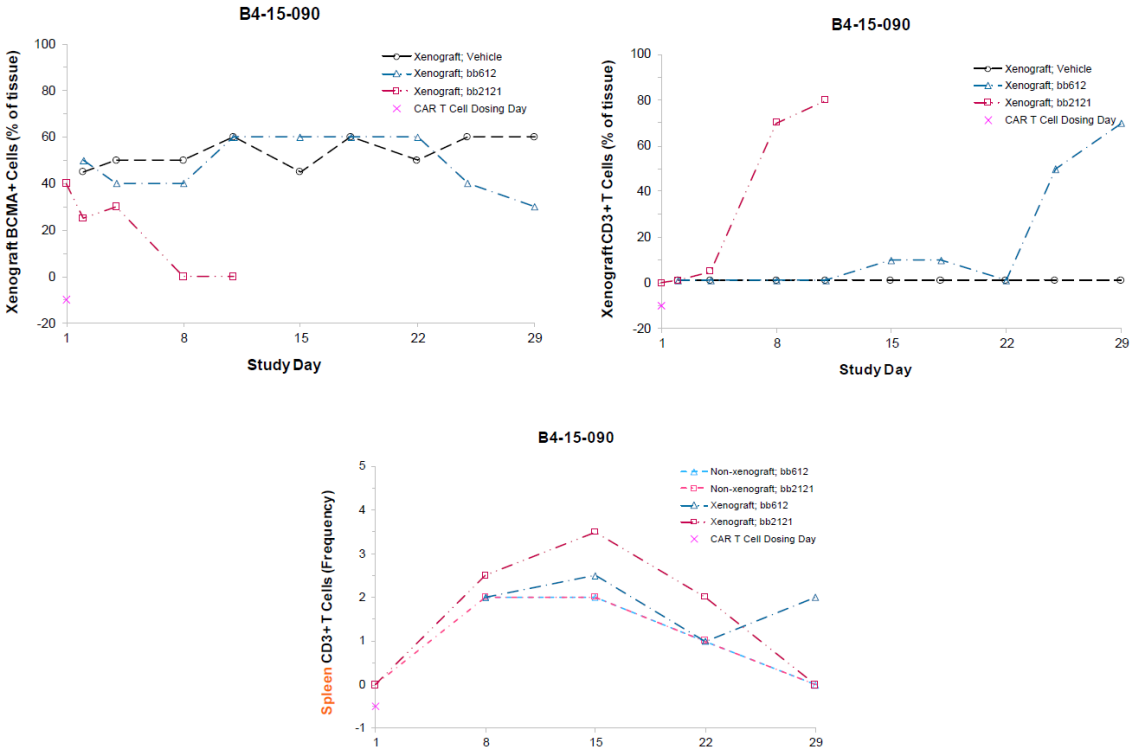
Group	Xenograft	Test or Control Article*	No. of ♀ Mice (n)	Dose		Concentration of Dosing Suspensions			Dose Vol. (mL)	Route	Dosing Day (Post-dosing)
				CAR+ T Cells (# x10^6)	Total T Cells (# x10^6)	Total T Cells (# x10^6/mL)	%CAR+ T Cells (%)	CAR+ T Cell (# x10^6/mL)			
A	None	Vehicle	9	NA	NA	NA	NA	NA	0.2	IV	1
B	None	bb612	13	3	7.9	100	38.2	38.2	0.2	IV	1
C	None	bb2121	14	3	5.0	100	60.4	60.4	0.2	IV	1
D	RPMI-8226	Vehicle	9	NA	NA	NA	NA	NA	0.2	IV	1
E	RPMI-8226	bb612	13	3	7.9	100	38.2	38.2	0.2	IV	1
F	RPMI-8226	bb2121	14	3	5.0	100	60.4	60.4	0.2	IV	1

*bb612 CAR T cells used bb612 LVV Lot No. 11913. bb2121 CAR T cells used BCMA02 LVV Lot No. 11213. Both were manufactured under Experiment No. TC14094, using T cells from healthy human Donor No. 800499.
♀ = female; bb612 = anti-CD19Δ CAR T cells; bb2121 = anti-BCMA CAR T cells.

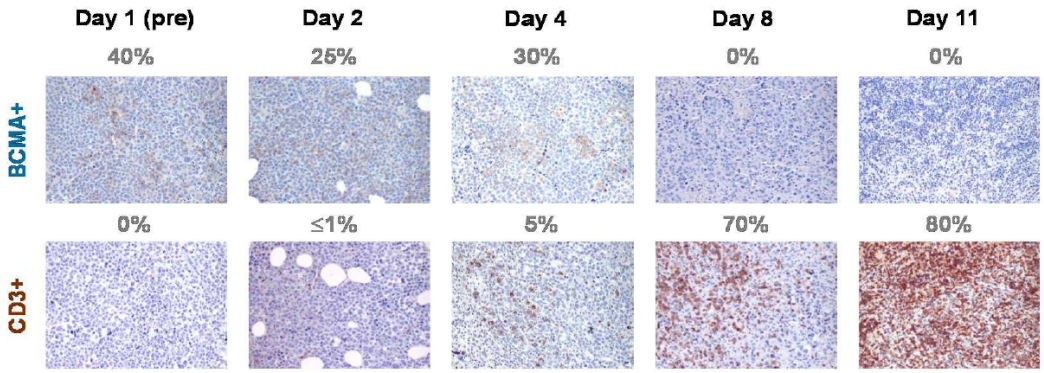
Ide-cel reduced the growth of MM tumour xenografts similar to the other *in vivo* studies with RPMI-8226. Further, the level of CD3+ T cells in peripheral blood went through several phases, with an initial peak the first days after injection of ide-cel, followed by a decline before an antigen-triggered proliferation, and lastly a steady decline after the tumour cells were cleared. Only up to 60% of the cells in the xenograft expressed BCMA. It is not clear if the remaining tumour cells are RPMI-8226 cells not expressing BCMA or if they are other cells recruited to the tumour. Nonetheless, after ide-cel treatment, the whole tumours rapidly were eliminated. Within liver, kidney or BM, CD3+ T cells were generally not present or very rare. Within spleen and lung, CD3+ T cells peaked at a frequency of rare to rare-to-occasional on Days 8 and 15, suggesting that these tissues provided temporary residence for these cells after dosing (Figure 10 and 11).

Figure 10:**Ide-cel Effects on Multiple Myeloma Tumour Xenografts**





Day 1 = dosing (25 days after injection with tumor cells). Day 29 = in-life completed.

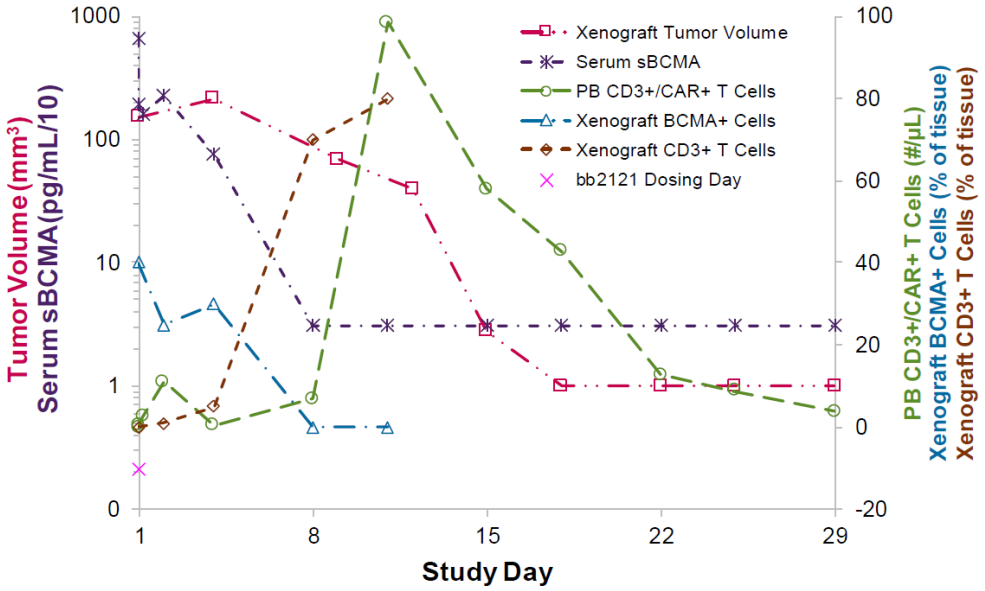


BCMA = B cell maturation antigen; CAR = chimeric antigen receptor; CD = cluster of differentiation; PB = peripheral blood.

Ide-cel (bb2121) anti-BCMA CAR+ T cells induce BCMA+ RPMI-8226 MM tumor cell xenograft regression in a model of MM in NSG mice. On Day 1 of dosing (×), groups of mice without (○, △, □) or with (○,△,□) ~150 mm^3 tumors received a single IV administration of 0.2 mL of a cell suspension containing either the vehicle alone (vehicle control, ○, ○), 3 x 10^6 CAR+ bb612 (negative control, △, △), or 3 x 10^6 CAR+ ide-cel (test article, □, □). A tumor volume of 1 mm^3 was assigned to tumors that were no longer detectable (0 mm^3) to allow graphical representation on log scale. ide-cel resulted in sustained tumor elimination (first row/left) and no change to body weights (first row/right). Peripheral blood (PB) CD3+ (and CD3+/CD4+ and CD3+/CD8+) T cell counts peaked initially at Day 2 and again at Day 11 (linear, second row/left; log, second row/right); CAR+ cells represented ~25% of the T cells (log, third row/left). Within xenograft tissue, BCMA+ tumor cells decreased from 40% of the tumor tissue to undetectable by Day 8 (fourth row/left and bottom row), while CD3+ T cells increased from undetectable to 80% by Day 11 (fourth row/right and bottom row). Spleen (and liver, lung, kidney and bone marrow) tissue CD3+ T cells peaked on Days 8 or 15 and declined by Day 29 (fifth row).

Source: Report B4-15-090.

Figure 11: Ide-cel Pharmacokinetics/Pharmacodynamics Relationships in Mice with BCMA+ Multiple Myeloma Xenografts



bb2121 = ide-cel; BCMA = B cell maturation antigen; CAR = chimeric antigen receptor; CD = cluster of differentiation; PB = peripheral blood; sBCMA = soluble BCMA.
Day 1 = dosing (25 days after injection with tumor cells). Day 29 = in-life completed.
Ide-cel (bb2121) anti-BCMA CAR T cell PK/PD relationship in NSG mice with BCMA+ RPMI-8226 MM tumor cell xenografts. Peripheral blood (PB) CD3+/CAR+ T cell counts (○) increase initially on Day 2, as CD3+ T cells begin to enter the xenograft tissue (◇). As the relative number of CD3+ T cells in the tumor tissue increased, the percentage of BCMA+ cells in the tumor tissue decreased (△), resulting in decreasing tumor volume (□). A second, ~20-fold higher peak in PB CD3+/CAR+ T cell counts occurred on Day 11, when CD3+ T cells represent 80% of the tumor tissue and BCMA+ tumor cells were undetectable. As the tumor was cleared (□), the circulating CD3+ /CAR+T cell counts (○) declined. Tumor tissue was not available after Day 11 as tumors were not detectable after Day 18. PB CD3+/CD4+/CAR+ and CD3+/CD8+/CAR+ T cell counts followed a similar pattern. Likewise, a transient increase in CD3+ T cell counts was observed in lung, liver, spleen, kidney and bone marrow (not shown) on Days 8 or 15. These PK/PD results for animals with BCMA+ xenografts receiving ide-cel indicated that: 1) PB CAR+ T cell counts were a useful PK marker that correlated with relative numbers of CD3+ T cells within MM tumor xenografts and with the BD of CD3+ T cells within other tissues and 2) serum sBCMA concentrations were a useful PD marker that directly correlated with BCMA+ tumor volume and relative numbers of BCMA+ tumor cellsFor calculation of mean values and graphical representation, a tumor volume of 1 mm^3 was assigned to tumors that were no longer detectable (0 mm^3) and the value of the LLOQ (31.25 pg/mL) was assigned to sBCMA concentrations that were <LLOQ. To allow graphical representation, the mean values for sBCMA were divided by 10 and expressed in units of pg/mL/10.
Source: Report B4-15-090.

Secondary pharmacodynamic studies

Studies of unintended off-target binding of anti-BCMA antibodies on cellular microarrays expressing BCMA-related and non-BCMA-related human proteins, and tissue cross-reactivity of anti-human BCMA antibody immunostaining of normal human tissues showed no evidence for secondary PD effects (data not shown).

Safety pharmacology programme and Pharmacodynamic drug interactions

No dedicated Safety pharmacology and Pharmacodynamic drug interactions studies have been performed. Based on the nature of the product and in line with the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014), this was considered acceptable.

2.3.3. Pharmacokinetics (PK)

Conventional PK studies were not conducted as ide-cel is an autologous human cell-based product. The PK and biodistribution of ide-cel were evaluated in NSG mice with and without BCMA+ xenografts. Because ide-cel-derived CAR+ T cells proliferate only upon binding to BCMA+ tumour cells, the use of animals with and without xenografts allowed an understanding of the kinetics of CD3+ T cells within tumour and non-tumour tissues, and of the BD of ide-cel.

In NSG mice administered ide-cel, mean peripheral blood CD3+/CAR+ T cell counts initially peaked on Day 2 and then declined; the peak on Day 2 was similar in all mice and may represent the movement of T cells from tissues where they temporarily resided after dosing. A second peak (≈20-fold higher) on Day 11 in mice with xenografts is consistent with proliferation of the CAR+ T cells upon recognition of the BCMA+ tumour cells; these circulating T cells declined after the tumour was cleared (figure 16 above). For mice with xenografts administered ide-cel, the CD3+ T cell kinetics within non-tumour tissues mirrored the proliferation of CD3+ T cells within peripheral blood, suggesting that the increased T cell frequencies in tissues reflected T cell movement in blood. These PK results for mice with BCMA+ xenografts administered ide-cel indicated that the peripheral blood CAR+ T cell count correlated with relative numbers of CD3+ T cells within MM tumour xenografts and with the biodistribution of CD3+ T cells within other tissues and is a useful PK marker.

No other nonclinical PK, biodistribution (BD), metabolism, excretion, or PK interaction studies were conducted with ide-cel. Such studies for this type of human cell therapy in nonclinical species have limited utility for translational purposes or understanding exposure-effect relationships in humans.

2.3.4. Toxicology

Conventional animal studies employing common toxicology study designs are not appropriate for ide-cel since autologous human T cells do not graft in immunocompetent animals and thus, *in vivo* nonclinical general safety, genotoxicity, carcinogenicity, developmental safety or reproductive safety studies were not conducted.

The safety of ide-cel was assessed by evaluating the potential genotoxic effects of the vector via insertional mutagenesis, and the potential transformation of transduced cells.

Single and repeat-dose toxicity

No single or repeat-dose toxicity studies were conducted with ide-cel as traditional animal studies employing common toxicology study designs are not appropriate for ide-cel since autologous human T cells do not graft in immunocompetent animals.

Genotoxicity

Ide-cel is an autologous human cellular product and therefore, standard genotoxicity studies eg, Ames assay, clastogenicity assessments were not conducted. However, vector insertion site analysis (ISA) was conducted to assess the potential risk for insertional mutagenesis due to lentiviral vector (LVV) integration into the genome resulting in the theoretical potential to disrupt the function of normal genes and/or activate oncogenes, potentially driving malignant transformation.

The LVV was identical for all studies. The design safety features of the anti-BCMA02 CAR LVV considerably reduce both the likelihood of mobilisation of the provirus from the host genome and the potential to activate transcription of adjacent oncogenes which might be localised near the proviral

insertion site. The integrated anti-BCMA02 LVV is flanked by identical HIV-1 based ΔU3 regions that contain a deletion of the U3 enhancer/promoter, conferring the self-inactivating (SIN) property that prevents LTR- driven transcription of the transgene and neighbouring genes reducing the probability of oncogenesis related to insertional mutagenesis. However, the potential genotoxic risk associated with transduction of T cells with the anti-BCMA02 CAR LVV was assessed by evaluating the vector integration pattern of the anti-BCMA02 transgene in the genome of CAR T cells from clinical ide-cel drug product (DP)_ lots.

Twenty clinical ide-cel DP lots were selected based on their respective surface CAR expression (% CAR+) and vector copy number (VCN) characteristics, that were representative of the range of clinical manufacturing experience. All the tested drug product lots were infused into patients in pivotal Study BB2121-MM-001 or supportive Study CRB-401.

The insertion site analysis of ide-cel lots from healthy donors and patients indicated no concerns of oncogenicity. There was no preferred integration in or near genes previously involved in severe adverse events in gene therapy trials (eg, CCND2, LMO2, MDS1/EVI1 [MECOM], MN1. The insertion site analysis data suggest an LVV insertion preference consistent with WT HIV and other LVV described in the literature. The analyses revealed no concerns related to integration site, polyclonality, or site preference.

Insertion site analyses of all tested drug product samples were representative of the range of vector copy number in ide-cel clinical studies to date. High Confidence -Insertion Sites showed statistically significant correlation with VCN (Spearman's ρ values of 0.8256 and 0.4797 for copies/diploid genome and copies/CAR+ T cell, respectively) (data not shown).

The insertion profile of anti-BCMA LVV demonstrated preference for the coding regions of expressed genes versus regulatory elements, which decreases the likelihood of insertions that disrupt gene regulation and therefore the probability of oncogenesis via malignant transformation (data not shown).

A highly polyclonal vector integration profile was observed across all samples.

Also, the vector exists as a single proviral sequence in 99.7% of vector containing reads indicating that the majority of vector genomes present are not in concatemeric orientation. There was no specificity of vector integration relative to the transcription start sites of known oncogenes.

Carcinogenicity

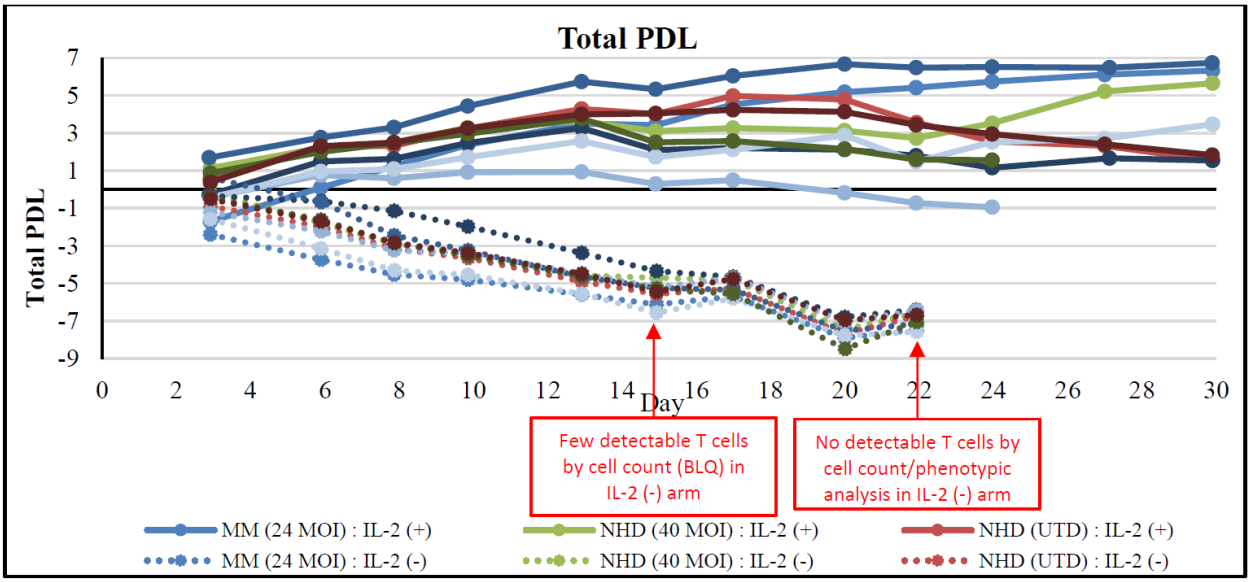
The potential of ide-cel to transform transduced T cells was assessed in an *in vitro* study of T cell growth in the presence of and absence of IL-2 (study report RPT-018530). The transition from IL-2-dependent to IL-2-independent T cell growth is known to arise following the malignant transformation of HTLV-I-infected T cells (Ahsan, 2006; Maeda, 1985; Migone, 1995; Yoshida, 2001) and is used as an indication of mutagenesis and transformation.

VCN/transduced cell in patients and normal healthy donor T cells, expanded with or without transduction with anti-BCMA02 CAR LVV, were cultured in the presence or absence of IL-2. The cells were harvested at various time points and evaluated for phenotypic composition (by flow cytometry) and T cell receptor clonal diversity (by T cell receptor [TCR] sequence analysis). Cells cultured with supplemental IL-2 were used as controls for homeostatic maintenance. The primary indicator of transformation was considered to be the expansion of cells without IL-2; secondarily, changes in phenotypic characteristics and TCR clonality provided supporting data.

For all T cell cultures (transduced or untransduced) without IL-2, the total cell numbers decreased and population doubling levels (PDLs) were negative (Figure 12). On Day 22, analysis of the culture confirmed no detectable cells. There were no increases in CAR+ expression frequency in cultures

without IL-2; changes in cultures with IL-2 were variable and donor-dependent). An overall decrease in clonal diversity was observed for all cultures, including untransduced cells but this was not considered indicative of transformation but rather a consequence of the decreasing heterogeneity over time in culture as overall T cell numbers decreased.

Figure 12: Growth profile for MM Patient and Normal Healthy Donor (NHD) DP



IL = interleukin; MM = multiple myeloma; MOI = multiplicity of infection; NHD = normal healthy donor; PDL = population doubling level; UTD = untransduced. Source: Report 018530.

Reproductive and developmental toxicity

No reproductive and developmental toxicity studies have been conducted.

Local tolerance

Although no dedicated local tolerance studies in nonclinical species were conducted, ide-cel was administered to mice as a single IV injection via tail vein with no abnormal observations recorded at the injection site.

The absence of local tolerance studies was acceptable.

Other toxicity studies

The unintended off-target binding of four anti-human BCMA antibodies to BCMA-related and non-BCMA-related proteins was assessed using a cellular microarray of HEK293 cell lines, each transfected with a vector coding for a green fluorescent protein that confirms transfection efficiency, and a single, specific transgenic human protein, which is expressed on the cell plasma membrane surface. The results indicated that HEK293 cells do not normally express BCMA or other related TNFRSF member proteins, or unrelated proteins that would be recognised by an anti-BCMA antibody, and that the tested anti-human BCMA Abs specifically bind to BCMA/TNFRSF17 only. These Abs did not bind to any of the 22 tested TNFRSF member proteins, or to any of 358 unrelated proteins (data not shown).

Furthermore, BCMA does not appear to share cross-reactive epitopes with other TNFRSF member proteins (data not shown).

A GLP-compliant tissue cross-reactivity study was conducted to address the target and off-target binding in normal human tissues. Target and off-target binding studies of anti-BCMA antibodies and a tissue reactivity study confirmed the expression and distribution of BCMA in normal human tissues. Staining of plasma membrane and cytoplasm was observed of resident, migrating, and/or infiltrating mononuclear cells in several human tissues including colon, Fallopian tube, oesophagus, small intestine, stomach, lymph node, parathyroid, prostate, salivary gland, thymus, and tonsil (data not shown). In addition, staining of spindle cells in thyroid and tonsil were also seen. The spindle cell staining was considered unexpected due to lack of supportive literature, but since staining was observed in only two tissues, nonspecific staining of this cell type cannot be ruled out. The staining of the membrane and cytoplasm of resident, migrating, and/or infiltrating mononuclear cells in human tissues was expected, based on supportive literature reports of BCMA expression on plasma cells in normal human tissues (Bellucci, 2005; Carpenter, 2013; Kalled, 2005; Laabi, 1994; Laabi, 1992; Ng, 2004; O'Connor, 2004).

2.3.5. Ecotoxicity/environmental risk assessment

For ide-cel drug product, the criteria listed in the "Good Practice on the assessment of genetically-modified organism (GMO)-related aspects in the context of clinical trials with human cells genetically modified by means of retro/lentiviral vectors, Version 3" are considered fulfilled. The submission of a simplified environmental risk assessment (ERA) report is therefore appropriate.

Environmental risk associated with ide-cel is considered negligible. Human cells cannot proliferate in the environment and the applicant has demonstrated the absence of replication competent lentivirus (RCL) in the ide-cel final drug product as well as for in-process controls. Potential hazards is therefore only related to human health and thus potential exposure of, in particular, immune-incompetent persons. Potential hazards to animal health or the environment are not applicable.

2.3.6. Discussion on the non-clinical aspects

Pharmacology

The pharmacological data show that ide-cel has a BCMA antigen-specific dose-dependent activity against both low and high BCMA+ expressing tumours, and that it secretes cytokines, proliferates and kills a variety of multiple myeloma and lymphoma tumour cell lines. Collectively, immunohistochemistry data demonstrate the ability of ide-cel to express the anti-BCMA CAR, to specifically recognise and bind to BCMA on MM and B cell malignancy tumour cells, and then undergo signalling of the CAR and activation of the CAR+ T cells. This ide-cel activity resulted in BCMA specific release of IFN-γ, BCMA-specific cytolysis of BCMA+ tumour cells but not BCMA-negative cells, and subsequent BCMA-specific proliferation of the CAR+ T cells. The primary pharmacodynamics activity ie. cytolysis of BCMA+ tumour cells, was demonstrated by reduction in tumour volume, elimination of BCMA+ tumour xenografts, and decreases of tumour-associated serum soluble BCMA. Rapid elimination of both subcutaneous and systemic tumours and increased survival was demonstrated in NSG mice with BCMA+ xenografts after a single dose of ide-cel. Ide-cel activity was shown in both high and low BCMA+ tumour cell lines. In mice, the minimum effective dose (MED) for a single dose of ide-cel to eliminate multiple myeloma tumours was 6.16×10^5 CAR+ T cells with relatively high BCMA expression which represents the human equivalent dose (HED) of 2.05×10^8 CAR+ T cells for a 100-kg human. Collectively, the pharmacological data provide sufficient evidence for pharmacological activity and a proof of concept for the use of ide-cel in the treatment of patients with multiple myeloma. As

well, the *in vivo* pharmacology studies indicated that a single dose of ide-cel has potent, dose-dependent activity against both low and high density BCMA+ expressing tumours and provides a strong mechanistic basis for the use of ide-cel in BCMA+ malignancies. The data support the hypothesis that all primary human MM should be recognised and killed by ide-cel, as ide-cel is able to secrete cytokines, proliferate and kill tumours cell lines with low receptor density. It is also expected that ide-cel will deplete healthy plasma cells that express BCMA.

Pharmacokinetics

Conventional pharmacokinetics evaluation was not conducted with ide-cel. However, sufficient characterisation of CAR T cell kinetics and biodistribution to selected organs was performed.

Toxicology

Lack of toxicity studies

Due to the lack of appropriate animal models for toxicity evaluation, no conventional toxicity studies were conducted.

Risk of insertional mutagenesis and tumorigenic transformation

A tailored safety evaluation was conducted which focused on the investigation of the risk of insertional mutagenesis due to lentiviral integration in the genome of ide-cel CAR T cells and the potential of tumorigenic transformation induced in the manufacture of the product.

The insertion site analysis data indicated no concerning observations related to integration, polyclonality, or insertion site preference across the range of vector copy number (VCN) observed in clinical studies. The results for the lentiviral vector insertion preference were consistent with wild type HIV virus and other described lentiviral vectors. There was also no preferred integration in or near genes previously involved in severe adverse events in gene therapy trials (eg, CCND2, LMO2, MDS1/EVI1, or MN1.)

No tumorigenic transformation of T cells following transduction in the ide-cel manufacturing process was observed in the IL-2 independent growth study. Moreover, there were no substantial changes in CAR T cell phenotypes or CD4:CD8 ratio, or substantial decreases in clonal diversity under any condition tested. These indicate that the tumorigenic risk related to the ide-cel manufacturing process is negligible.

Reproductive and developmental toxicity

It is argued that germline transmission is unlikely since residual infectious anti-BCMA02 CAR LVV particles were not detected in ide-cel drug product, and it has been demonstrated that VSV-G pseudotyped lentiviral vectors can be expected to be inactivated by the human serum complement. Further, the Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors, EMEA/273974/2005 indicates that the risk of germline transmission associated with the administration of genetically modified human cells is considered to be low and, as animal testing of human cells may be difficult or not meaningful, non-clinical germline transmission studies of human genetically modified cells are not recommended.

ERA

Environmental risk associated with ide-cel is considered to be negligible.

The CHMP endorse the CAT discussion on the non-clinical aspects as described above.

2.3.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic *in vitro* and *in vivo* studies provided adequate evidence that ide-cel specifically target BCMA which leads to CAR+ T cell activation, proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Ide-cel comprises engineered human T cells, therefore there are no representative *in vitro* assays, ex vivo models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for drug development were not performed.

Genotoxicity assays and carcinogenicity studies were not conducted.

In vitro expansion studies from healthy donors and patients showed no evidence for transformation and/or immortalisation and no preferential integration near genes of concern in ide-cel T cells.

Given the nature of the product, non-clinical studies on fertility, reproduction and development were not conducted.

In conclusion the non-clinical data provided are considered acceptable.

The CHMP endorse the CAT conclusions on the non-clinical aspects as described above.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Table 2:

Clinical Studies Supporting the Ide-cel MAA

Study	Title	Data Cutoff Date	Number of Subjects
Pivotal Study (Efficacy and Safety)			
MM-001	A Phase 2, Multicenter Study to Determine the Efficacy and Safety of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma (KarMMa)	16 Oct 2019[a]	140 Enrolled 128 Treated[b]
Supportive Study (Efficacy and Safety)			
CRB-401	A Phase 1 Study of bb2121 in BCMA-expressing Multiple Myeloma	22 Jul 2019[c]	67 Enrolled 62 Treated[b]
Other Ongoing Studies (Safety)			
MM-001-Japan[d]	A Phase 2, Multicenter Study to Determine the Efficacy and Safety of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma	16 Oct 2019	9 Enrolled 3 Treated[e]
MM-002	A Phase 2, Multicohort, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma and in Subjects With Clinical High-Risk Multiple Myeloma (KarMMa-2)	16 Oct 2019	51 Enrolled 31 Treated[e]
MM-003	A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Regimens in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3)	16 Oct 2019	–[f]
Long-term Follow-up Studies (Safety)			
GC-LTFU-001[g]	Long-term Follow-up Protocol for Subjects Treated With Gene-modified T Cells	22 Jul 2019 (CRB-401) 16 Oct 2019 (MM-001)	15 Enrolled[h]
LTF-305[g]	Long-term Follow-up of Subjects Treated With bb2121	22 Jul 2019	20 Enrolled

bb2121 = ide-cel; BCMA = B-cell maturation antigen; ide-cel = idecabtagene vicleucel; LTFU = long-term follow-up; MAA = Marketing Authorisation Application; RRMM = relapsed and refractory multiple myeloma.

a. The data cutoff date for Study MM-001 is 10 months after the last subject was infused with ide-cel (CSR MM- 01 Section 9.7.1).
b. Number of subjects who received ide-cel as of the data cutoff date.
c. The data cutoff date for Study CRB-401 is approximately 7 months after the last subject was infused with ide-cel (CSR CRB-401 Section 9.7.1).
d. Study MM-001-Japan is being conducted only in Japan and is considered a separate study from Study MM-001.
e. Number of subjects who received ide-cel as of 30 Aug 2019 with approximately 2 months of follow-up.
f. A total of 23 subjects were randomised as of 16 Aug 2019 with at least 2 months of follow-up. A total of 22 subjects were treated in 2 treatment arms (ide-cel and standard of care). To preserve the randomisation of this ongoing comparative study, only aggregated data from the 2 treatment arms are presented. The number of subjects exposed to ide-cel is not reported separately.
g. Safety data from subjects in the 2 LTFU studies (GC-LTFU-001 and LTF-305) were integrated and are presented with the safety data for the corresponding parent study in which the subjects were originally enrolled (ie, Studies MM-001 and CRB-401, as appropriate). Subjects are counted only once under the parent study.
h. Includes 5 subjects from Study MM-001 and 10 subjects from Study CRB-401; 4 of 10 subjects from Study CRB-401 were initially enrolled in Study LTF-305 and later transitioned to Study GC-LTFU-001.

2.4.2. Pharmacokinetics

Pharmacokinetics

Analytical methods

Bioanalytical methods used in the clinical studies for Ide-cel include a qPCR to detect Ide-cel Transgene in Whole Blood and CD3-Enriched Blood as well as an electrochemiluminescent (ECL) assay for the detection of Anti-drug Antibodies to Ide-cel in Serum. In addition, an ELISPOT assay for determination of cellular immunogenicity is presented.

A real-time quantitative polymerase chain reaction (qPCR) assay was used to quantify ide-cel transgene in gDNA isolated from CD3+ cells for pharmacokinetic exposure/effect analysis in clinical studies MM-001 and CRB-401. In this method Ide-cel transgene copies per reaction are determined through the quantification of Psi-Gag, which is a gene that is present in the lentiviral vector that is used to transduce cells. Human RNaseP, a housekeeping gene, is used to normalise gDNA input for each sample. The assay has been validated to quantify ide-cel transgene copies in genomic DNA (gDNA) isolated from enriched CD3-positive (CD3+) cells and/or directly from whole blood.

An electrochemiluminescent (ECL) immunoassay on MSD platform was used to detect Antidrug antibodies in human serum samples in clinical studies MM-001 and CRB-401. Detection of ADA was based on the bivalent nature of antibodies and the assay utilises a reagent that corresponds to the extracellular domain of the ide-cel CAR, BB2121-CAR-ECD. In this assay, samples are pre-incubated with biotinylated BB2121-CAR-ECD and ruthenylated BB2121-CAR-ECD, and any anti-drug antibodies present in the serum sample will form a bridge between the conjugated reagents. The complex is then bound to a blocked MSD-Streptavidin (MSD-SA) plate, and detected by a chemiluminescent signal. The resulting electrochemiluminescent signal (ECL or relative lights units, RLU) is directly proportional to the amount of ADA present in the human serum.

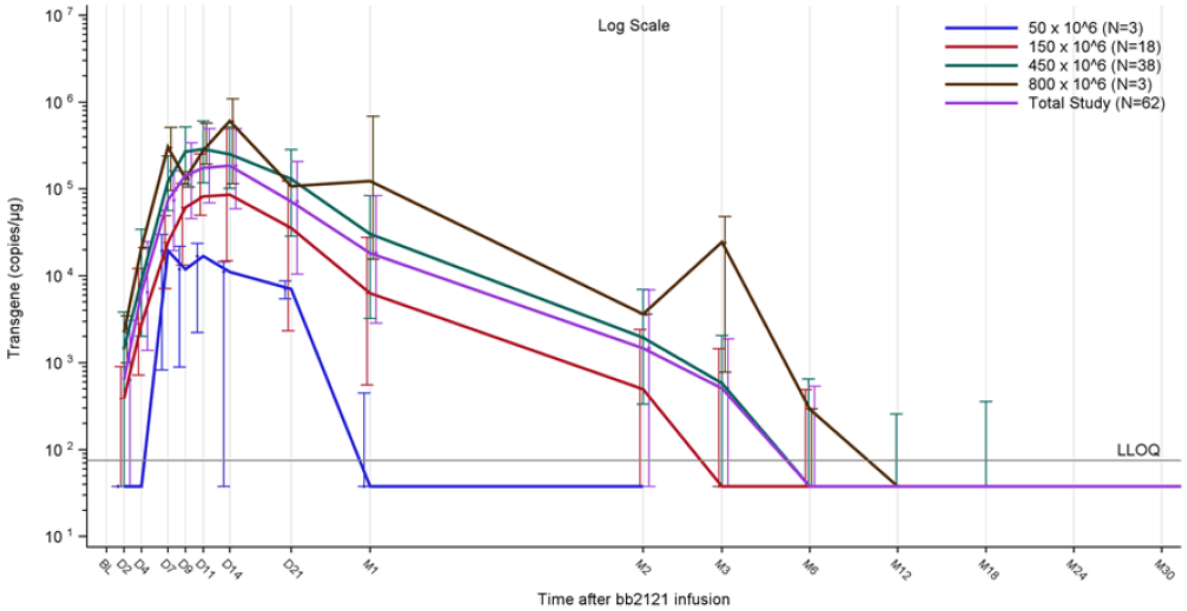
Cell-mediated immune responses were evaluated using an IFN-γ ELISPOT assay in clinical study MM-001. In this assay, the subject's PBMC samples were stimulated ex-vivo using peptides that spanned the extracellular domain of the CAR construct. An antigen-specific cellular immune response and the resulting production of IFN-γ were detected by ELISPOT where the secreted IFN-γ is captured by the anti-IFN-γ antibody immobilised on PVDF surface, detected using a biotinylated second anti-IFN-γ antibody, and visualised as coloured spots using streptavidin-HRP conjugate and BCIP/NBT substrate.

Pharmacokinetics

The application dossier consisted of interim results from two clinical trials, CRB-401 and MM-001. Study CRB-401 was a first-in-human, 2-part, nonrandomised, open-label, multicentre, Phase 1 study in subjects with relapsed or refractory multiple myeloma (RRMM). An exploratory objective of study CRB-401 was to characterise the expansion of CAR+ T cells in the peripheral blood.

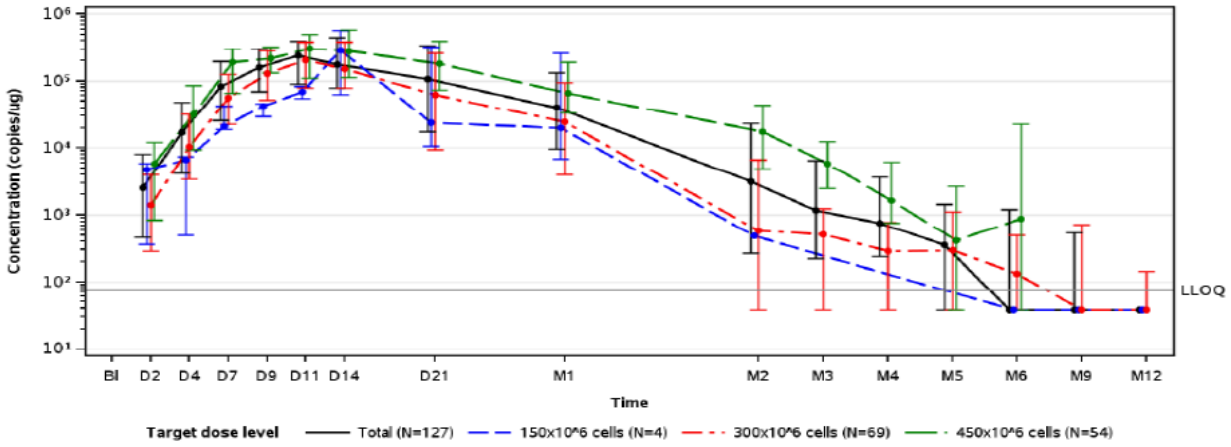
Study MM-001 was an open-label, single-arm, multicentre, multinational, Phase 2 study to evaluate the efficacy and safety of ide-cel in subjects with relapsed or refractory MM. One of the secondary objectives of MM-001 was to characterise the expansion of CAR+ T cells in the peripheral blood. The pharmacokinetic (PK) analysis population included 127 subjects. The time course data for these two trials is shown in Figures 13 and 14 the relevant PK parameters are shown in Tables 3 and 4.

Figure 13: Study CRB-401 Transgene Level Versus Time by Ide-cel Target Dose (Semi-log Scale) (PK Analysis Population)



bb2121 = ide-cel; CAR = chimeric antigen receptor; D = day; LLOQ = lower limit of quantitation; M = month; Q = quartile.
Solid grey horizontal line represents the limit of quantification (75 copies/µg). The plot shows median (Q1, Q3) time course profiles.
Note: One subject dosed at 205 × 10^6 CAR+ T cells in Part B Cohort 1 and 1 subject dosed at 305 × 10^6 CAR+ T cells in Part B Cohort 3 are included under the target dose of 450 × 10^6 CAR+ T cells.
Data cutoff date: 23 Apr 2019.
Source: Figure 14.2.6.4.3

Figure 14: Study MM-001 Transgene Versus Time Course by Ide-cel Target Dose (Semi-log Scale) (PK Analysis Population)



B = baseline; D = day; LLOQ = lower limit of quantification; M = month; PK = pharmacokinetic.
Solid grey horizontal line represents lower limit of quantification (75 copies/ug).
The plot shows median (Q1, Q3) time course profile.
Data cutoff date = 19 Apr 2019.
Source: Figure 14.2.7.3.1.

Table 3:

Summary of Study CRB-401 Ide-cel Pharmacokinetic Parameters (PK Analysis Population)

Pharmacokinetic Parameter	Parts A and B Combined by Ide-cel (CAR+ T Cells) Target Dose				RP2D (N = 56)[a]	Total Study (N = 62)[a]
	50×10^6 (N = 3)[a]	150×10^6 (N = 18)[a]	450×10^6 (N = 38)[a]	800×10^6 (N = 3)[a]		
C_{max}, copies/µg	10,907 (245)	107,335 (489)	306,727 (133)	389,278 (114)	218,866 (242)	194,650 (295)
T_{max}, days	7 (7, 10)	11 (4, 22)	11 (7, 20)	11 (10, 14)	11 (4, 22)	11 (4, 22)
T_{last}, days	21 (10, 30)	29.5 (14, 344)	91 (14, 555)	175 (90, 178)	84 (14, 555)	84 (10, 555)
$AUC_{0\text{-}28days}$, days*copies/µg	82,184 (722)	1,141,448 (509)	3,483,374 (155)	5,166,140 (184)	2,433,626 (271)	2,142,260 (366)
$AUC_{0\text{-}3M}$, days*copies/µg	288,445 [n = 1]	1,960,965 (468) [n = 16]	4,264,100 (171) [n = 36]	7,205,195 (262)	3,357,570 (252) [n =52]	3,347,769 (262) [n = 56]
$AUC_{0\text{-}6M}$, days*copies/µg	288,445 [n = 1]	2,614,645 (432) [n = 13]	4,433,749 (179) [n = 35]	7,432,030 (272)	3,842,848 (232) [n = 48]	3,797,980 (245) [n = 52]
$AUC_{0\text{-}9M}$, days*copies/µg	288,445 [n = 1]	2,628,137 (433) [n = 13]	4,465,385 (179) [n = 35]	7,461,621 (270)	3,868,211 (233) [n = 48]	3,821,989 (246) [n = 52]

$AUC_{0\text{-}28days}$ = area under the curve of the transgene level from time of dose to 28 days; $AUC_{0\text{-}3M}$ = area under the curve of the transgene level from time of dose to 3 months; $AUC_{0\text{-}6M}$ = area under the curve of the transgene level from time of dose to 6 months; $AUC_{0\text{-}9M}$ = area under the curve of the transgene level from time of dose to 9 months; C_{max} = maximum transgene level occurring at T_{max}; CV = coefficient of variation; max = maximum; min = minimum; RP2D = recommended Phase 2 dose (150 to 450 × 10^6 CAR+ T cells); T_{last} = time of last measurable transgene level; T_{max} = time of maximum observed transgene level.

[a] For each target dose column, sample size is provided in parenthesis, unless otherwise noted by square brackets for specific PK parameter.

Note: One subject dosed at 205 × 10^6 CAR+ T cells in Part B Cohort 1 and 1 subject dosed at 305 × 10^6 CAR+ T cells in Part B Cohort 3 are included under the target dose of 450 × 10^6 CAR+ T cells.

Data are shown as geometric mean (%geometric CV) except for T_{max} and T_{last} which are shown as median (min, max). Median values for all PK parameters are presented in Table 14.2.8.2.3.

Data cutoff date: 23 Apr 2019.

Source: Table 14.2.8.2.3

Table 4:

Summary of Study MM-001 Ide-cel Pharmacokinetic Parameters (PK Analysis Population)

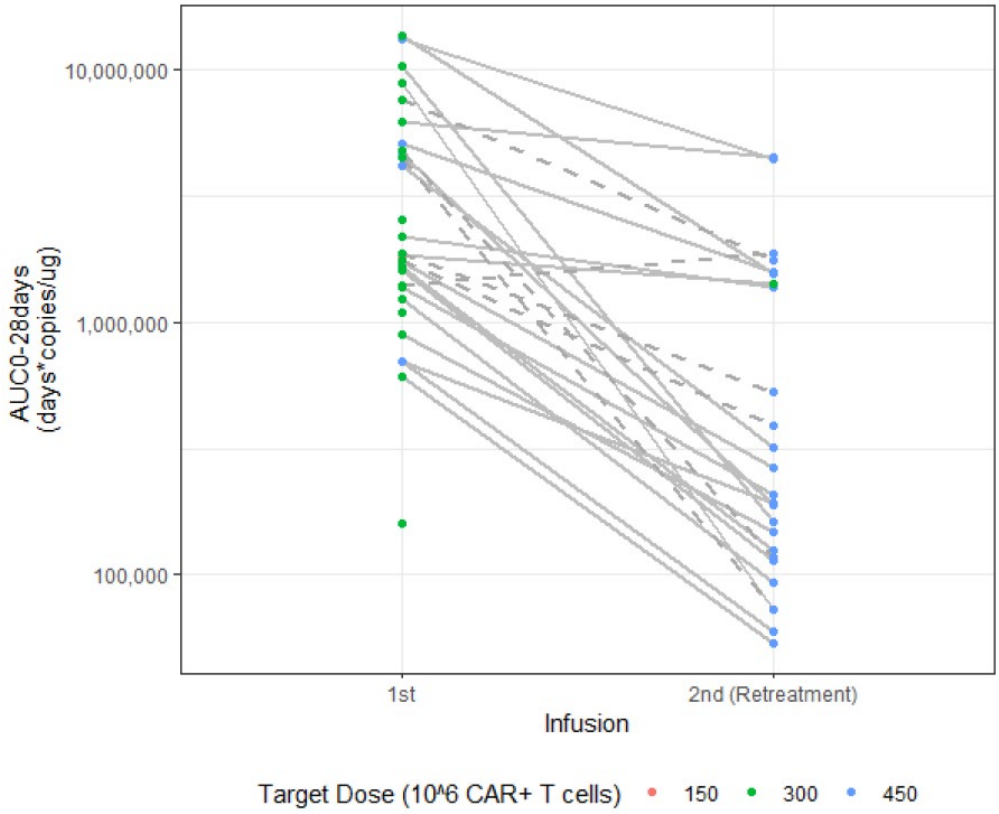
Pharmacokinetic Parameter	Ide-cel (CAR+ T cells) target dose			
	150×10^6	300×10^6	450×10^6	Total 150 to 450×10^6
C_{max} (copies/µg)	204,229 (169) N =4	180,185 (210) N = 69	321,117 (126) N = 54	231,278 (178) N = 127
T_{max} (days)	14 (11-14) N =4	11 (7-30) N =69	11 (7-28) N = 54	11 (7-30) N= 127
T_{last} (days)	58 (29-142) N =4	119 (21-365) N =69	115 (22-184) N = 54	119 (21-365) N =127
$AUC_{0\text{-}28days}$ (days*copies/µg)	1,942,929 (154) N = 4	2,138,414 (215) N = 68	4,277,327 (152) N = 53	2,860,340 (197) N = 125
$AUC_{0\text{-}3M}$ (days*copies/µg)	4,372,535 (1023) N = 2	2,952,312 (213) N = 62	5,955,266 (170) N = 51	4,057,643 (208) N = 115
$AUC_{0\text{-}6M}$ (days*copies/µg)	4,413,811 (997) N = 2	3,249,486 (214) N =59	6,528,331 (180) N = 47	4,427,242 (213) N = 108
$AUC_{0\text{-}9M}$ (days*copies/µg)	4,420,074 (993) N = 2	3,276,494 (225) N = 56	6,572,367 (181) N = 47	4,499,940 (219) N = 105

$AUC_{0\text{-}28\ days}$ = area under the curve of the transgene level from time of dose to 28 days; $AUC_{0\text{-}3M}$ = area under the curve of the transgene level from the time of dose to 3 months; $AUC_{0\text{-}6M}$ = area under the curve of the transgene level from the time of dose to 6 months; $AUC_{0\text{-}9M}$ = area under the curve of the transgene level from the time of dose to 9 months; C_{max} = the maximum transgene level occurring at T_{max}; CV = coefficient of variation; max = maximum; min = minimum; N = number of subjects; PK = pharmacokinetic; T_{max} = the time of maximum observed transgene level; T_{last} = time of last measurable transgene level.
Note: Data are presented as geometric mean (%geometric CV) except T_{max} and T_{last} shows the median (min – max). Median values for all PK parameters can be found in Table 14.2.8.2.1.
Data cutoff date = 19 Apr 2019.
Source: Table 14.2.8.2.1

Regarding persistence of ide-cel over time, study CRB-401 found that 4/18 samples had detectable ide-cel transgene copy numbers at 12 months, and the respective number was 4/11 for study MM-001. This suggests that ide-cel can persist in peripheral blood for up to 1 year post-infusion, or longer.

As of the data cutoff dates, 17 subjects in study CRB-401 and 29 subjects in study MM-001 received a second dose of ide-cel at a target dose ranging from 150 to 450 × 10^6 CAR+ T cells. Comparing cell expansion parameters after first and second fusion in retreated study CRB-401 subjects, $AUC_{0\text{-}28days}$ and Cmax were 21-fold and 16-fold lower, respectively, when subjects were retreated (data not shown). Similarly, cell expansion parameters after the first and second infusion in the 29 retreated study MM-001 subjects, the $AUC_{0\text{-}28days}$ and Cmax were 7-fold and 6-fold lower, respectively, when subjects were retreated. Figure 15 displays the individual $AUC_{0\text{-}28days}$ for the first and second infusion, stratified by objective response. Cellular expansion parameters after first infusion in retreated subjects were comparable with the overall population.

Figure 15: $AUC_{0\text{-}28days}$ following first and second infusion for retreated subjects in study MM-001



Dashed grey lines represent subjects who achieved an objective response after retreatment; solid grey lines represent subjects who did not achieve an objective response after retreatment. For subject's first infusion, objective response is reported based on the Independent Response Committee (IRC) adjudicated assessment according to International Myeloma Working group (IMWG) Uniform Response Criteria for Multiple Myeloma. For subject's retreatment, objective response is reported as Investigator Reported Assessment. Data cut off: 07 Apr 2020.

Study MPK-001: Covariate-exposure, exposure-response and exposure-efficacy analyses

A PK characterisation analysis was performed using data from the Pivotal Study MM-001 through characterisation of impact of covariates on cellular expansion and estimation of the PK exposure parameters for relevant subject subgroups. Individual exposure parameters were obtained through noncompartmental analysis methods from the cellular expansion time course data. The specific parameters that were included as part of the evaluations were: Cmax, $AUC_{0\text{-}28days}$ and $AUC_{0\text{-}3M}$. All PK parameters were dose-normalised prior to analysis, unless stated otherwise.

Several pre-specified covariates were explored for graphical trends with cellular expansion parameters. Briefly, the evaluated covariates were in the following major categories:

- Baseline demographic factors, including sex, age, body weight, body surface area (BSA), race, and ethnicity;
- Disease factors, such as number of prior multiple myeloma (MM) regimens, last prior multiple myeloma (MM) therapy (such as corticosteroids), extramedullary disease, Eastern Cooperative Oncology Group (ECOG) performance status, concomitant medications of tocilizumab or corticosteroids administered to manage cytokine release syndrome (CRS), bridging therapy
- Baseline/Preinfusion variables, for instance, serum sBCMA levels, urine monoclonal protein (m-protein); serum m-protein; and

- Antidrug antibody (ADA) status: Development of postinfusion ADAs (as binary variable) was evaluated on cell expansion kinetics.

A graphical assessment of all covariate-parameter combinations was performed (data not shown). Based on these evaluations, covariates, such as age, race, ethnicity, sex, ADA status, and number of prior anti-MM therapies were not found to influence the cell expansion parameters.

Table 5 shows the results of statistically significant (continuous) covariates for $AUC_{0\text{-}28days}$, for each attempted functional form of the model. Since BSA is highly correlated with body weight, these effects are considered secondary to the effects of body weight, and any further assessment of the clinical relevance of these effects focused on body weight.

Table 5:

Univariate Correlations between Dose-Normalised $AUC_{0\text{-}28days}$ and Statistically Selected Continuous Covariates: Study MM-001

Covariate	Model	AIC	Estimate (%RSE)	P-value[a]
Body weight	Linear	4179.2	-57427 (43.6%)	0.0235*
	Exponential	4178.3	-0.0165 (38.5%)	0.0105*
	Power	4176.9	-1.309 (32.0%)	0.0022*
Body Surface Area	Linear	4091.0	-3088725 (50.6%)	0.0506
	Exponential	4090.2	-0.922 (42.2%)	0.0195*
	Power	4089.3	-1.858 (36.7%)	0.0074*
Baseline Soluble BCMA	Linear	4149.4	2093 (62.5%)	0.1125
	Exponential	4150.0	0.00035 (74.6%)	0.1828
	Power	4146.7	0.197 (47.0%)	0.0353*

AIC = Akaike Information Criterion; $AUC_{0\text{-}28days}$ = area under the curve of the transgene level from time of dose to 28 days postinfusion; CAR = chimeric antigen receptor; BCMA = B-cell maturation antigen; %RSE = Relative standard error (as percent).

[a] P-value of no effect of covariate on dose-normalized $AUC_{0\text{-}28days}$.

* Statistically significant ($P < 0.05$)

The dose-normalized $AUC_{0\text{-}28days}$ values were normalized to a dose of 300 $x10^6$ CAR+ T cells

Source: Report MPK-001, Table 9

When stratified by target dose, there was an apparent graphical relationship between body weight and absolute (i.e. not dose-normalised) $AUC_{0\text{-}28days}$ and $AUC_{0\text{-}3M}$ following 300 x 10^6 target dose ($p<0.01$), but no trend of any relationship at the 450 x 10^6 target dose level ($p>0.84$).

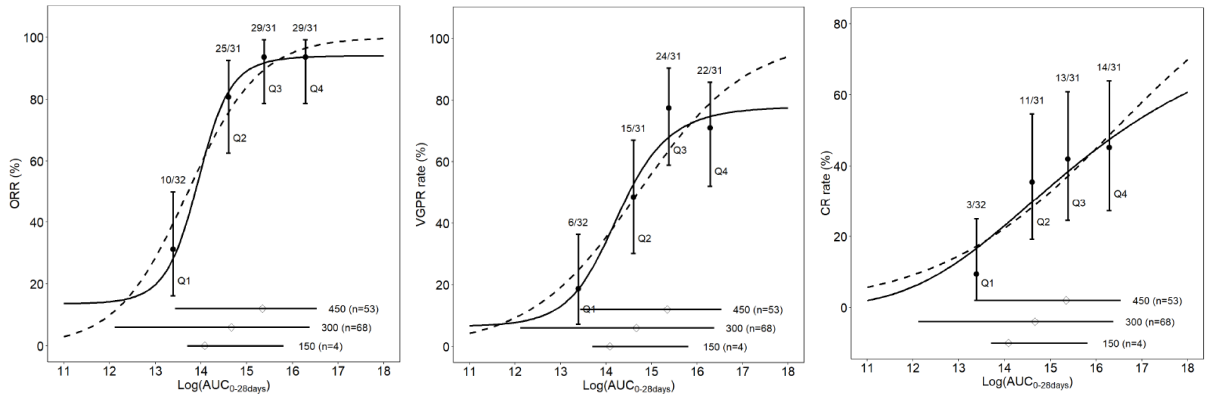
Retreatment baseline sBCMA for subjects in MM-001 had an approximate range between 0-1200 ng/mL, and showed comparable distribution as baseline before the initial infusion There was a statistically significant relationship between retreatment baseline sBCMA and $AUC_{0\text{-}28days}$ ($r=0.50$, $p=0.014$), but not C_{max} ($r=0.15$, $p=0.44$).

The exposure-response (ER) analyses characterised the relationship between individual observed exposures (and other covariates) and efficacy endpoints from Study MM-001. The exposure-efficacy analyses were performed using a data cutoff date of 19 Apr 2019, corresponding to ≥ 3 months of follow-up after the last subject was infused with ide-cel. Subject-level exposures were calculated through noncompartmental methods. A total of 127 subjects had both evaluable PK parameters and efficacy endpoints. The objective of these analyses was to evaluate the ER of ide-cel efficacy endpoints and characterise established ER relationships through model-based simulations and provide support for the proposed dose range. The key efficacy endpoints examined for relationship to exposure parameters

summarised in this document include overall response rate (ORR), very good partial response (VGPR) or better, complete response (CR) rate, and progression-free survival (PFS).

Both a linear and (sigmoid) Emax functional form was attempted in the logistic regression E-R framework. Figure 16 shows observed mean ORR, VGPR and CR at each quartile of log($AUC_{0-28days}$) along with model predicted curves from linear and (sigmoid) Emax models. For ORR and VGPR, the sigmoid Emax model was selected as the final model to perform model-based simulations. Sex (M/F) was included as a covariate into the ER model for ORR because it was identified as a statistically significant predictor of ORR from the stepwise covariate selection process. Race and ethnicity were not considered for inclusion in the final model, and were excluded from the covariate selection process, because they were unknown for more than 10% of the subjects in the ER analysis. For CR, the linear model was selected as the final model to perform model-based simulations. The stepwise covariate selection process identified baseline serum m-protein level as a significant covariate. This covariate was dichotomised to ≤10 g/L and >10 g/L in the current analysis. The model indicates a higher CR rate for subjects with baseline serum m-protein level ≤10 g/L at baseline than for subjects with baseline serum m-protein level >10 g/L at baseline.

Figure 16: Observed and Model-predicted ORR, VGPR and CR Rate by Log($AUC_{0-28days}$): Study MM-001



$AUC_{0-28days}$ = area under the curve of the transgene level from time of dose to 28 days postinfusion; ORR = overall response rate; VPGR=very good partial response or better; CR=complete response.
The error bars represent the observed mean ORR with associated 95% CI for quartiles of log($AUC_{0-28days}$) and are plotted at the median log($AUC_{0-28days}$) of each quartile (Q1-Q4). The numbers above the error bars (x/y) represent the number of subjects who achieved the response (x) and the total number of subjects (y) within each of the quartiles. The solid and dashed lines show the model-predicted exposure-response (ER) relationship based on the sigmoid E_{max} model and the linear model, respectively. The horizontal lines with diamonds represent medians and 90% log($AUC_{0-28days}$) ranges at each target dose level (x 10^6 CAR+ T cells), with n the number of subjects at each dose level. The horizontal lines illustrate the strong overlap of exposure across the target dose levels.

Similar to the analyses for efficacy endpoints, exposure safety analyses were performed using data from the Pivotal Study MM-001. Safety events that were evaluated in relation to $AUC_{0-28days}$ included: CRS requiring tocilizumab (tCRS), CRS requiring corticosteroids (sCRS), higher grade CRS (defined as CRS ≥ Grade 3), investigator identified neurotoxicity (iiNT), and cytopenia. Subject-level exposures were calculated through noncompartmental methods. The exposure-safety analyses were performed using a data cutoff date of 19 Apr 2019, corresponding to ≥ 3 months of follow-up after the last subject was infused with ide-cel.

For exposure-response analyses of tCRS and sCRS, subjects were categorised based on occurrence of CRS that required treatment with tocilizumab (n=66) or steroids (n=18), respectively, and subjects who experienced CRS but did not require treatment with these medications and subjects who did not have CRS. All subjects who experienced an sCRS event also required treatment with tocilizumab, and the ER

characterisation for tCRS would therefore be identical to the results of an analysis using a combined CRS end point. Graphical evaluation showed an exposure-response trend for $AUC_{0.28d}$ and Cmax vs. tCRS, primarily driven by lower rates in the first exposure quartile. There appeared to be no further increase in tCRS rates in the higher three exposure quartiles. An apparent ER relationship for sCRS was also observed with a lower proportion of subjects with this adverse event (AE) in the lowest two quartiles (Q1, Q2); events appeared to plateau in the highest two (Q3, Q4) exposure quartiles.

For higher grade CRS (Grade ≥ 3), given the limited number of events observed in the study, an exposure-response trend was not observed. Neurotoxicity was defined as iiNT. With the limited number of these safety events, graphical evaluation of Grade 2 or higher iiNT and iiNT requiring treatment with corticosteroids, showed no clear relationship to exposures. Graphical evaluation of thrombocytopenia and neutropenia recovery (for subjects who experienced this safety event) showed no apparent relationship to exposure. Subsequently, no exposure-response modeling was attempted for higher grade CRS, iiNT, or thrombocytopenia and neutropenia recovery.

2.4.3. Pharmacodynamics

Various pharmacodynamics parameters were explored. The assessments included

- Characterisation of immune-related soluble factors (cytokine levels)
- Blood and Bone Marrow Analysis for CAR and BCMA.
- Transgene Levels: Transgene levels were determined from DNA in whole blood, blood T cells, and bone marrow to monitor for persistence of vector sequences.
- Blood Lymphocyte Subset Analysis: Blood was collected and analysed for immune cell subsets, including B cells, natural killer (NK) cells, and T cell subsets.
- CAR T Cell Phenotyping, including the analysis of CAR T cell subsets and markers of memory, activation, trafficking, and/or markers of T cell exhaustion.

Cytokine expression and BCMA expression are discussed in this section as pharmacodynamic markers of Abecma activity.

Immune-related Soluble Factors

The cytolytic mechanism of action of Abecma relies on antigen-dependent activation and proliferation of CAR T cells via engagement of BCMA expressed on the cell surface of normal or tumour plasma cells. An analysis was conducted to evaluate 27 soluble factors (including markers of inflammation, CRP and ferritin) as markers of activation to understand pharmacodynamic changes post Abecma infusion. Soluble factors characteristic of T cell activation were induced, with most soluble factors showing a dose dependent relationship. Peak elevation of most of the soluble factors was generally observed within the first 7 days after Abecma infusion and returned to baseline levels within the first month after infusion.

Increases in interleukin-2 (IL-2), IL-6, interferon- γ (IFN-γ), and tumour necrosis factor (TNF) levels as examples are shown in **Error! Reference source not found.**.

No significant associations of immune-related soluble factors at screening, or baseline were found between subjects with low versus high tumour burden (≥ 50%, < 50% bone marrow CD138+ expression by immunohistochemistry), by tumour BCMA expression level or presence of extramedullary plasmacytoma. Some differences in C_{max} concentrations were observed by sBCMA levels (higher levels of ferritin and MIP-1α were observed in subjects with high baseline sBCMA and higher levels of IL-4 were observed in subjects with low baseline sBCMA).

Table 6: Baseline and C_{max} IL-2, IL-6, IFN-γ, and TNF Levels Up to Month 1 by Target Dose (MM-001)

Soluble Factor (units)	Endpoint	Ide-cel (CAR+ T cells) Target Dose			
		$150x10^6$ (N = 4) Median Q1, Q3	$300x10^6$ (N = 66) Median Q1, Q3	$450x10^6$ (N = 54) Median Q1, Q3	Total 150 to $450 x 10^6$ (N = 124) Median Q1, Q3
IL-2 (pg/mL)	Baseline	8.30 7.2, 9.1	8.35 5.4, 14.0	18.00 9.8, 34.0	11.00 6.6, 21.0
	C_{max}	17.50 13.5, 25.0	40.00 23.0, 23.0	57.00 37.0, 85.0	44.00 28.0, 71.5
IL-6 (pg/mL)	Baseline	7.85 7.0, 9.8	12.00 6.6, 20.0	13.00 8.2, 25.0	12.00 7.2, 22.0
	C_{max}	76.50 31.0, 5952.0	304.00 60.0, 4130.0	3840.00 216.0, 15950.0	821.00 75.0, 9645.0
INF-γ (pg/mL)	Baseline	26.5 21, 31	27.5 11, 55	78.0 40,162	40.5 19, 87
	C_{max}	67.0 57, 80	244.5 131, 647	1130.0 340, 9030	453.0 170, 1850
TNF (pg/mL)	Baseline	19.5 17, 28	19.0 14, 25	26.0 20, 33	22.0 17, 29
	C_{max}	46.5 31, 60	69.5 51, 90	114 62, 192	79.5 53, 131

C_{max} = maximum observed value measured up to M1; ide-cel = idecabtagene vicleucel; IL = interleukin; IFN-γ= interferon gamma; Q = quartile; TNF = tumor necrosis factor.
Note: Baseline = day of ide-cel infusion;
Data cutoff date: 16 Oct2 019
Source: Table 1.1.

Cytokine levels and CRS

Pre-infusion soluble factor levels were investigated for potential prognostic value to subjects developing CRS. There was no association of pre-infusion soluble factor levels at screening, at baseline, or the fold change between screening/baseline for any grade CRS.

Ten immune-related soluble factors: GM-CSF, IFN-γ, IL-10, IL-13, IL-2, IL-6, IL-8, Ang-2, IL-15 and IL-2Rα were rapidly induced to significantly higher levels in subjects with any grade CRS (≥ 1) compared with subjects with no CRS within the first day after infusion, and 9 factors (all but IL-15) remained significantly higher through peak concentration (C_{max}). At the time of peak concentrations, seven additional soluble factors, including CRP and TNF, were significantly elevated.

Ang-2 is released upon endothelial cell activation. Post-infusion, the C_{max} of Ang-2 (among other factors) was associated with CRS requiring tocilizumab or corticosteroids. Ang-2 also trended higher in subjects with Grade 1 + 2 (N = 18) iiNT but not Grade ≥ 3 iiN (N = 4), but the low number of patients prohibits reliable comparisons. There was no difference in baseline Ang-2 levels based on CRS grade, but higher peak levels were seen in patients with Grade ≥3 CRS. The plasma concentration peak was observed approximately two days after ide-cel treatment. Ang-2 levels were similar in patients with grade 0-2 CRS, and small differences and high variation were observed. Only levels in Grade ≥3 CRS were clearly higher, but the number of patients is small (n=7) and variation is considerable. Thus, Ang-2 plasma levels seem to correlate to CRS severity, but do not appear to be a useful tool to identify patients at high risk of severe CRS.

Cytokine concentrations and neurotoxicity

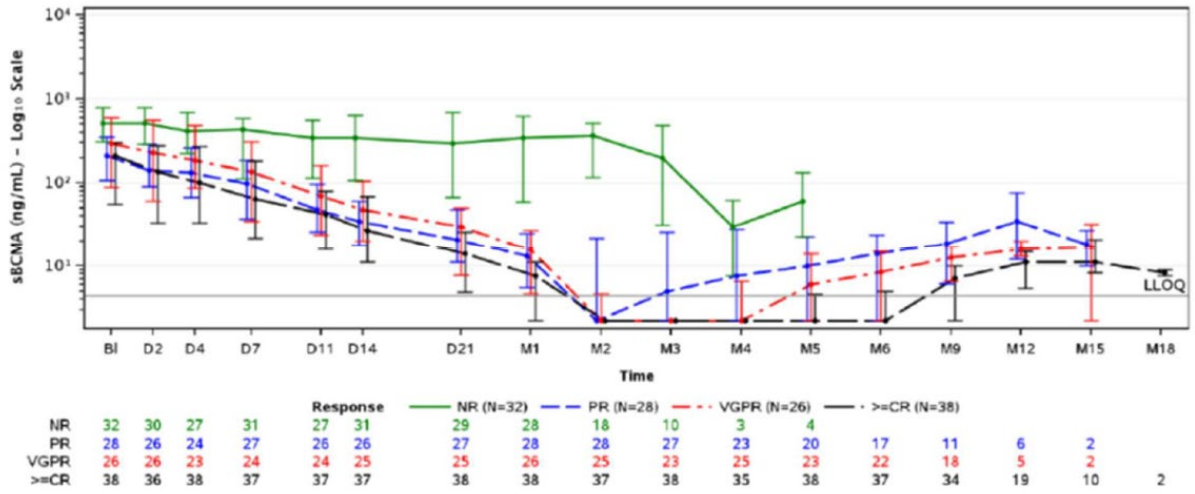
Several soluble factors, reported in literature to correlate with CRS and neurotoxicity, were highly induced within 24 hours after Abecma infusion and significantly associated with CRS and iiNT. Early

post-infusion, GM-CSF, IFN-γ, IL-10, IL-15, IL-2, IL-6, and IL-8 concentration on D1 and the fold change between D1/baseline were associated with Grade ≥ 1, Grade ≥ 2, and Grade ≥ 3 investigator identified neurotoxicity (iiNT). In addition, the fold change between D1/baseline of IL-13, IL-2Rα, MIP-1β, and TNF were also associated with Grade ≥ 1, Grade ≥ 2, and Grade ≥ 3 iiNT.

Soluble BCMA

Soluble BCMA is a peripherally accessible biomarker of myeloma disease burden that correlates with the total number of normal and malignant plasma cells. As a marker of plasma cell abundance, serum sBCMA may provide a composite biomarker of disease burden for patients. Median serum sBCMA levels decreased from baseline values following Abecma infusion. Overall, the median concentration over time decreased from 276.0 ng/mL at baseline to below LLOQ (4.4 ng/mL) at Month 2; after that time, the median concentration remained relatively stable. A summary of levels of circulating sBCMA at baseline and over time following Abecma infusion is shown by best response in Figure 17.

Figure 17: sBCMA median concentration across the target dose levels by best overall response over time (MM-001)



Soluble BCMA concentration at screening, baseline, and nadir were evaluated for non-responders versus responders and further compared between non-responders and best overall response of PR, VGPR, or ≥ CR. Higher median sBCMA concentrations were observed in non-responders compared to responders at screening and baseline, but there was no discreet pre-infusion threshold of sBCMA concentration prognostic of nonresponse, and overlap of the quartile ranges were observed. Post-infusion, minimum median concentration of sBCMA at nadir was below LLOQ in responders (4.40 ng/mL) compared to non-responders (283.00 ng/mL).

The association of sBCMA concentration to various factors was studied, and the results can be summarised as follows:

- Subjects with low tumour burden had lower levels of pre-infusion sBCMA at screening and baseline compared to subjects with high tumour burden. Elimination of sBCMA post-infusion was not associated with baseline tumour burden.
- There was no association of pre or post infusion sBCMA levels with low versus high baseline BCMA expression on tumour in bone marrow biopsies, although it should be noted that only 3 (2.7%) out of 112 subjects had < 50% CD138+ plasma cells expressing BCMA.

- Post infusion, subjects with lower baseline sBCMA (< 75th percentile) achieved a minimum median concentration to below LLOQ (4.4 ng/mL) at nadir, while subjects with high (≥ 75th percentile) sBCMA maintained a measurable level of sBCMA at nadir (25.00 ng/mL).
- Subjects with EMP had higher levels of sBCMA at baseline compared to subjects without EMP (p = 0.0339). Post infusion, there was no difference in median sBCMA concentration, as both subgroups achieved a minimum median concentration to below LLOQ (4.4 ng/mL) at nadir.

Preinfusion sBCMA concentration at screening and baseline were not associated with CRS Grade ≥ 1, Grade ≥ 2, or Grade ≥ 3. There was no association of sBCMA levels pre or post infusion with any grade iiNT.

BCMA expression and lack or loss of response

The status of BCMA target antigen expression, through levels of serum sBCMA as well as by expression on CD138+ tumour cells by IHC, was evaluated at time of disease progression to understand the prevalence of antigen loss or escape as a mechanism of relapse.

BCMA expression on CD138+ cells

Pre-infusion evaluation of tumour-associated BCMA expression was performed by IHC on CD138+ MM cells. All subjects demonstrated BCMA expression on CD138+ cells pre-infusion with 97.3% of subjects expressing ≥ 50% and the median percentage of CD138+ cells that expressed BCMA being 100%. Most patients had ≥ 50% of the CD138+ plasma cells expressing BCMA: 109 (97.3%) out of 112 baseline bone marrow biopsies had ≥ 50% CD138+BCMA+ plasma cells and only 3 (2.7%) out of 112 subjects had < 50% CD138+BCMA+ plasma cells. There was no correlation of percent BCMA-expressing CD138+ plasma cells and response, but it should be noted that only three patients had BCMA expression on <50%, precluding reliable comparisons.

Bone marrow biopsies were evaluated for BCMA expression on CD138+ plasma cells at baseline, post infusion, and at the time of disease progression in subjects who achieved PR or ≥ VGPR and had a disease progression biopsy available. At baseline 12 out of 12 (100%) bone marrow biopsies collected from subjects who achieved PR, and 11 out of 11 (100%) bone marrow biopsies collected from subjects who achieved ≥ VGPR presented with CD138+ tumour cells that were ≥ 90% positive for BCMA expression.

CD138+ BCMA tumour expression by IHC was available for a total of 38 of the 91 progressing subjects. Five patients showed low or no BCMA expression on CD138+ cells at the time of PD, and thus, 13% of the patients with evaluable BCMA expression results demonstrated antigen loss.

Soluble BCMA

At time of progressive disease, serum soluble BCMA (sBCMA) concentrations were available for 90 of 91 subjects. sBCMA was measurable in 95.5% (N = 44) of responders compared to 100% (N = 27) of non-responders (N = 27). sBCMA was below the LLOQ (4.4 ng/mL) at the time of disease progression in 4.5% (N = 2) subjects who achieved a response suggestive of antigen loss.

Results of the three patients with potential antigen loss are presented in Table 7.

Table 7: Summary of BCMA-expression and sBCMA levels at disease progression for subjects with potential antigen escape (MM-001)

		%BCMA+ and % CD138+ Expression by IHC at PD		
Subject ID	Best Overall Response	% CD138+	% BCMA+	Serum sBCMA at PD ng/mL
5011001	PR	60	1	2.2[a]
1031004	SD	25	0	5.3
1031009	≥ VGPR	Not Available[b]	Not Available[b]	2.2[a]

BCMA = B-cell maturation antigen; ID = identification; ide-cel = idecabtagene vicleucel; IHC = immunohistochemistry; PD = progressive disease; LLOQ = lower limit of quantification; PR = partial response; VGPR = very good partial response.
[a] For biomarker-based assays where LLOQ values are available, all concentrations below the LLOQ were imputed to LLOQ/2. sBCMA LLOQ is 4.4 ng/mL, imputed as 2.2 ng/mL.
[b] PD bone marrow biopsy for subject 1031009 not
Note: % BCMA is the % of CD138+ tumor cells that express any level of BCMA.
Data cutoff date:16 Oct 2019
Source: Listing 3.2, Listing 2.4.1

Loss of antigen expression does not appear to be the principal mechanism for loss of efficacy.

Mechanism of action

Abecma is a chimeric antigen receptor (CAR)-positive T cell therapy targeting B-cell maturation antigen (BCMA), which is expressed on the surface of normal and malignant plasma cells. The CAR construct includes an anti-BCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of Abecma results in CAR-positive T cell proliferation, cytokine secretion and subsequent cytolytic killing of BCMA-expressing cells.

2.4.4. Discussion on clinical pharmacology

Bioanalytics

In general, the bioanalytical methods to quantify ide-cel transgene in gDNA and to detect anti-drug antibodies (ADA) to the CAR have been appropriately described and validated at PPD Laboratories, USA, according to relevant guidelines. In addition to the two validated methods, the qualification of an ELISPOT assay for determination of cellular immunogenicity is presented. The ELISPOT assay data is provided as supportive data and not intended to be used to support any clinical claims.

Pharmacokinetics

As the treatment consists of modified living cells, the ide-cel PK markedly differs from the PK of small-molecule drugs or from the PK of monoclonal antibodies. After infusion, the cells start to proliferate in the body and undergo rapid multi-log expansion (rate of proliferation exceeds the rate of cell death), which is then followed by a bi-exponential decline(cell death rate exceeds cell duplication rate). The median time of maximal expansion in peripheral blood (Tmax) occurred 11 days after infusion. The expansion phase may be considered a part of the "response" and therefore parameters such as Cmax and AUC do not necessarily reflect PK alone; they can be interpreted to reflect PD as well. Variability in Cmax and AUC is high compared to the variability observed in the respective parameters after small-molecule or monoclonal antibody administration.

The analytical method measures number of transgene copies in µg of CD3-positive genomic DNA (gDNA). The total amount of copies in blood is therefore dependent on the amount of relevant CD3-positive cells,

from which the DNA is extracted. The ide-cel covariate-exposure relationships found thus far have been modest compared to the overall inter-individual variability. This suggests that the data transformation would likely not significantly improve the power to detect covariate-exposure relationships for ide-cel.

Dose-proportionality was tested by fitting a linear regression model of ide-cel PK parameters (Cmax, $AUC_{0\text{-}28\ days}$, $AUC_{0\text{-}3M}$, $AUC_{0\text{-}6M}$ and $AUC_{0\text{-}9M}$) as a function of dose. The p-value for the slope of the regression line being other than zero was consistently greater than 0.1. In general, the PK parameters (Cmax and AUC) showed dose-related increases in the studied dose range.

Abecma can persist in peripheral blood for up to 1 year post-infusion.

No distribution data were presented in the dossier, and given that the treatment consists of living cells, which start to expand immediately upon administration, it would be difficult to study ide-cel distribution kinetics of the treatment via traditional compartmental PK modelling methods.

In 17 study CRB-401 patients who received a second dose of ide-cel, the one-month AUC after the second dose was reduced by 21-fold on average, when compared to the values after the first dose. In 29 study MM-001 patients, the AUC after the second dose was reduced by 6-fold. These data suggest that after subjects receive a second infusion, subsequent cellular expansion is substantially limited. There was a positive relationship between increasing retreatment baseline sBCMA levels and $AUC_{0\text{-}28days}$, but no apparent relationship for $C_{max.}$ However, there was no discernible relationship between baseline retreatment sBCMA and objective response, but this could be due to the low number of retreatment responders (6/29). Subjects were also retreated regardless of ADA status, and it is unknown if this affected exposure after the second dose. The proposed SmPC does not propose multiple doses of ide-cel, however neither does the SmPC strictly forbid the administration of a second dose.

Overall, it seems that variability is higher at lower doses. In a cross-study comparison, the manufacturing process was not found to be a significant predictor of PK parameters Cmax and $AUC_{0\text{-}28\ days}$. In study MM-001, all of the drug product was prepared with the same manufacturing process.

Coadministration of tocilizumab or corticosteroids was associated with higher ide-cel exposures. This association can potentially be explained by subjects with higher initial exposures having a greater risk of CRS, which is treated with tocilizumab and corticosteroids. Nonetheless, the available data indicate that tocilizumab and corticosteroids at least do not dramatically suppress the ide-cel expansion, and the potential effect of immunostimulant G-CSF is not high enough to stand out from the overall variability in PK parameters.

The applicant has performed analyses of dose-exposure, covariate-exposure, exposure-efficacy and exposure-safety relationships on the basis of data from study MM-001. The data of study CRB-401 are only used for external validation. Of these, the exposure-efficacy analyses are not considered particularly important.

The absolute exposure data stratified by dose level showed that body weight was inversely associated with one-month AUC and three-month AUC for 300 x 10^6, but not the 450 x 10^6 CAR+T cell target dose. The baseline soluble BCMA was positively associated with absolute three-month AUC (but not one-month AUC) for both 300 and 450 x 10^6 dose levels. However, the impact of these covariates was modest in the presence of high overall variability with geometric CV in the range of 100-500% in most PK parameters. While the relationship with sBCMA may theoretically reflect more extensive expansion in patients with higher tumour burden, the mechanism by which body weight may affect exposure is not clear, and it is also unknown why only exposure following 300 x 10^6 CAR+T doses was affected. Again, these effects are considered relatively modest in the context of the overall variability observed in ide-cel exposures. The available data do not indicate that dose adjustments are necessary in specific subpopulations.

The exposure-efficacy analyses found a positive association between one-month AUC and the response variables. The usefulness of this analysis is unclear because the ide-cel expansion, which affects the one-month AUC, may already be considered a part of the "response", and therefore the analysis may be considered to predict response with another form of response. The exposure-efficacy analyses also found that females have a higher overall response rate. Lower serum m-protein levels were predictive of higher complete response rates. The models are descriptive and data-driven, without mechanistic elements, and should not be used for prediction or simulation purposes.

Abecma transgene levels were positively associated with objective tumour response (partial response or better). The median Cmax levels in responders (N = 93) were approximately 4.5 fold higher compared to the corresponding levels in non-responders (N = 34). Median AUC0-28days in responding patients (N = 93) was approximately 5.5 fold higher than non responders (N = 32).

For the exposure-safety relationship, the relevant adverse effect cytokine release syndrome seems to occur during the first days after ide-cel treatment, i.e. before ide-cel Tmax. As such, the exposure-safety relationship uses exposure parameters to predict safety events that occur before the exposure parameters; future data are used to predict past data. It seems more relevant to assume that the current transgene levels predict the risk of e.g. cytokine release syndrome than to assume that the future transgene levels would predict the risk. Therefore, these apparent relationships should be interpreted with caution.

The proposed target dose (450 x 10^6 CART+ cells) is the highest dose tested in the pivotal study. It showed overall greater expansion than the two lower doses tested (150 and 300 x 10^6 cells), and the exposure-efficacy relationship appears not to have achieved plateau (for the CR and PFS end points) while the exposure-CRS relationship appeared relatively flat at higher expansion values. Thus, these preliminary analyses support the selection of the highest tested dose as the target dose among the doses tested. It is unknown whether a higher dose could have further improved the treatment effect without compromising on safety.

Pharmacodynamics

Dose-proportional increases were observed in concentrations of various soluble factors and cytokines. However, no association with tumour characteristics, and there was no association of pre-infusion soluble factors at screening or baseline with response. No markers useful for patient selection or tumour characterisation were identified. Many soluble factors and cytokines reported in literature to correlate with CRS and neurotoxicity, were highly induced within 24 hours after Abecma infusion and significantly associated with CRS and iiNT. Early post-infusion, GM-CSF, IFN-γ, IL-10, IL-15, IL-2, IL-6, and IL-8 concentrations were increased. However, the concentration ranges were largely overlapping in patients with and without CRS/NT, and no marker that could be used to identify patients at high risk of these events was identified.

Soluble BCMA is a peripherally accessible biomarker of myeloma disease burden that correlates with the total number of normal and malignant plasma cells. Higher median sBCMA concentrations were observed in non-responders compared to responders at screening and baseline. Soluble BCMA was not associated with tumour characteristics apart from presence of extramedullary plasmacytoma. sBCMA concentration at screening and baseline were not associated with CRS Grade ≥ 1, Grade ≥ 2, or Grade ≥ 3. There was no association of sBCMA levels pre or post infusion with any grade iiNT. Therefore, sBCMA concentrations did not provide significant new information that could guide patient selection or help to identify patients at high risk of adverse events (CRS or NT).

Loss of detectable levels of sBCMA in peripheral blood, despite documented disease progression, was reported in two patients. This may indicate loss of target antigen as a potential mechanism of loss of response.

BCMA was consistently expressed on CD138+ cells, and in majority of the patients, expression was observed on ≥50% of CD138+ cells in the BM. The mean expression level (percentage BCMA+CD138+cells) was 91.3% in non-responders and 95.9% in responders at baseline. In patients with loss of response (PD), loss of BCMA expression on CD138+ cells was documented in three patients, and very low expression (1-5%) in two patients. Due to large proportion of missing data, loss of BCMA expression was thus documented in 5/38 (13%) of patients with evaluable BM samples available.

The pharmacodynamics markers thus describe the time course of Abecma activation and describe the anti-tumour activity of Abecma, but do not provide tools to guide patient selection, identification of high-risk patients in terms of toxicities, or clinically relevant new tools for monitoring Abecma treatment.

Finally, pharmacokinetic and pharmacodynamic data support a dose range of 260 to 500 x 10^6 CAR positive viable T cells. There are tendencies of inferior expansion and PD responses in the limited number of patients who received the lowest dose in the pivotal study (150 x 10^6 cells), conferring uncertainty to whether this dose should be used and indeed it has not been included as part of the proposed posology range.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of ide-cel seem to be adequately characterised for the proposed indication.

Preliminary exposure-response analyses support the 450 x 10^6 CAR+ T cell dose and is considered the preferred target dose (within a dose range of 260 to 500 x 10^6 CAR positive viable T cells) among the doses tested in the pivotal study.

The available data do not indicate that dose adjustments are necessary in specific subpopulations.

The pharmacodynamics of Abecma have been adequately characterised. The selected methods are considered adequate, and the results demonstrate both induction of cytokine response and anti-tumour activity of Abecma.

The CHMP endorse the CAT assessment regarding the conclusions on the Clinical pharmacology as described above.

2.5. Clinical efficacy

2.5.1. Dose response study

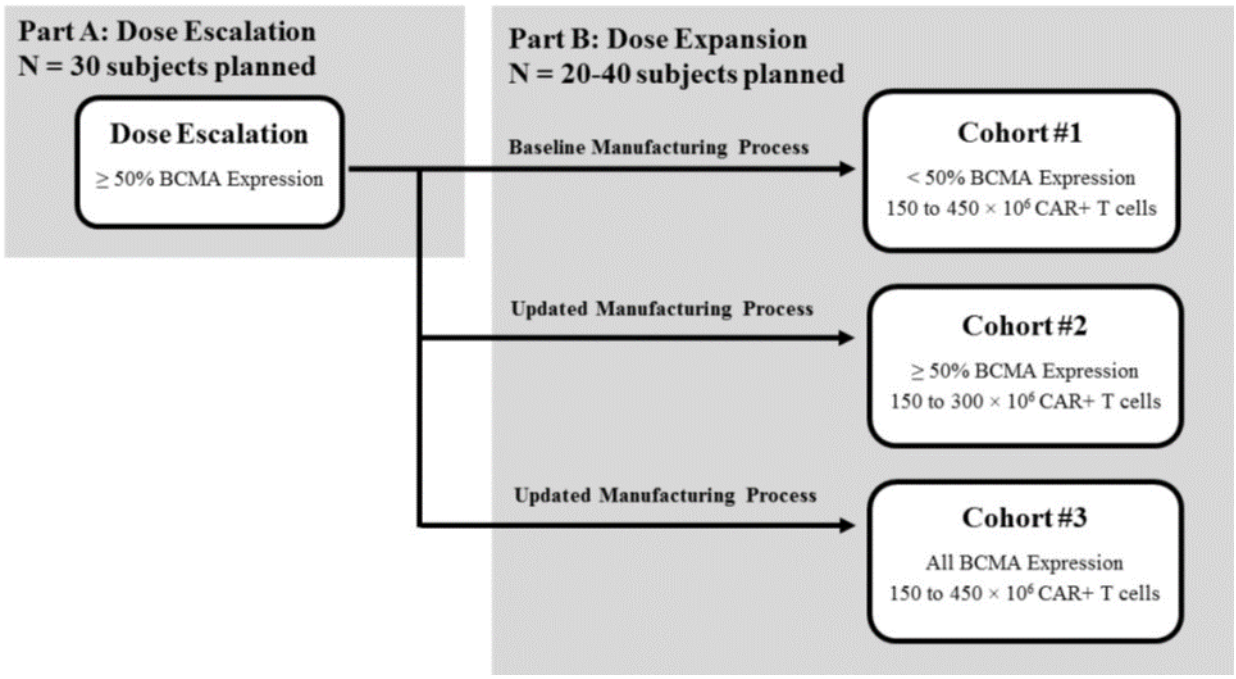
The CRB-401 study is described in more detail under supportive studies. A brief summary is provided below.

Study CRB-401 was a 2-part, nonrandomised, open-label, multicentre, dose escalation plus dose expansion cohort study of ide-cel in subjects with RRMM. The study was ongoing at the data cutoff date (22 Jul 2019) with enrolment complete.

Part A (3+3 dose escalation) was designed to determine the maximum tolerated dose (MTD) of ide-cel, and to select a recommended Phase 2 dose (RP2D). Part A enrolled RRMM subjects with ≥50% BCMA expression, who had received at least 3 different prior lines of therapy, including an immunomodulatory agent and a PI, or were double-refractory to both classes of drugs.

Part B was designed to confirm the safety of the doses chosen in Part A, and enrolled RRMM subjects with previous exposure to an immunomodulatory agent, a PI, and daratumumab, and who were refractory (based on IMWG criteria) to their last line of therapy.

Figure 18: Schematic of CRB-401 Study Design



BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor, Source: CSR CRB-401 Figure 3.

Results

Part A: A total of 24 subjects were enrolled and 21 subjects received ide-cel at a target dose of 50 (N = 3), 150 (N = 6), 450 (N = 9), or 800 (N = 3) x 10^6 CAR+ T cells (± 20% of the respective target dose as allowed per the study protocol).

The safety review committee (SRC) met on 16 Jun 2017 to review the available safety and efficacy data from Part A and to select the Abecma doses (ie, RP2D) for Part B of the study based upon an overall risk-benefit assessment.

Efficacy data from Part A of the study were summarised using a data cutoff date of 4 May 2017. As of this date, 18 of the 21 Abecma infused subjects had completed their first 4-week tumour assessment and were evaluable for response.

The SRC declared the dose range of 150 to 450 x 10^6 CAR+ T cells as the RP2D for further testing, based on the following key findings:

- Only 1 transient PR was observed at a target dose of 50×10^6 CAR+ T cells and all 3 subjects in this dose cohort had progressive disease. In addition, CAR+ T cell expansion was lower at this target dose. Therefore, the 50×10^6 CAR+ T cells dose was considered a suboptimal dose.
- Among the 15 evaluable subjects treated with ide-cel target doses $\geq 150\times10^6$ CAR+ T cells, the ORR was 100% (95% CI: 78, 100) and no subjects had shown disease progression after a follow-up period ranging from 8 to 54 weeks.

- One out of the 3 subjects with low tumour burden had a Grade 3 CRS event at the highest ide-cel target dose of 800 x 10^6 CAR+ T cells.

Part B: Part B included 3 cohorts, using two different manufacturing processes. Cohort 3 was added through a Protocol Amendment (v. 5.0, dated 09 May 2018) to evaluate ide-cel CAR+ T cells at the 450 x 10^6 dose-level, using the updated manufacturing process. Across the three cohorts, a total of 43 subjects were enrolled and 41 subjects received ide-cel at the target dose levels of 150 x 10^6 (N=12) and 450 × 10^6 (N=29) CAR+ T cells (± 20%).

Table 8: Response Rate by IRC Assessment Based on IMWG Criteria (Ide-cel-treated and Enrolled Populations) (Excerpt from table 17 in Clinical Assessment Report)

	Ide-cel-treated Population						
	Parts A and B Combined by Ide-cel (CAR+ T Cells) Target Dose						
	50 × 10^6 (N = 3)	150 × 10^6 (N = 18)	450 × 10^6 (N = 38)	800 × 10^6 (N = 3)	RP2D (N = 56)	Total Study (N = 62)	Enrolled Population (N = 67)
Confirmed best overall response, n (%)							
ORR, n (%)[b]	1 (33.3)	10 (55.6)	32 (84.2)	3 (100.0)	42 (75.0)	46 (74.2)	46 (68.7)
95% CI[c]	0.8, 90.6	30.8, 78.5	68.7, 94.0	29.2, 100.0	61.6, 85.6	61.5, 84.5	56.2, 79.4
VGPR rate, n (%)[b]	0	7 (38.9)	27 (71.1)	3 (100.0)	34 (60.7)	37 (59.7)	37 (55.2)
95% CI[c]	0.0, 70.8	17.3, 64.3	54.1, 84.6	29.2, 100.0	46.8, 73.5	46.4, 71.9	42.6, 67.4
CR rate, n (%)[b]	0	6 (33.3)	14 (36.8)	2 (66.7)	20 (35.7)	22 (35.5)	22 (32.8)
95% CI[c]	0.0, 70.8	13.3, 59.0	21.8, 54.0	9.4, 99.2	23.4, 49.6	23.7, 48.7	21.8, 45.4

b The ORR was defined as the rate of subjects whose response was PR or better (ie, PR, VGPR, CR, or sCR). The VGPR rate was defined as the rate of subjects whose response was VGPR or better (ie, VGPR, CR, or sCR). The CR rate was defined as the rate of subjects whose response was CR or better (ie, CR or sCR). The denominator used for rate calculation was the number of subjects in the designated study population.
c Clopper-Pearson exact CI.
Note: One subject dosed at 205 × 10^6 CAR+ T cells in Part B Cohort 1 and 1 subject dosed at 305 × 10^6 CAR+ T cells in Part B Cohort 3 are included under the target dose of 450 × 106 CAR+ T cells.

After 18 Oct 2017, an updated manufacturing process was implemented in both CRB-401 and MM-001 studies. Given the lack of clinical experience with this updated manufacturing process, the dose range for initiation of the MM-001 study was determined at 150 to 300 x 10^6 CAR+ T cells, with the intent of treating 80 subjects. Based on an emerging dose response relationship observed in the CRB-401 study and acceptable ongoing safety at both the 150 and 300 x 10^6 target dose levels in MM-001, the dose range in MM-001 was subsequently modified to a dose range of 150 to 450 x 10^6 CAR+ T cells along with an expansion of the total sample size, with the intent of targeting the remaining subjects at 450 x 10^6 CAR+ T cells.

2.5.2. Main study

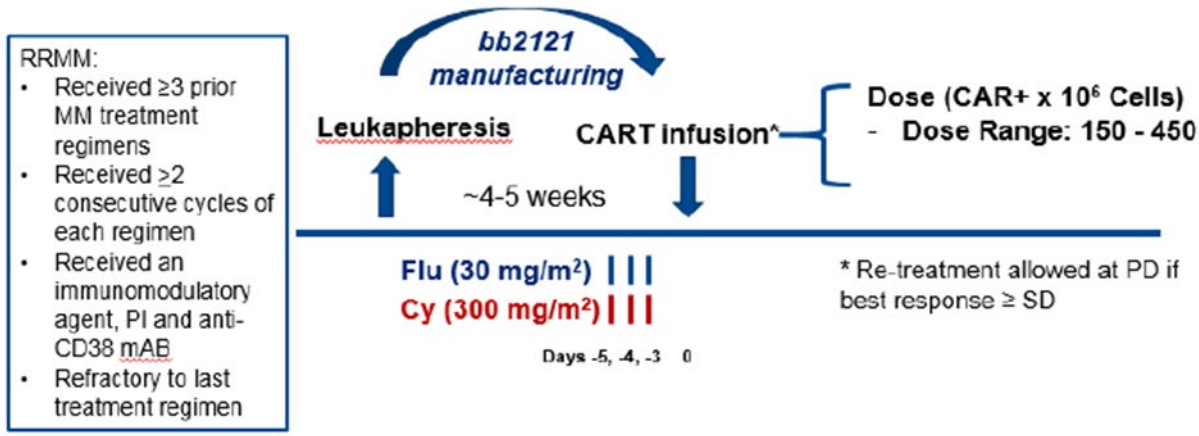
Title of Study

Study MM-001 (KarMMa): A Phase 2, Multicenter Study to determine the Efficacy and Safety of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma

Methods

Study MM-001 was an open-label, single-arm, multicentre, multinational, Phase 2 study to evaluate the efficacy and safety of ide-cel in subjects with RRMM who had received at least 3 prior regimens including an immunomodulatory agent, a PI, and an anti-CD38 antibody, and who were refractory to their last prior treatment regimen. The study consisted of 3 stages: pretreatment (screening, leukapheresis, and bridging therapy [if administered]), treatment (lymphodepleting chemotherapy [LDC] and ide-cel infusion) and posttreatment (post-ide-cel infusion) (ongoing). Ide-cel was administered across a dose range of 150, 300 and 450 x 10^6 CAR+ T cells.

Figure 19: Overall Study Design



Abbreviations: CAR = chimeric antigen receptor; Cy = cyclophosphamide; Flu = fludarabine; mAB = monoclonal antibody; PD = progressive disease;

PI = proteasome inhibitor; SD = stable disease.

Study Participants

Main Inclusion Criteria

1. Adult subjects (≥ 18 years of age) with a documented diagnosis of MM:
    - 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 was to be 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 an immunomodulatory agent, a PI, and an anti-CD38 antibody.
    - Must have been refractory to the last treatment regimen. Refractory was defined as documented PD during or within 60 days (measured from the last dose) of completing treatment with the last antimyeloma drug regimen before study entry.
2. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.
3. Subjects must have had 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 than or equal to 10 mg/dL (100 mg/L) provided serum FLC ratio was abnormal.

Main Exclusion Criteria

1. Subjects with known central nervous system (CNS) involvement with myeloma.

2. History or presence of clinically relevant CNS pathology.

3. Subjects with active or history of plasma cell leukaemia, Waldenstrom's macroglobulinaemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or clinically significant amyloidosis.

4. Subjects with solitary plasmacytomas or nonsecretory myeloma without other evidence of measurable disease.

5. Inadequate hepatic function, renal function, BM function, cardiac function or pulmonary function (for definitions please refer to Clinical Assessment Report (AR).

6. Ongoing treatment with chronic immunosuppressants (eg, cyclosporine or systemic steroids at any dose).

7. 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.

8. Evidence of human immunodeficiency virus (HIV) infection, seropositive for and with evidence of active viral infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV).

9. Subjects with second malignancies in addition to myeloma if the second malignancy had required therapy in the last 3 years or was not in complete remission.

Treatments

The ide-cel pre-treatment/treatment phase included leukapheresis, bridging chemotherapy (optional) and lymphodepletion chemotherapy (LDC). Retreatment with ide-cel could be considered after disease progression.

Leukapheresis

Manufacturing slots for ide-cel product generation were allocated to the study sites prior to subject leukapheresis. Once screening eligibility was met, subjects were enrolled and a leukapheresis collection was performed. Subjects who had a product manufacturing failure or a product manufactured with a dose of less than 150 x 10^6 CAR+ T cells could proceed to a second leukapheresis procedure for a second attempt at ide-cel manufacturing.

Bridging therapy

Per investigator discretion, subjects could receive bridging therapy for myeloma disease control while ide-cel was being manufactured, as long as the last dose of bridging therapy was administered $\geq$ 14 days prior to the initiation of LDC. Bridging therapies could include corticosteroids, alkylating agents, immunomodulatory agents, PIs, and/or anti-CD38 antibodies as single agents or in combination. Experimental agents and myeloma therapies to which the subject had not been previously exposed were not to be used as bridging therapy. A new baseline evaluation including disease restaging was performed within 72 hours of initiating LDC.

Lymphodepletion

Subjects received a conditioning regimen consisting of IV cyclophosphamide 300 mg/m2 and fludarabine 30 mg/m2 given concurrently in a 3-day cycle starting 5 days prior to ide-cel infusion.

To be eligible to start LDC patients were required to have adequate renal, hepatic and BM function, International normalized ratio (INR) and PTT $\leq$ 1.5 x upper limit normal (ULN), no active urinary outflow obstruction, no presence of active infections and no intercurrent illness or toxicity that would place the subject at undue risk.

Ide-cel treatment

Ide-cel was administered IV on Day 04 (+ 7-day window) at a target dose of 150, 300, or 450 x 10^6 CAR+ T cells/infusion, corresponding to 133, 260 and 420 x 10^6 viable cells. The maximum dose (540 x 10^6 CAR+ T cells) was defined by the upper limit of 450 x 10^6 CAR+ T cells plus 20%, as detailed in the study protocol. The target dose was modified to 450 x 10^6 CAR+ T cells starting with Protocol Amendment 2.0.

To proceed with ide-cel infusion, subjects must not have had a significant worsening in clinical status compared to initial eligibility criteria, suspected or active systemic infection, onset of fever ($\geq$ 38°C) not related to underlying disease, requirement for supplemental oxygen, uncontrolled cardiac arrhythmias, hypotension requiring vasopressor support, new onset or worsening of nonhematological dysfunction $\geq$ Grade 3 and in subjects taking any prohibited medications. If infusion could not occur by Day 7, subjects could receive ide-cel infusion following a second round of LDC after a minimum of 4 weeks from last LDC.

Retreatment

Subjects were eligible to receive a second infusion of ide-cel if there was evidence of disease progression (according to the IMWG criteria), at least 8 weeks had passed since the first ide-cel infusion and the best response to initial ide-cel infusion was stable disease (SD) or better.

Starting with protocol Amendment 4.0, retreatment required sufficient cryopreserved ide-cel drug product to be available (i.e. re-manufacture of ide-cel from cryopreserved PBMCs and repeat leukapheresis was not allowed). Furthermore, starting with protocol Amendment 4.0 (see Section 9.8.1), there was no drug class restriction for bridging therapy used prior to retreatment, but bridging therapy was to be completed at least 14 days prior to start of LDC

Prohibited medications

Systemic steroids were not allowed unless used for the treatment of CRS or neurotoxicity. Therapeutic doses of corticosteroids (> 20 mg/day prednisone or equivalent) were allowed within 72 hours prior to LDC. 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.

Any systemic MM therapy within 14 days prior to leukapheresis and within 14 days of LDC was prohibited. As was any concurrent chemotherapy, immunotherapy, biologic, experimental or hormonal therapy following bb2121 infusion (follow-up period) for treatment of MM prior to documentation of PD.

Live vaccines during and for 3 months following fludarabine treatment was also not allowed.

Objectives

The primary objective was to evaluate the efficacy, defined as ORR of ide-cel in subjects with RRMM.

The secondary objectives included the assessment of safety, as well as the evaluation of additional efficacy outcomes, including CR rate, time to response (TTR), DoR, PFS, time to progression (TTP), minimal residual disease (MRD), OS and changes in health-related quality of life (HRQoL).

Outcomes/endpoints

Primary Endpoint

Overall Response Rate (ORR), defined as the percentage of subjects who achieved partial response (PR) or better (stringent CR (sCR) + CR + VGPR + PR) as assessed by an Independent Response Committee (IRC) according to International IMWG response criteria (Kumar, 2016). The primary efficacy analysis was conducted based on the mITT (infused) patient population.

Secondary Endpoints

- Complete response (CR) rate (key secondary) defined as the percentage of subjects who achieved CR or sCR as assessed by the IRC according to IMWG response criteria (Kumar, 2016).
- Time to response (TTR) defined as the time from ide-cel infusion to the first date of documented response (PR or better).
- Duration of response (DoR) defined as the time from the date of the first documented response (PR or better) to the first documentation of PD or death, whichever was earlier.
- Progression-free survival (PFS) defined as the time from ide-cel infusion to the first date of documented PD or death from any cause during the study, whichever occurred earlier.
- Time to progression (TTP) defined as time from ide-cel infusion to the first documented progression.
- Overall survival (OS) defined as time from ide-cel infusion to death due to any cause.
- Minimal residual disease (MRD) in the BM defined as the proportion of subjects who achieved ≥ CR and MRD-negative status at any timepoint within 3 months prior to achieving ≥ CR until the time of PD/death, using a sensitivity level of 10-5 nucleated cells.
- Health Related Quality of Life (HRQoL) defined as changes over time in European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30, European Quality of Life-5 Dimensions health state classifier to 5 levels (EQ-5D-5L), and EORTC-QLQ-MY20.

Randomisation Blinding (masking)

Not applicable.

Statistical methods

For the primary efficacy endpoint, ORR, the sample size was based on one sample binomial test with normal approximation. The null hypothesis to be tested was that the ORR (defined as the proportion of subjects with at least a PR based on all bb2121 treated subjects) was ≤ 50%; the alternative hypothesis was that the ORR is > 50%, with a target ORR of 70%. With these hypotheses, a sample size of 119 bb2121-Treated subjects would provide more than 99% power at a one-sided 0.025 alpha

level. This criterion required that the lower limit of the 95% confidence intervals (CIs) for the ORR was 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 could be enrolled.

The selection of a null hypothesis of 50% ORR was 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 immunomodulatory drug (IMiD) and a proteasome inhibitor (PI) or who were double refractory. The null hypothesis of 50% ORR represented an approximately 50% improvement over daratumumab. The target ORR of 70% was based on the preliminary efficacy observed with bb2121 in the Phase 1 study, including an ORR of 81% in 36 evaluable patients receiving bb2121 doses of 150 - 800 x 10^6 CAR+ T cells. A target ORR of 70% was considered achievable based on the existing clinical efficacy data with bb2121 and also represented an approximately 100% improvement over daratumumab.

If the ORR was tested positive, CR rate (CRR) would be tested using a stepdown approach to control the overall alpha level, which remained at the one-sided 0.025 level. For CR rate, the null hypothesis was ≤ 10%, with a target CR rate of 20%. The null hypothesis of 10% CRR represented an approximately 100% improvement over daratumumab, and the target of 20% CRR was considered clinically meaningful. 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 required that the lower limit of the two-sided 95% CIs for the CR rate was greater than 10%.

Subgroup analyses

Subgroup analyses were performed where an adequate number of subjects were available in each subgroup to allow for meaningful interpretation of results. Analyses were performed within a number of subgroups described further in the Results section.

ORR, CR rate, and DOR were evaluated for each subgroup. The exact 95% CI (Clopper-Pearson) was provided for ORR and CRR together with the forest plot for ORR and CRR.

Subgroup analyses for the following subgroups could be performed for PFS:

- bb2121 target dose level (150, 300, and 450x10^6 cells), Bridging anti-MM therapies (Yes, no), Prior anti-myeloma regimen per year (≤ 1 per year, > 1 per year).
- Subgroup analysis by bb2121 target dose level (150, 300, and 450x10^6 cells) were also performed for OS.

Adjustment for Multiplicity

A stepdown procedure was used to control the family-wise Type I error rate. The primary efficacy endpoint ORR was tested first. The key secondary efficacy endpoint CR rate was only to be tested if the test of primary efficacy endpoint was positive. There was no adjustment for multiplicity for other secondary or exploratory endpoints.

Interim analyses

There was no planned interim analysis. The primary analysis for efficacy and safety was to be performed at approximately 10 months after last subject was infused with bb2121 (approximately 9 months after the first response assessment) to allow for sufficient follow-up time. The hypothesis testing for the primary and key secondary endpoints were based on the analysis at this timepoint. In addition to analysis at the specified time point of 10 months post last infusion, analyses (including those on the primary and secondary endpoints) could be performed at other time points as needed,

and an updated analysis will be performed at 24 months after the last subject has received bb2121 infusion. Such additional analyses may not be used for decision making or conclusion for the trial, and therefore no alpha adjustment was made.

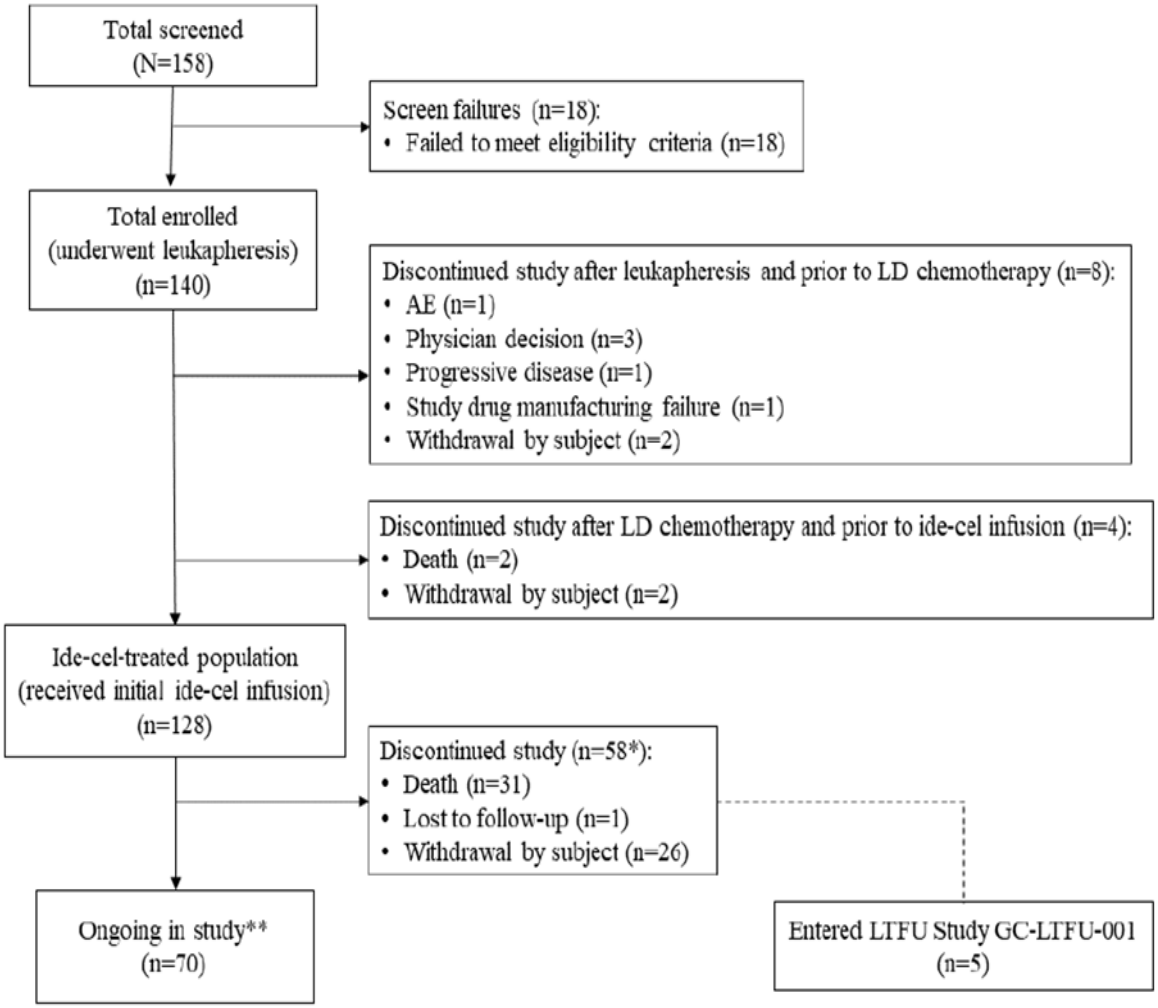
Censoring

Censoring rules based on FDA and EMA guidance for cancer trial endpoints were applied for PFS. The PFS analysis based on the FDA censoring rules was considered as primary. Additional sensitivity analyses could be performed to account for other scenarios as appropriate. PFS was summarised for the bb2121-Treated population using KM statistics. The median PFS along with the two-sided 95% CI for the median was estimated. In addition, the event-free rates at specific time-points was computed. PFS for Enrolled population was also analyzed. For this analysis, PFS started from the date of the enrollment (i.e., leukapheresis). For enrolled but not bb2121-Treated population, the censoring rules remained the same, except for subjects enrolled but not treated with bb2121, if there is no response assessment or documented event after enrollment, they were to be censored at the date of leukapheresis instead of date of bb2121 infusion. For enrolled and bb2121-Treated population, the event/censoring date was the same as bb2121- Treated population, just changed to the start date to be leukapheresis date instead of bb2121 infusion date.

Results

Participant flow

Figure 20: Subject disposition Study MM-001



AE = adverse event; ide-cel = idecabtagene vicleucel; LD = lymphodepleting.
*Includes 41 subjects who discontinued study after initial ide-cel infusion without entering retreatment period and 17 subjects who discontinued study during retreatment period. Retreatment period includes retreatment screening, retreatment baseline, retreatment, and retreatment follow-up.
**Includes 58 subjects ongoing after initial ide-cel infusion without entering retreatment period and 12 subjects ongoing after entering retreatment period. Subjects ongoing in retreatment follow-up include subjects who were screened for retreatment and have not discontinued the study as of the data cutoff date, regardless of whether or not the subject actually received ide-cel retreatment.
Data cutoff date = 16 Oct 2019.

Of the 158 screened patients, 140 patients fulfilled the eligibility criteria and were enrolled (underwent leukapheresis). As of the data cutoff date 16 October 2019 for the primary analysis, a total of 128 subjects received ide-cel infusion and 70 (54.7%) of these subjects were ongoing in the study.

As latest data cut off of 7 Apr 2020, 55 (39.3%) of subjects had died and 58 (41.4%) were still ongoing in study without an event, 23 were withdrawn whereof 21 still in follow-up for OS, and 4 were lost to follow- up.

Recruitment

Study initiation date was 16 Oct 2017 (first subject first visit). First subject was enrolled 03 Jan 2018 (leukapheresis) and last subject's first infusion was 20 Dec 2018. DCO date for the primary analysis

was 16 Oct 2019 (the study is ongoing). The study is conducted at 20 sites (9 in the United States, 1 in Canada, 2 in Spain, 2 in Italy, 3 in Germany, 2 in France, and 1 in Belgium).

Conduct of the study

Summary of main protocol amendments

The original protocol dated 25 Aug 2017 was amended 4 times prior to the data cutoff date of 16 Oct 2019. Protocol Amendment 1.0, dated 09 Nov 2017 was implemented prior to enrolment of any study subjects.

A summary of the key changes implemented with the remaining three amendments is described below:

Protocol Amendment 2.0, dated 14 Jun 2018

This amendment was implemented to 1) increase the ide-cel dose range, 2) increase the sample size, 3) modify the ide-cel overdose definition, and 4) incorporate feedback from health authorities:

- The dose range was expanded from 300 x 10^6 to 450 x 10^6 CAR+ T cells, based on the preliminary safety and efficacy results observed in the ide-cel Phase 1 Study CRB-401, suggesting a dose response across the 150 to 450 x 10^6 CAR+ T cell dose range.
- Sample size was increased to allow up to 140 subjects to be enrolled with up to 119 subjects treated with ide-cel.
- The protocol definition of overdose for ide-cel was changed from > 10% to > 20% of the protocol-specified dose.
- Incorporation of feedback received from health authorities in order to clarify selected screening exclusion and LDC criteria.
- The option for repeat leukapheresis was 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.

Protocol Amendment 3.0, dated 28 Sep 2018

Amendment was implemented in response to a death within 28 days of ide-cel infusion in Study MM-001 to provide further guidance on intercurrent illness or toxicity that is considered to place the subject at undue risk of proceeding to ide-cel infusion and for which ide-cel infusion should be delayed.

Protocol Amendment 4.0, dated 18 Jul 2019

Amendment was implemented primarily to change the MRD assessment by EuroFlow from a secondary objective and endpoint to an exploratory objective and endpoint.

Important protocol deviations are summarised in Table 9.

Table 9: Important Protocol Deviations (Ide-cel-treated Population)

Important Protocol Deviation Categories Subcategory	Ide-cel (CAR+ T cells) target dose [150 to 450 x 10^6] (N = 128) n (%)
Subjects with at least 1 important protocol deviation	46 (35.9)
ICF Issues	**16 (12.5)**
ICF - other	6 (4.7)
ICF signature and date issues	5 (3.9)
ICF version issues	9 (7.0)
ICF not present/not obtained prior to study procs.	3 (2.3)
Laboratory	**1 (0.8)**
Laboratory sample(s) not collected	1 (0.8)
Other	**22 (17.2)**
GCP - other	1 (0.8)
Safety - other	2 (1.6)
Safety - SAE reporting error	19 (14.8)
Procedures / Tests	**10 (7.8)**
14 days mandatory hospitalization post-ide-cel infusion	2 (1.6)
Chain of identity related deviation	2 (1.6)
Procedure not done	4 (3.1)
Subject temperature self-monitoring deviations	2 (1.6)
Study Drug	**3 (2.3)**
Ide-cel administration related deviations	2 (1.6)
Lymphodepleting chemotherapy related deviations	1 (0.8)

BB2121 = ide-cel; CAR = chimeric antigen receptor; GCP = good clinical practice; ICF = informed consent form; ide-cel = idecabtagene vicleucel; SAE = serious adverse event.
Data cutoff date = 16 Oct 2019.

Baseline data

Table 10: Demographic and Baseline Characteristics (Ide-cel-treated Population and Enrolled Population) - Study MM-001

	Ide-cel-treated Population Ide-cel (CAR+ T cells) Target Dose				
Characteristic	150×10^6 (N = 4)	300×10^6 (N = 70)	450×10^6 (N = 54)	150 to 450×10^6 (N = 128)	Enrolled Population (N = 140)
Age (years)					
Median	54.0	60.5	62.0	60.5	60.5
Min, max	49, 69	33, 76	43, 78	33, 78	33, 78
Age category, n (%)					
< 65 years	3 (75.0)	47 (67.1)	33 (61.1)	83 (64.8)	92 (65.7)
≥ 65 years	1 (25.0)	23 (32.9)	21 (38.9)	45 (35.2)	48 (34.3)
< 75 years	4 (100.0)	69 (98.6)	51 (94.4)	124 (96.9)	135 (96.4)
≥ 75 years	0	1 (1.4)	3 (5.6)	4 (3.1)	5 (3.6)
Sex, n (%)					
Male	4 (100.0)	38 (54.3)	34 (63.0)	76 (59.4)	82 (58.6)
Female	0	32 (45.7)	20 (37.0)	52 (40.6)	58 (41.4)
Race, n (%)					
Asian	0	3 (4.3)	0	3 (2.3)	3 (2.1)
Black or African American	0	3 (4.3)	3 (5.6)	6 (4.7)	8 (5.7)
White	4 (100.0)	58 (82.9)	41 (75.9)	103 (80.5)	113 (80.7)
Unknown	0	2 (2.9)	8 (14.8)	10 (7.8)	10 (7.1)
Other	0	4 (5.7)	2 (3.7)	6 (4.7)	6 (4.3)
Ethnicity, n (%)					
Hispanic or Latino	0	7 (10.0)	4 (7.4)	11 (8.6)	13 (9.3)
Not Hispanic or Latino	4 (100.0)	58 (82.9)	41 (75.9)	103 (80.5)	112 (80.0)
Not reported	0	1 (1.4)	8 (14.8)	9 (7.0)	9 (6.4)
Unknown	0	4 (5.7)	1 (1.9)	5 (3.9)	6 (4.3)
Weight (kg)					
Median	86.9	76.1	77.1	76.3	76.0
Min, max	69.4, 96.5	42.6, 125.6	48.0, 106.1	42.6, 125.6	42.6, 125.6

Almost three-quarters (73.6%) of enrolled subjects were from the US, 1 subject (0.7%) was from Canada, and the remaining from the EU (25.7%).

Table 11: Baseline Disease Characteristics (Ide-cel Treated and Enrolled Populations) - Study MM-001

Characteristic	Ide-cel-treated Population Ide-cel (CAR+ T cells) Target Dose				Enrolled Population (N = 140)
	150×10^6 (N = 4)	300×10^6 (N = 70)	450×10^6 (N = 54)	Total 150 to 450×10^6 (N = 128)	
Time since initial diagnosis (years)					
Median	9.5	6.6	5.8	6.0	6.0
Min, max	6.0, 12.3	1.7, 17.9	1.0, 16.8	1.0, 17.9	1.0, 17.9
ECOG Performance Status, n (%)					
0	3 (75.0)	31 (44.3)	23 (42.6)	57 (44.5)	60 (42.9)
1	1 (25.0)	38 (54.3)	29 (53.7)	68 (53.1)	77 (55.0)
2[a]	0	1 (1.4)	2 (3.7)	3 (2.3)	3 (2.1)
Presence of extramedullary plasmacytoma, n (%)					
Yes	0	34 (48.6)	16 (29.6)	50 (39.1)	52 (37.1)
No	4 (100.0)	36 (51.4)	38 (70.4)	78 (60.9)	85 (60.7)
Missing	0	0	0	0	3 (2.1)
Tumor burden[b], n (%)					
Low (< 50%)	1 (25.0)	33 (47.1)	23 (42.6)	57 (44.5)	62 (44.3)
High (≥ 50%)	3 (75.0)	34 (48.6)	28 (51.9)	65 (50.8)	70 (50.0)
Missing	0	3 (4.3)	3 (5.6)	6 (4.7)	8 (5.7)
Tumor BCMA expression, n (%)					
< 50% BCMA+	0	1 (1.4)	2 (3.7)	3 (2.3)	3 (2.1)
≥ 50% BCMA+	4 (100.0)	60 (85.7)	45 (83.3)	109 (85.2)	109 (77.9)
Unknown	0	9 (12.9)	7 (13.0)	16 (12.5)	28 (20.0)
β2 microglobulin, n (%)					
< 3.5 mg/L	1 (25.0)	37 (52.9)	22 (40.7)	60 (46.9)	61 (43.6)
3.5 to < 5.5 mg/L	2 (50.0)	18 (25.7)	18 (33.3)	38 (29.7)	43 (30.7)
≥ 5.5 mg/L	1 (25.0)	15 (21.4)	14 (25.9)	30 (23.4)	36 (25.7)
Lactate dehydrogenase above upper limit of normal, n (%)					
Yes	2 (50.0)	40 (57.1)	30 (55.6)	72 (56.3)	80 (57.1)
No	2 (50.0)	30 (42.9)	24 (44.4)	56 (43.8)	60 (42.9)

Characteristic	Ide-cel-treated Population Ide-cel (CAR+ T cells) Target Dose				Enrolled Population (N = 140)
	150×10^6 (N = 4)	300×10^6 (N = 70)	450×10^6 (N = 54)	Total 150 to 450×10^6 (N = 128)	
R-ISS stage at baseline (derived)[c], n (%)					
Stage I	0	12 (17.1)	2 (3.7)	14 (10.9)	14 (10.0)
Stage II	3 (75.0)	43 (61.4)	44 (81.5)	90 (70.3)	97 (69.3)
Stage III	1 (25.0)	12 (17.1)	8 (14.8)	21 (16.4)	26 (18.6)
Unknown	0	3 (4.3)	0	3 (2.3)	3 (2.1)
ISS stage at baseline (derived)[d], n (%)					
Stage I	0	31 (44.3)	17 (31.5)	48 (37.5)	49 (35.0)
Stage II	3 (75.0)	24 (34.3)	23 (42.6)	50 (39.1)	55 (39.3)
Stage III	1 (25.0)	15 (21.4)	14 (25.9)	30 (23.4)	36 (25.7)
Baseline cytogenetic risk, n (%)					
High risk[e]	1 (25.0)	20 (28.6)	24 (44.4)	45 (35.2)	46 (32.9)
Non-high risk	3 (75.0)	38 (54.3)	25 (46.3)	66 (51.6)	73 (52.1)
Not evaluable/missing	0	12 (17.1)	5 (9.3)	17 (13.3)	21 (15.0)
Number of prior antimyeloma regimens[f]					
Median (min, max)	8.5 (4, 12)	6.0 (3, 16)	5.0 (3, 13)	6.0 (3, 16)	6.0 (3, 17)
Distribution of prior antimyeloma regimens, n (%)					
3	0	8 (11.4)	7 (13.0)	15 (11.7)	16 (11.4)
4	1 (25.0)	8 (11.4)	10 (18.5)	19 (14.8)	20 (14.3)
5	0	11 (15.7)	11 (20.4)	22 (17.2)	23 (16.4)
6	1 (25.0)	12 (17.1)	10 (18.5)	23 (18.0)	25 (17.9)
≥ 7	2 (50.0)	31 (44.3)	16 (29.6)	49 (38.3)	56 (40.0)
Number of prior antimyeloma regimens[f] per year since diagnosis, n (%)					
≤ 1	2 (50.0)	34 (48.6)	32 (59.3)	68 (53.1)	68 (48.6)
> 1	2 (50.0)	36 (51.4)	22 (40.7)	60 (46.9)	60 (42.9)
Not available	0	0	0	0	12 (8.6)
Creatinine clearance (mL/min), n (%)					
< 30	0	0	1 (1.9)	1 (0.8)	3 (2.1)
30 to < 45	0	4 (5.7)	4 (7.4)	8 (6.3)	9 (6.4)
45 to < 60	0	4 (5.7)	6 (11.1)	10 (7.8)	13 (9.3)
60 to < 80	1 (25.0)	22 (31.4)	13 (24.1)	36 (28.1)	38 (27.1)
≥ 80	3 (75.0)	40 (57.1)	30 (55.6)	73 (57.0)	77 (55.0)

Characteristic	Ide-cel-treated Population Ide-cel (CAR+ T cells) target dose				Enrolled Population (N = 140)
	150 × 10^6 (N = 4)	300 × 10^6 (N = 70)	450 × 10^6 (N = 54)	Total 150 to 450 × 10^6 (N = 128)	
Prior stem cell transplant for MM, n (%)					
Yes	4 (100.0)	67 (95.7)	49 (90.7)	120 (93.8)	131 (93.6)
1 prior transplant	1 (25.0)	44 (62.9)	31 (57.4)	76 (59.4)	82 (58.6)
> 1 prior transplant	3 (75.0)	23 (32.9)	18 (33.3)	44 (34.4)	49 (35.0)
No	0	3 (4.3)	5 (9.3)	8 (6.3)	9 (6.4)
Prior radiation therapies for MM, n (%)					
Yes	2 (50.0)	45 (64.3)	24 (44.4)	71 (55.5)	75 (53.6)
No	2 (50.0)	25 (35.7)	30 (55.6)	57 (44.5)	65 (46.4)
Prior refractory status, n (%)					
Immunomodulatory agent	4 (100.0)	70 (100.0)	52 (96.3)	126 (98.4)	138 (98.6)
Proteasome inhibitor	4 (100.0)	63 (90.0)	49 (90.7)	116 (90.6)	126 (90.0)
Anti-CD38 antibodies	4 (100.0)	66 (94.3)	50 (92.6)	120 (93.8)	131 (93.6)
Daratumumab	3 (75.0)	61 (87.1)	45 (83.3)	109 (85.2)	120 (85.7)
Immunomodulatory agent and PI (double-refractory)	4 (100.0)	63 (90.0)	47 (87.0)	114 (89.1)	124 (88.6)
Immunomodulatory agent, PI, and anti-CD38 antibodies (triple refractory)	4 (100.0)	60 (85.7)	44 (81.5)	108 (84.4)	117 (83.6)
Penta-refractory[g]	1 (25.0)	24 (34.3)	8 (14.8)	33 (25.8)	37 (26.4)
Any bridging therapies for MM, n (%)					
Yes	4 (100.0)	61 (87.1)	47 (87.0)	112 (87.5)	119 (85.0)
No	0	9 (12.9)	7 (13.0)	16 (12.5)	21 (15.0)
Measurable disease[h] at baseline, n (%)					
Yes	4 (100.0)	65 (92.9)	53 (98.1)	122 (95.3)	122 (87.1)
No	0	5 (7.1)	1 (1.9)	6 (4.7)	6 (4.3)
Not available	0	0	0	0	12 (8.6)

BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; ECOG = Eastern Cooperative OncologyGroup; ide-cel = idecabtagene vicleucel; ISS = International Staging System; LDC = lymphodepleting chemotherapy; Max = maximum; Min = minimum; MM = multiple myeloma; PI = proteasome inhibitor; PS = performance status; R-ISS = Revised International Staging System

a These subjects had ECOG PS scores of < 2 at screening for eligibility but subsequently deteriorated to ECOG PS scores of ≥ 2 at baseline prior to start of LDC.

b Tumour burden was determined by bone marrow biopsy CD138+ plasma cell. Low tumour burden: < 50%, high tumour burden: ≥ 50%.

c R-ISS was derived using baseline ISS stage, cytogenetic abnormality, and serum lactate dehydrogenase.

d Derived ISS was calculated using baseline values of albumin and β2 microglobulin.

e High-risk defined as del(17p), t(4;14), or t(14;16).

f Induction with or without hematopoietic stem cell transplant and with or without maintenance therapy was considered a single regimen.

g Penta-refractory defined as refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, all 5 drugs.

h Measurable disease was determined by the Independent Response Committee according to International Myeloma Working Group criteria.

Data Cutoff date: 16 Oct 2019

Bridging Antimyeloma Therapies;

The majority of subjects (87.5%) received bridging therapy for myeloma control during the ide-cel manufacturing period, with the most common therapies being corticosteroids (73.4%), PIs (42.2%), alkylating agents (40.6%), monoclonal antibodies (29.7%) and immunomodulatory agents (22.7%). The mean treatment duration of bridging therapy (N=112) was 12.8 days (SD 6.02) with a median of 14.5 days (range 1-33).

Of the 112 subjects in the ide-cel-treated population who received bridging therapy, 5 subjects had an unconfirmed response to bridging therapy of PR (4 subjects) or VGPR (1 subject) based on investigator assessment. A total of 6 (4.7%) subjects overall no longer had measurable disease at baseline prior to LDC.

Post-ide-cel infusion, these subjects were to be assessed by the IRC only for at least a CR or disease progression in accordance with IMWG 2016 guidelines.

Lymphodepletion Chemotherapy

In the ide-cel treated population all the subjects (128) were dosed with fludarabine for 3 days, with a median daily dose of 29.5 mg/m2 received (range: 17.8 to 31.9). All subjects were dosed with cyclophosphamide for 3 days, with a median daily dose of 298.6 mg/m2 received (range: 274 to 318.9).

Ide-cel Infusion

All ide-cel-treated subjects received an actual dose between 150.5 and 518.4 x 10^6 CAR+ T cells, which was within the allowance of 20% over the target dose of 450 x 10^6 CAR+ T cells (ie, less than 540 x 10^6 CAR+ T cells). The median time from leukapheresis to ide-cel administration was 40 days (range 33-79 days), with a median time from leukapheresis to product release of 32 days (range 24-55 days) and time from product release to ide-cel administration of 7 days (range 5-44 days).

Numbers analysed

The analysis populations of MM-001 are summarised in the following table.

Table 12: Analysis populations

Analysis population	Ide-cel (CAR+ T cells) target dose [150 to 450 x 10^6] (N = 140) n (%)
Enrolled population[a]	140 (100.0)
Ide-cel-treated population[b]	128 (91.4)
Ide-cel-retreated population[c]	27 (19.3)
EE population[d]	127 (90.7)
PK analysis population[e]	127 (90.7)
Retreatment PK analysis population[f]	15 (10.7)
PRO analysis population[g]	
EORTC QLQ-C30 questionnaire	121 (86.4)
EORTC QLQ-MY20 questionnaire	120 (85.7)

The enrolled population includes all subjects in the Screened population who underwent leukapheresis.

The ide-cel-treated population includes all subjects in the enrolled population who received ide-cel infusion.

The ide-cel-retreated population includes all subjects who received ide-cel retreatment.

The EE population includes all subjects in the ide-cel-treated population who had a baseline and at least one postbaseline (ie,post-ide-cel infusion) efficacy assessment.

The PK analysis population includes all subjects who received at least one ide-cel infusion and had evaluable transgene level (ie, at least one measurable timepoint).

The retreatment PK analysis population includes subjects who received the ide-cel retreatment dose and had evaluable transgene level (ie, at least one measurable timepoint post-retreatment dose) for the retreatment period.

The PRO analysis population includes all subjects who completed their baseline PRO questionnaires and had at least one postbaseline PRO measurement in the ide-cel-treated population.

Of the total 140 subjects enrolled 128 subjects received ide-cel infusion and were included in the ide-cel-treated population. This population was defined by the applicant as the primary efficacy population. For the purpose of this regulatory assessment, the analyses based on the ITT (enrolled) population will be considered the primary efficacy analyses.

Outcomes and estimation

The primary analysis was performed using a data cutoff date of 16 October 2019, which is approximately 10 months after the last subject was infused with Abecma. Data from later data cut-off's i.e. 14 Jan 2020 and 7 Apr 2020, were also provided.

As of the 16 Oct 2019 data cutoff date, the median duration of follow-up after ide-cel infusion, which includes duration up to death for subjects who died and duration up to last date known alive for surviving subjects, was 11.3 months (range: 0.2, 18.6), with 54 (42.2%) subjects having been followed for ≥ 12 months from infusion. The median follow-up durations were 17.8 months, 13.9 months, and 9.7 months in subjects who received target doses of 150, 300, and 450 x 10^6 CAR+ T cells, respectively.

At the time of the 7 April 2020 data cut-off, the median duration of follow-up was 15.4 months for the whole study population. By dose level, the patients who received 450 x 10^6 CAR+ T cells had the shortest follow-up time (15.0 months).

Primary efficacy endpoint - ORR

The ORR in the enrolled population was 67.1% (95% CI: 59.4, 74.9) ($p < 0.0001$) across the target dose levels of 150 to 450 x 10^6 CAR+ T cells. At the later data cut-off's i.e. 14 Jan 2020 and 7 Apr 2020 (table 17) there was no change in ORR in the enrolled population relative to the 16 Oct 2019 data cutoff.

Complete response (CR) (key secondary) and Very good partial response (VGPR)

In the enrolled population 28.6% (40/140, 95% CI: 21.1, 36.1) of subjects achieved a response of CR or better and 47.1% of subjects achieved a response of VGPR or better. At the 7 April 2020 data cutoff the CR rate (CR or better) increased to 30.0% (95% CI: 22.4, 37.6) (table 17).

The response rates were consistent based on investigator assessments: ORR was 69.3% (95% CI: 61.6, 76.9), and 29.3% of patients achieved a response of CR or better in the enrolled population.

Table 13: Best Overall Response Based on IMWG Criteria by IRC Review (Ide-cel Treated and Enrolled Populations) – Study MM-001 (Data cut-off 16 Oct- 2019)

	Ide-cel Treated Population Ide-cel (CAR+ T cells) target dose				Enrolled Population (N = 140)
	150 x 10^6 (N=4)	300 x 10^6 (N=70)	450 x 10^6 (N=54)	150 to 450 x 10^6 (N=128)	
Best Overall Response - n (%)					
sCR	1 (25.0)	19 (27.1)	19 (35.2)	39 (30.5)	39 (27.9)
CR	0	1 (1.4)	0	1 (0.8)	1 (0.7)
VGPR	1 (25.0)	10 (14.3)	15 (27.8)	26 (20.3)	26 (18.6)
PR	0	18 (25.7)	10 (18.5)	28 (21.9)	28 (20.0)
MR	0	2 (2.9)	0	2 (1.6)	2 (1.4)
SD	1 (25.0)	14 (20.0)	7 (13.0)	22 (17.2)	22 (15.7)
PD	1 (25.0)	6 (8.6)	1 (1.9)	8 (6.3)	8 (5.7)
NE[a]	0	0	2 (3.7)	2 (1.6)	14 (10.0)
ORR - n (%)	**2 (50.0)**	**48 (68.6)**	**44 (81.5)**	**94 (73.4)**	**94 (67.1)**
95% CI[b]	(6.8 , 93.2)	56.4, 79.1	68.6, 90.7	65.8, 81.1	59.4, 74.9
p-value[c]	-	-	-	< 0.0001	< 0.0001
CR or better rate - n (%)	**1 (25.0)**	**20 (28.6)**	**19 (35.2)**	**40 (31.3)**	**40 (28.6)**
95% CI	(0.6 , 80.6)	18.4, 40.6	22.7, 49.4	23.2, 39.3	21.1, 36.1
p-value[c]	-	-	-	< 0.0001	< 0.0001
VGPR or better - n (%)	**2 (50.0)**	**30 (42.9)**	**34 (63.0)**	**66 (51.6)**	**66 (47.1)**
95% CI	(6.8 , 80.6)	31.1, 55.3	48.7, 75.7	42.9, 60.2	38.9, 55.4

CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response; ide-cel = idecabtagene vicleucel; IMWG = International Myeloma Working Group; IRC = Independent Response Committee; MR = minimal response; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response

a Including subjects who did not have any response assessment data, or whose only assessment was response not evaluable.

b For "Total" and "Enrolled population": Wald CI; for individual target doses: Clopper-Pearson exact CI.

c p-value from one-sample exact binominal test, one-sided. Data cutoff date: 16 Oct 2019

Table 14: Summary of efficacy based on the KarMMa study (data cut-off 07 April 2020)

	Enrolled[a] (N = 140)	Treated population Target dose of Abecma (CAR-positive T cells)			
		150 x 10^{6b} (N = 4)	300 x 10^6 (N = 70)	450 x 10^6 (N = 54)	Total 150 to 450 x 10^6 (N = 128)
Overall response rate (sCR+CR+VGPR+PR), n (%)	**94 (67.1)**	**2 (50.0)**	**48 (68.6)**	**44 (81.5)**	**94 (73.4)**
95% CI[c]	59.4, 74.9	6.8, 93.2	56.4, 79.1	68.6, 90.7	65.8, 81.1
CR or better, n (%)	**42 (30.0)**	**1 (25.0)**	**20 (28.6)**	**21 (38.9)**	**42 (32.8)**
95% CI[c]	22.4, 37.6	0.6, 80.6	18.4, 40.6	25.9, 53.1	24.7, 40.9
VGPR or better, n (%)	**68 (48.6)**	**2 (50.0)**	**31 (44.3)**	**35 (64.8)**	**68 (53.1)**
95% CI[c]	40.3, 56.9	6.8, 93.2	32.4, 56.7	50.6, 77.3	44.5, 61.8
MRD-negative status[d] and ≥ CR					
Based on treated patients	–	**4**	**70**	**54**	**128**
n (%)	–	1 (25.0)	17 (24.3)	15 (27.8)	33 (25.8)
95% CI	–	0.6, 80.6	14.8, 36.0	16.5, 41.6	18.5, 34.3

	Enrolled[a] (N = 140)	Treated population Target dose of Abecma (CAR-positive T cells)			
		150 x 10^{6}[b] (N = 4)	300 x 10^{6} (N = 70)	450 x 10^{6} (N = 54)	Total 150 to 450 x 10^{6} (N = 128)
Time to response, n	**94**	**2**	**48**	**44**	**94**
Median (months)	1.0	1.0	1.0	1.0	1.0
Min, max	0.5, 8.8	1.0, 1.0	0.5, 8.8	0.9, 2.0	0.5, 8.8
Duration of response (PR or better)[e], n	**94**	**2**	**48**	**44**	**94**
Median (months)	10.6	13.0	8.5	11.3	10.6
95% CI	8.0, 11.4	2.8, 23.3	5.4, 10.9	10.3, NE	8.0, 11.4

CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response; MRD = minimal residual disease; NE = not estimable; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

[a] All patients who underwent leukapheresis.

[b] The 150 x 10^{6} CAR-positive T cell dose is not part of the approved dose range.

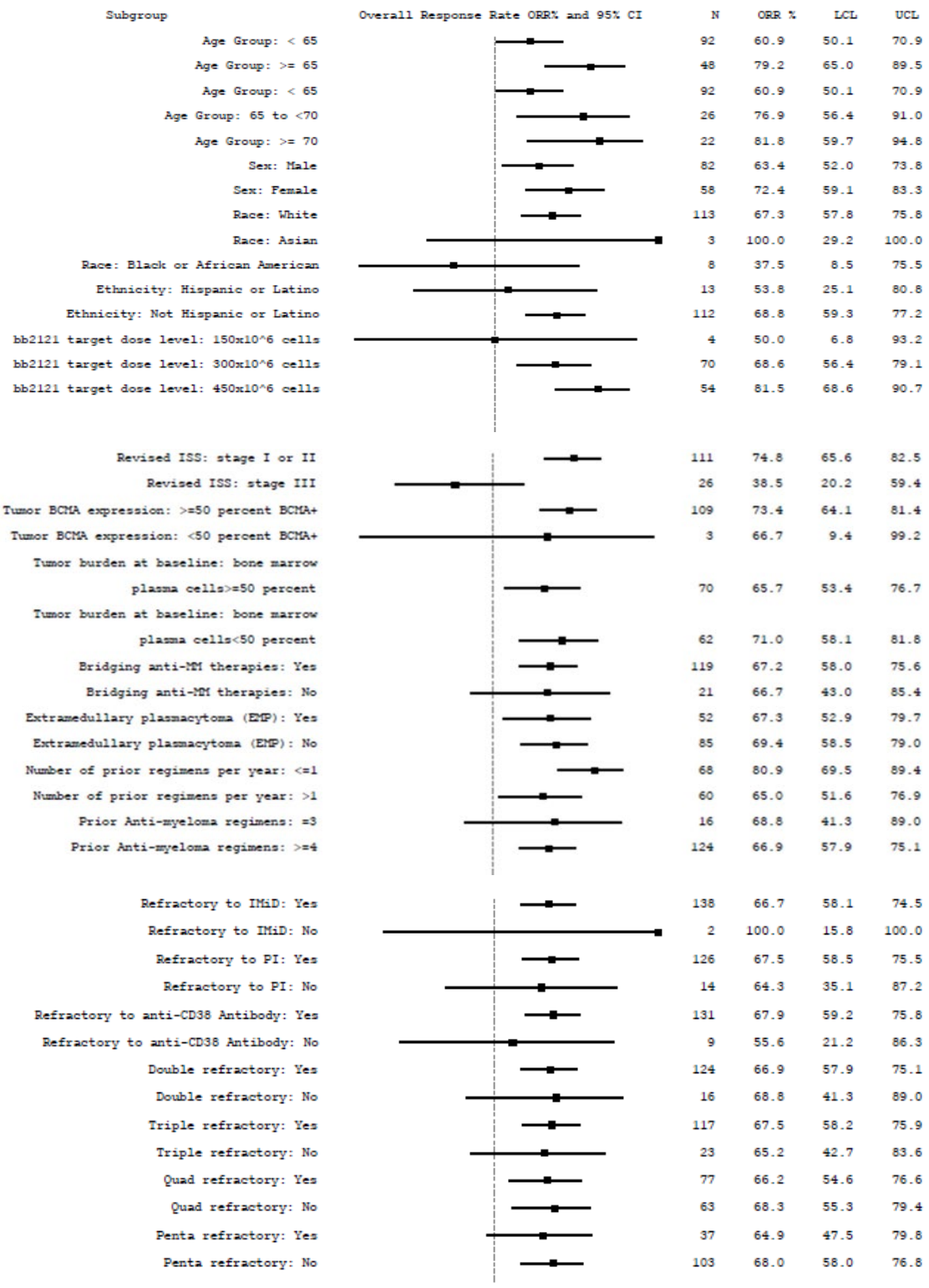
[c] For "Total (Treated population" and "Enrolled population"): Wald CI; for individual target dose levels: Clopper-Pearson exact CI.

[d] Based on a threshold of 10^{-5} using a next-generation sequencing assay. 95% CI for percentage of MRD negativity use Clopper-Pearson exact CI for individual target dose levels as well as for Treated population.

[e] Median and 95% CI are based on the Kaplan-Meier approach.

Note: The target dose is 450 x 10^{6} CAR-positive T cells within a range of 150 to 540 × 10^{6} CAR-positive T cells. The 150 x 10^{6} CAR-positive T cell dose is not part of the approved dose range.

Figure 21: Forest Plot of Overall Response Rate by Subgroup Based on IRC Review According to IMWG Criteria – Study MM-001 (Ide-cel-Enrolled Population)



BCMA = B-cell maturation antigen; CI = confidence interval; ide-cel = idecabtagene vicleucel; IMiD = immunomodulatory agent; IMWG = International Myeloma Working Group; ISS = International Staging System; LCL = lower bound of 95% CI; MM = multiple myeloma; N = number of subjects in the subgroup; ORR = overall response rate; PI = proteasome inhibitor; UCL = upper bound of 95% CI. Data cutoff date: 07 Apr 2020

Minimal Residual Disease Measured by Next-generation Sequencing

At the primary data cutoff date (16 Oct 19), 31 subjects (24.2%, 95% CI: 17.1, 32.6) achieved at least CR and MRD-negative status based on next generation sequencing (NGS) (10^{-5} sensitivity level).

At the updated data cut-off's (14 Jan 2020 and 7 Apr 2020), results were similar, with 2 additional subjects, both at the target dose of 450 x 10^6 CAR+ T cells, achieving MRD-negative status and ≥ CR (25.8%) (table 17).

Time to Response

Median TTR based on IRC according to IMWG Criteria was 1.0 months (range 0.5 – 8.8 months), with 96.8% of patients responding within the first two months of infusion.

Duration of Response

As of the 16 Oct 2019 data cutoff date, the median duration of follow-up after ide-cel infusion for all ide-cel-treated subjects was 11.3 months (range: 0.2, 18.6), increasing to 13.3 months (range: 0.2, 21.2) at the data cutoff 14 Jan 2020. The median follow-up durations were 18.0, 15.8, and 12.4 months in subjects who received target doses of 150, 300, and 450 x 10^6 CAR+ T cells, respectively.

As of the DCO date 16 Oct 2019 the KM estimate for median DoR among responders was 10.5 months (95% CI: 8.0, 11.3) with only a minor change at the data cut off 07 Apr 2020 (**Error! Reference source not found.**5).

Applying FDA censoring rules showed similar results to the analyses applying EMA censoring rules.

Table 15:

Duration of Response for Subjects who Achieved at Least Partial Response by IRC Assessment Based on IMWG Criteria (EMA Censoring Rules) (Ide-cel Treated Population)

	Data Cutoff Date = 16 Oct 2019				Data Cutoff Date = 07 Apr 2020			
	Ide-cel (CAR+ T Cells) Target Dose				Ide-cel (CAR+ T Cells) Target Dose			
	150 × 10^6 (N = 2)	300 × 10^6 (N = 48)	450 × 10^6 (N = 44)	150 to 450 × 10^6 (N = 94)	150 × 10^6 (N = 2)	300 × 10^6 (N = 48)	450 × 10^6 (N = 44)	150 to 450 × 10^6 (N = 94)
Duration of response, n (%)								
Censored	1 (50.0)	13 (27.1)	26 (59.1)	40 (42.6)	0	11 (22.9)	19 (43.2)	30 (31.9)
Progressed/died	1 (50.0)	35 (72.9)	18 (40.9)	54 (57.4)	2 (100)	37 (77.1)	25 (56.8)	64 (68.1)
Progressed	1 (50.0)	34 (70.8)	18 (40.9)	53 (56.4)	2 (100)	35 (72.9)	25 (56.8)	62 (66.0)
Died without PD	0	1 (2.1)	0	1 (1.1)	0	2 (4.2)	0	2 (2.1)
Duration of response[a, b] (months)								
Median	NE	8.5	11.3	10.5	13.0	8.5	11.3	10.6
95% CI	2.8, NE	5.4, 10.9	9.2, 11.4	8.0, 11.3	2.8, 23.3	5.4, 10.9	10.3, NE	8.0, 11.4
3 mo event-free % (SE)	50.0 (35.36)	85.4 (5.09)	93.2 (3.80)	88.3 (3.32)	50.0 (35.36)	85.4 (5.09)	93.2 (3.80)	88.3 (3.32)
6 mo event-free % (SE)	50.0 (35.36)	62.5 (6.99)	79.5 (6.08)	70.2 (4.72)	50.0 (35.36)	62.5 (6.99)	79.5 (6.08)	70.2 (4.72)
9 mo event-free % (SE)	50.0 (35.36)	50.0 (7.22)	72.7 (6.71)	60.5 (5.06)	50.0 (35.36)	50.0 (7.22)	70.5 (6.88)	59.6 (5.06)
12 mo event-free % (SE)	50.0 (35.36)	30.0 (6.75)	–	32.0 (6.18)	50.0 (35.36)	32.6 (6.84)	42.6 (7.79)	38.1 (5.12)
15 mo event-free % (SE)	50.0 (35.36)	24.8 (6.52)	–	26.9 (6.17)	50.0 (35.36)	28.3 (6.58)	40.0 (7.75)	34.4 (5.04)
18 mo event-free % (SE)	–	–	–	–	50.0 (35.36)	23.1 (6.31)	NE	28.7 (5.60)

[a] Response is defined as achieving sCR, CR, VGPR, or PR.

[b] Median and event-free rates are based on Kaplan-Meier estimation.

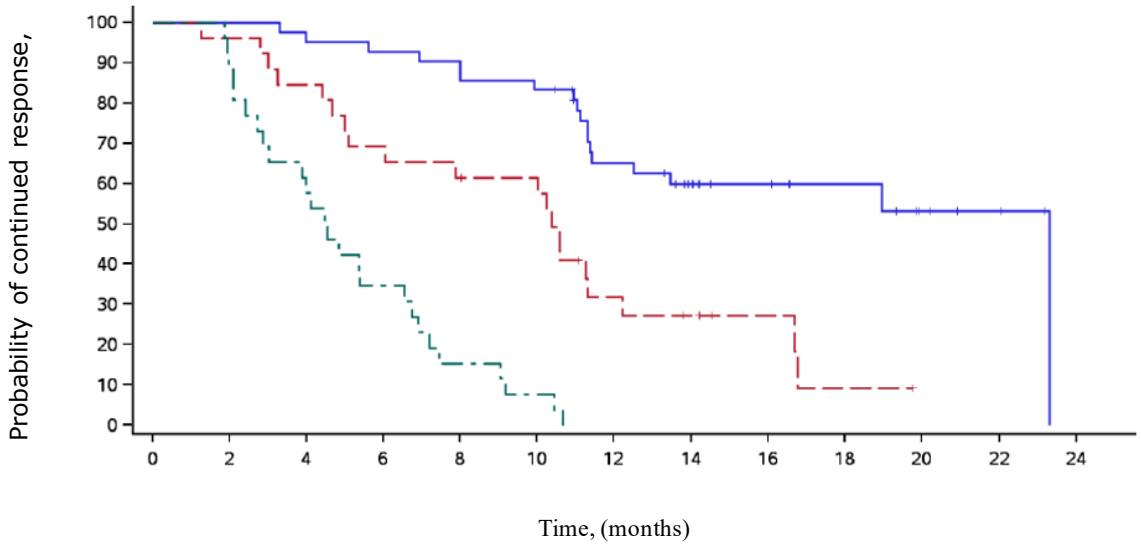
As of 07 Apr 2020, the median follow-up for ongoing responders was 14.2 months with a reported median DoR of 11 months (95% CI 8.0, 11.4) across the dose groups.

Kaplan-Meier curves of DoR at the 07 Apr 2020 data cutoff date based on IRC assessment, applying EMA censoring rules, are displayed in the figures below for all responders by best overall response and

by target dose. The DoR for CR or better responders has matured over time (median DoR of 19 months at the 14 Jan 2020 data cutoff date versus 23 months at the 07 Apr 2020 data cutoff date.

Figure 22: Kaplan-Meier curve of duration of response by best overall response by IRC review based on IMWG criteria, applying EMA censoring rules

Data cut off 7 April 2020

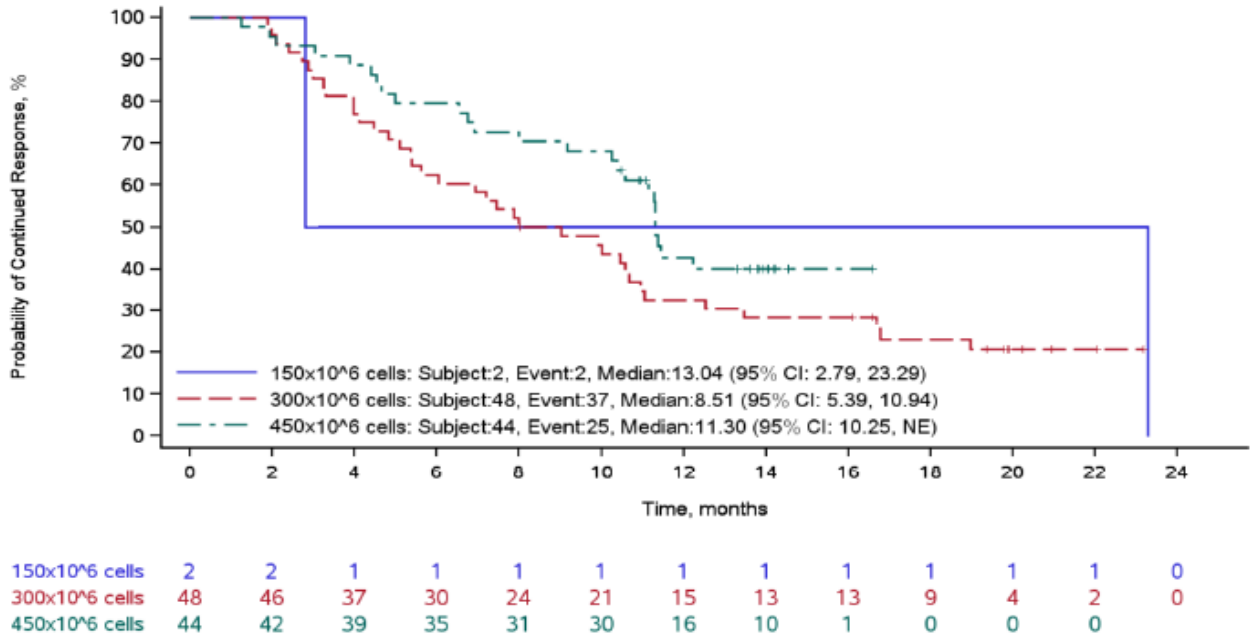


CR or better	42	42	40	39	36	35	25	19	12	9	5	3	0
VGPR	26	25	22	18	16	15	7	5	3	1	0	0	
PR	26	23	15	9	4	2	0	0	0	0	0	0	

CR or better: Subjects: 42; Events: 18; Median: 23.29 (95% CI: 11.43, 23.29)
VGPR: Subjects: 26; Events: 20; Median: 10.38 (95% CI: 5.09, 12.22)
PR: Subjects: 26; Events: 26; Median: 4.50 (95% CI: 2.86, 6.54)

CI= confidence interval; IMWG = International Myeloma Working Group; NE = not estimable. Two patients with 150 x 10^6 CAR-positive T cell dose, which is not part of the approved dose range, are included in Figure 1.

Figure 23: Kaplan-Meier Curve of Duration of Response Based on IRC Review According to IMWG Criteria Applying EMA Censoring Rules – by Target Dose (Subjects With at Least a Partial Response – Ide-cel-treated Population)



Data cut-off 7 April 2020

Progression-Free Survival

In the enrolled population PFS was calculated from enrolment (i.e. date of leukapheresis). At the 16 Oct 2019 data cutoff the median PFS was 8.3 months (95% CI: 6.7, 12.0), across the target dose levels of 150 to 450 x 10^6 CAR+T cells.

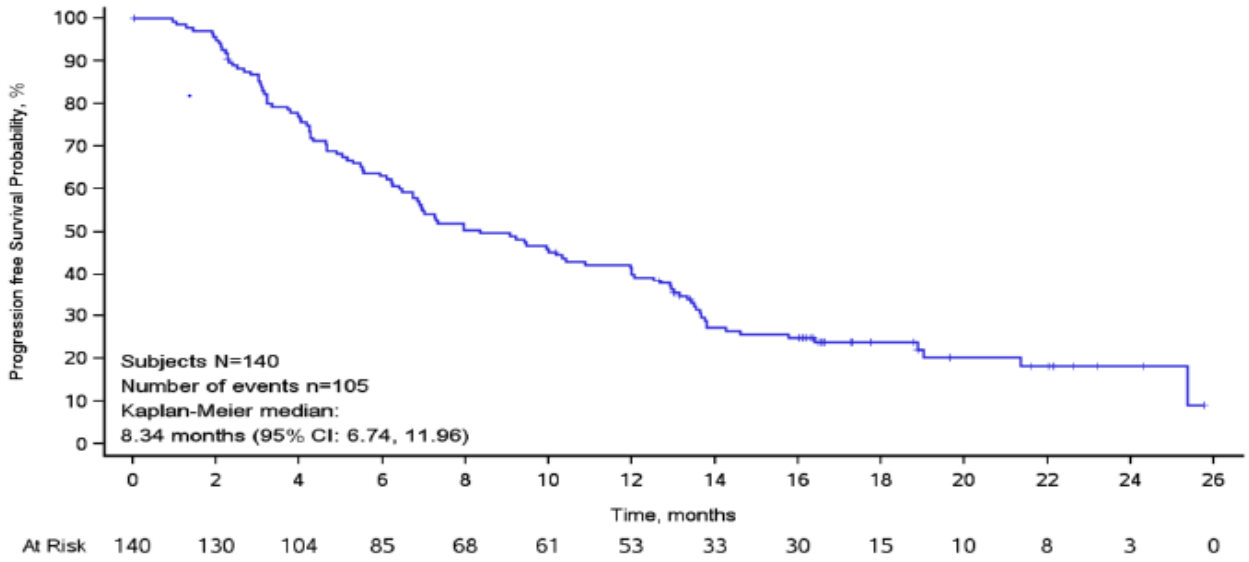
Table 16: Progression-free Survival Based on IRC According to IMWG Criteria Applying EMA Censoring Rules (Ide-cel-treated and Enrolled Populations)

	Data Cutoff Date = 16 Oct 2019					Data Cutoff Date = 07 Apr 2020				
	Ide-cel-treated Population Ide-cel (CAR+ T cells) Target Dose				Enrolled Population (N = 140)	Ide-cel-treated Population Ide-cel (CAR+ T cells) Target Dose				Enrolled Population (N = 140)
	150 × 10^6 (N = 4)	300 × 10^6 (N = 70)	450 × 10^6 (N = 54)	150 to 450 × 10^6 (N = 128)		150 × 10^6 (N = 4)	300 × 10^6 (N = 70)	450 × 10^6 (N = 54)	150 to 450 × 10^6 (N = 128)	
PFS, n (%)										
Censored	1 (25.0)	13 (18.6)	27 (50.0)	41 (32.0)	45 (32.1)	0	11 (15.7)	20 (37.0)	31 (24.2)	35 (25.0)
Progressed/died	3 (75.0)	57 (81.4)	27 (50.0)	87 (68.0)	95 (67.9)	4 (100)	59 (84.3)	34 (63.0)	97 (75.8)	105 (75.0)
Progressed	3 (75.0)	55 (78.6)	24 (44.4)	82 (64.1)	82 (58.6)	4 (100)	56 (80.0)	31 (57.4)	91 (71.1)	91 (65.0)
Died without PD	0	2 (2.9)	3 (5.6)	5 (3.9)	13 (9.3)	0	3 (4.3)	3 (5.6)	6 (4.7)	14 (10.0)
PFS time (months)										
Median[a]	2.8	5.9	11.3	8.2	8.3	2.8	5.9	12.1	8.2	8.3
95% CI	1.0, NE	4.2, 8.9	7.5, 12.4	5.6, 11.0	6.7, 12.0	1.0, 24.2	4.2, 8.9	7.5, 12.4	5.6, 11.1	6.7, 12.0
3 mo event-free % (SE)	50.0 (25.00)	71.4 (5.40)	81.2 (5.37)	74.9 (3.85)	86.7 (2.91)	50.0 (25.00)	71.4 (5.40)	81.2 (5.37)	74.9 (3.85)	86.7 (2.91)
6 mo event-free % (SE)	25.0 (21.65)	50.0 (5.98)	67.9 (6.41)	56.7 (4.40)	63.8 (4.14)	25.0 (21.65)	50.0 (5.98)	67.9 (6.41)	56.7 (4.40)	63.0 (4.15)
9 mo event-free % (SE)	25.0 (21.65)	37.1 (5.78)	60.3 (6.74)	46.3 (4.44)	49.7 (4.30)	25.0 (21.65)	37.1 (5.78)	58.5 (6.77)	45.7 (4.42)	49.7 (4.30)
12 mo event-free % (SE)	25.0 (21.65)	25.0 (5.25)	47.0 (8.60)	32.8 (4.70)	39.4 (4.36)	25.0 (21.65)	26.7 (5.33)	50.9 (6.88)	36.8 (4.30)	39.9 (4.22)
15 mo event-free % (SE)	25.0 (21.65)	16.7 (4.64)	–	19.4 (4.60)	21.9 (4.46)	25.0 (21.65)	19.3 (4.77)	33.2 (6.76)	25.4 (3.96)	25.5 (3.84)
18 mo event-free % (SE)	–	16.7 (4.64)	–	19.4 (4.60)	18.2 (4.42)	25.0 (21.65)	16.1 (4.49)	NE (NE)	21.5 (4.21)	23.7 (3.78)
21 mo event-free % (SE)	–	–	–	–	–	25.0 (21.65)	14.3 (4.33)	NE (NE)	19.3 (4.30)	20.2 (3.96)

BLA = Biologics License Application; CAR = chimeric antigen receptor; CI = confidence interval; FDA = Food and Drug Administration; ide-cel = idecabtagene vicleucel; IMWG = International Myeloma Working Group; mo = months; NE = not estimable; PD = progressive disease; PFS = progression-free survival; SE = standard error.Note: PFS was measured from the day of infusion for the ide-cel-treated population and from the day of enrolment (ie, leukapheresis) for the enrolled population.

At the 07 Apr 2020 data cut off the median PFS follow-up for censored subjects was 15.1 months, with a reported median PFS unchanged compared with the 14 Jan 2020 data cutoff date for the enrolled population and the 450 x 10^6 dose group.

Figure 24: Kaplan-Meier Curve of Progression-free Survival Based on IRC According to IMWG Criteria Applying EMA Censoring Rules - Ide-cel Enrolled Population)



Data cut–off 7 Apr2020

At the 07 Apr 2020 data cutoff date, 105 (75.0%) of subjects had progressed/died and 35 (25.0%) were censored. The most common reason for censoring was that subjects were ongoing without an event at the data cutoff date 29 (20.7%) subjects and 6 (4.3%) had discontinued in the study without progression/death.

Overall Survival (OS)

OS data at the 16 Oct 2019 and 07 Apr 2020 data cutoff dates are summarised in Table 17.

Table 17: Overall Survival - Study MM-001

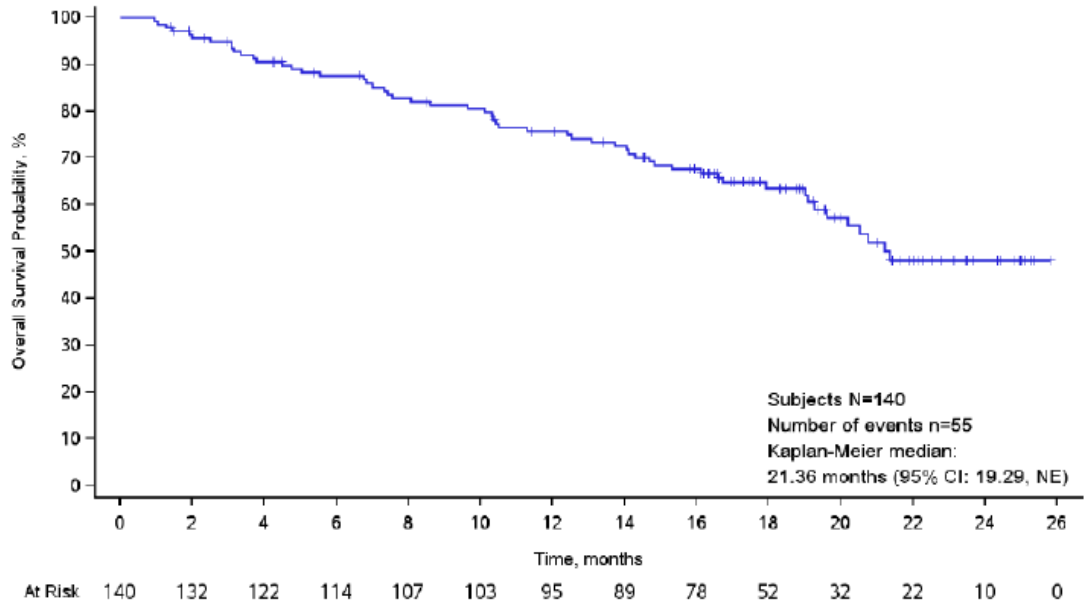
	Data Cutoff Date = 16 Oct 2019					Data Cutoff Date = 07 Apr 2020				
	Ide-cel-treated Population Ide-cel (CAR+ T cells) Target Dose				Enrolled Population (N = 140)	Ide-cel-treated Population Ide-cel (CAR+ T cells) Target Dose				Enrolled Population (N = 140)
	150 × 10^6 (N = 4)	300 × 10^6 (N = 70)	450 × 10^6 (N = 54)	150 to 450 × 10^6 (N = 128)		150 × 10^6 (N = 4)	300 × 10^6 (N = 70)	450 × 10^6 (N = 54)	150 to 450 × 10^6 (N = 128)	
OS, n (%)										
Censored	2 (50.0)	50 (71.4)	42 (77.8)	94 (73.4)	98 (70.0)	2 (50.0)	41 (58.6)	38 (70.4)	81 (63.3)	85 (60.7)
Died	2 (50.0)	20 (28.6)	12 (22.2)	34 (26.6)	42 (30.0)	2 (50.0)	29 (41.4)	16 (29.6)	47 (36.7)	55 (39.3)
OS time (months)										
Median[a]	18.2	NE	NE	18.2	19.3	18.2	NE	NE	NE	21.4
95% CI	9.4, 18.2	16.8, NE	NE, NE	18.0, NE	17.9, NE	9.4, NE	18.0, NE	NE, NE	18.9, NE	19.3, NE
3 mo event-free % (SE)	100 (0)	95.7 (2.44)	92.6 (3.56)	94.5 (2.02)	94.9 (1.86)	100 (0)	95.7 (2.44)	92.6 (3.56)	94.5 (2.02)	94.9 (1.86)
6 mo event-free % (SE)	100 (0)	89. 6 (3.71)	86.9 (4.61)	88.8 (2.82)	87.4 (2.85)	100 (0)	89.6 (3.72)	86.9 (4.61)	88.8 (2.82)	87.4 (2.85)
9 mo event-free % (SE)	100 (0)	86.6 (4.16)	79.1 (5.62)	83.9 (3.31)	81.3 (3.38)	100 (0)	86.5 (4.18)	79.3 (5.57)	83.9 (3.31)	81.2 (3.39)
12 mo event-free % (SE)	75.0 (21.65)	78.6 (5.09)	76.8 (5.92)	76.9 (3.96)	75.5 (3.78)	75.0 (21.65)	78.5 (5.11)	77.3 (5.76)	77.9 (3.76)	75.8 (3.74)
15 mo event-free % (SE)	75.0 (21.65)	72.7 (5.73)	–	71.6 (4.72)	67.3 (4.70)	75.0 (21.65)	71.9 (5.66)	69.1 (6.47)	70.9 (4.17)	68.4 (4.11)
18 mo event-free % (SE)	75.0 (21.65)	52.4 (13.0)	–	54.5 (11.16)	61.8 (5.75)	75.0 (21.65)	63.0 (6.19)	69.1 (6.47)	64.2 (4.75)	63.5 (4.37)
21 mo event-free % (SE)	0	–	–	–	–	37.5 (28.64)	51.0 (6.69)	NE (NE)	51.1 (5.85)	51.9 (5.35)

[a] Median and 95% CI are based on the Kaplan-Meier approach.

Note: Overall survival was measured from the day of infusion for the ide-cel-treated population and from the day of enrolment (ie, leukapheresis) for the enrolled population.

At the latest data cut off 07 Apr 2020, with a median follow-up time for all surviving subjects of 17.0 months, the reported median OS in the enrolled population was 21.4 months (95% CI: 19.3, NE); 39.3% of subjects had died and 85 (60.7%) were censored . The estimated survival rate at 18 months from leukapheresis was 64%.

Figure 25: Kaplan-Meier Curve of Overall Survival (Enrolled Population)



Data cut-off 7 Apr 2020

The most common reason for censoring was that subjects were ongoing without an event at the data cutoff date i.e 58 (41.4%). A total of 23 patients were withdrawn from the study (subject decision or physician), whereof 21 patients were still in follow-up for OS. In addition to the 23 withdrawn patients 4 were lost to follow-up.

Patients retreated with ide-cel

Of the 128 subjects who received ide-cel treatment, 31 (24.2%) were screened for retreatment and 29 subjects received ide-cel retreatment (07 April 2020 data cutoff date).

During ide-cel manufacture for retreatment, 6 (20.7%) of the 29 subjects who received ide-cel retreatment received bridging therapy for myeloma control prior to their repeat course of LDC before ide-cel retreatment. Of the 29 subjects who received retreatment, 28 had a target dose of 450 x 10^6 CAR+ T cells and 1 had a target dose of 300 x 10^6 CAR+ T cells for their second ide-cel infusion.

The ORR for retreated subjects based on investigator assessment was 20.7% (N=6, 95% CI: 8.0, 39.7), of which 5 patients achieved a best overall response of PR (17.2%) and one patient achieved a best overall response of VGPR (3.4%). All patients who achieved a response were ADA negative before retreatment (6/12 ADA negative patients) while none of the 17 ADA positive patients achieved a response.

As of the 07 Apr 2020 data cutoff date, all of the twenty-nine (29) ide-cel-retreated subjects had a PFS event after ide-cel retreatment (28 subjects progressed and 1 died). The KM estimate for median PFS starting from time of retreatment was 1.0 month (95% CI: 0.95, 1.97).

Subsequent antimyeloma therapies

As of the 16 Oct 2019 data cutoff date, 56 (43.8%) subjects received subsequent AMT (including ide-cel retreatment, bridging AMT for retreatment, or LDC prior to retreatment). The KM estimate for median time to subsequent AMT was 13.2 months (95% CI: 10.9, 15.1). Eight (14.3%) of the 56 subjects in the treated population who received subsequent AMT had a reported response of PR or better on subsequent AMT.

HRQoL

Patient-reported outcomes was assessed in the MM-001 study by the EORTC QLQ-C30, the EQ-5D-5L and the EORTC QLQ-MY20 instruments.

Results are reported until Month 15 since few subjects (>10) had responded to the questionnaires after Month 15 (16 Oct 2019 data cutoff). Only five domains from the EORTC QLQ-C30 (Fatigue, Pain, Physical Functioning, Cognitive Functioning, and Global Health/QoL) and two subscales of the EORTC QLQ-MY20 (Disease Symptoms and Side Effects) were analysed. The minimal important difference (MID) for mean changes from baseline was predefined for each subscale, based on the recommendation from the published literature (Cocks, 2012[1]).

For the EORTC QLQ-C30 Fatigue and Pain subscales clinically meaningful decreases (improvement) in mean scores from baseline to Month 9 were seen. Both in the EORTC QLQC30 Physical Functioning Subscale and in the Global Health/QoL domain a clinically meaningful increase (improvement) in mean score from baseline were seen. For the EORTC QLQ-MY20 Side Effects subscale scores a gradual increase (deterioration) in mean scores was observed from baseline to Month 9 but increases were not statistically significant nor clinically meaningful. In the EORTC QLQ-MY20 Disease Symptoms Subscale scores small clinically meaningful decreases (improvements) were observed from baseline to Months 4 through 15 posttreatment. The EORTC QLQ-C30 Cognitive Functioning subscale scores generally demonstrated stability from baseline to Month 9 and beyond with baseline mean scores close to that of the general population.

The applicant has compared the baseline scores on the EORTC QLQ-C30 and EORTC QLQMY20 domains only with the scores for the general population (Nolte, 2019[2]). Since no data for comparison of HRQoL in RRMM patient treated with standard of care is provided, contextualisation of the HRQoL data based on this single arm study is limited.

Ancillary analyses

Exploratory Multivariable Analysis for Efficacy

Baseline and disease characteristics identified as potential prognostic factors for response (ORR and CR rate), DoR, and PFS were investigated in exploratory regression analyses, including the effect of ide-cel dose on efficacy endpoints after controlling for some baseline variables. Contrasting results were observed on the potential roles of some baseline characteristics across the different endpoints. In

[1] Cocks K, King MT, Velikova G, de Castro G, Martyn St-James M, Fayers PM, et al. Evidencebased guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer. 2012;48(11):1713-21.
[2] Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. Eur J Cancer. 2019;107:153-63.

particular, a number of prognostic factors seem to have an impact on dose-effect, albeit any significant interactions between these baseline covariates and dose effect uncovered by the multivariate modeling tools may be of little statistical meaning due to multiplicity issues and small sample sizes. Overall, the relationship between dose and efficacy endpoints may be considered robust.

Comparison of Ide-cel to Real World Evidence: Study NDS-MM-003

NDS-MM-003: A global, non-interventional, retrospective, multi-center study to generate real-world evidence of subjects with relapsed and refractory multiple myeloma with prior exposure to an anti-CD38 antibody

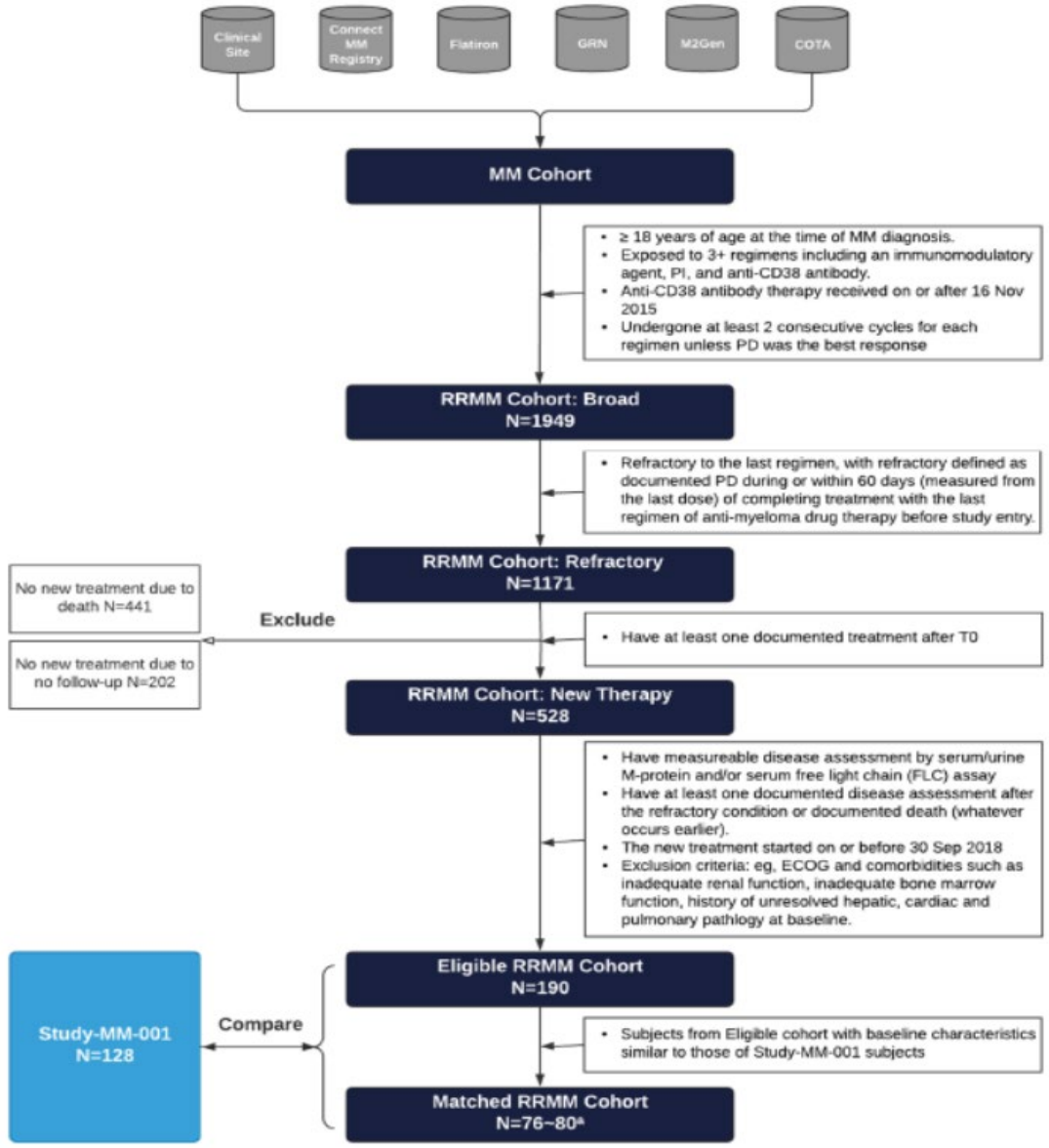
Study NDS-MM-003 was a global, non-interventional, retrospective study set up to generate an external comparison arm for study MM-001. Data from sources including clinical sites, registries, and research databases were collated in a single data model, and further analysed.

The patient eligibility period started in November 2015 and ended in September 2018. A data cutoff date of 30 Oct 2019 was used for the collection of the RW data.

Methods

Subject-level data were collected on 1949 RW subjects who had RRMM and who had received at least 3 prior regimens, including an immunomodulatory agent, a PI, and an anti-CD38 antibody (Broad RRMM cohort). From this cohort, subjects were subsequently selected based on having met eligibility criteria for Study MM-001 as closely as possible, including initiation of a new therapy after becoming refractory to the last regimen and lack of co- morbidities. Subject selection based on these criteria identified 190 subjects (eligible RRMM cohort) with similar characteristics to the MM-001 population.

Figure 26: **Construction of the RWD cohort**



ECOG = Eastern Cooperative Oncology Group; GRN = Guardian Research Network; max = maximum; min = minimum; MM = multiple myeloma; PD = progressive disease; PI = proteasome inhibitor; RRMM = relapsed and refractory multiple myeloma; T0 = baseline.
[a] Numbers (Min-Max) of matched subjects from 30 imputed datasets.

Primary Objectives

- Describe demographic and selected clinical characteristics of RW subjects with RRMM who received at least 3 prior myeloma regimens, including a PI, an immunomodulatory agent, and an anti-CD38 antibody (RRMM cohort).

- Describe demographics, disease characteristics, treatment patterns, and clinical outcomes of the above RW subjects and for the cohort of RW subjects who met eligibility criteria for Study MM 001 (Eligible RRMM cohort).

Endpoints

The primary endpoint was ORR, which was defined as the percentage of subjects who achieved a partial response (PR) or better. A PR was defined according to IMWG uniform response criteria for MM.

The secondary endpoints were VGPR rate, CR rate, TTR, DoR, OS and PFS.

Endpoints were calculated relative to each subject's baseline date (T0) defined as the date that the subject becomes refractory to the last regimen with refractory defined as documented PD during or within 60 days (measured from the last dose) of completing treatment with the last regimen of antimyeloma drug therapy before study entry. The index date (Study Day 1) was the start date of the first AMT after T0.

The ORR was calculated as the percentage of subjects who achieved PR or better according to the (IMWG Criteria) following the first treatment after baseline (T0).

The comparison of ORR for the Balanced RRMM cohort to the BB2121-MM-001 cohort was based on the relative risk regression with adjustment for confounding using PS produced with stabilised inverse probability of treatment weights (IPTW) for each balanced imputed dataset.

Other secondary endpoints were also analyzed (VGPR, OS, TTR and DoR, PFS). No safety data were collected.

Propensity score methods

Propensity score (PS) methodology was used to ensure that RW subjects in the Eligible RRMM cohort were comparable to the ide-cel cohort

The selected cohort of 190 RW subjects for the Eligible RRMM cohort provided an adequate match for only about 80 subjects in the Abecma cohort. As a result, the primary analysis method had to be changed. Trimmed stabilised IPTW was used as the primary analysis method for the effectiveness endpoints and are the data presented throughout this report. Matched-pair and untrimmed stabilised IPTW analyses were utilised as supporting analyses.

Covariates considered included age, sex, bone lesions, time from initial diagnosis, number of prior regimens, cytogenetic high risk/low risk, refractory to immunomodulatory agents, refractory to PI, refractory to anti-CD38 antibody, and baseline lab tests (platelet, hemoglobin, albumin, and calcium). As a conservative measure, the analysis allowed for as much as 30% missing data for highly prognostic covariates in the Eligible RRMM cohort. Covariates considered very important predictors of outcome by the scientific steering committee (ie, age, albumin, number of prior regimens) were forced into the model irrespective of a lack of association with group membership.

PSs were calculated on subject-level data to summarise the impact of covariates on treatment selection into a scalar value. These PS values were then used, through weighting individual subjects both in the Eligible RRMM cohort and the respective ide-cel cohort.

Results

In the Eligible RRMM cohort, the median duration of follow-up for all treated subjects, which includes duration up to death for subjects who died and duration up to last date known alive for surviving subjects, was 10.2 months (range: 0.2 to 24.0), as of the 30 Oct 2019 data cutoff date.

Compared to the ide-cel cohort, patients in the Eligible RRMM cohort (n=190) were older (median age: 64.0 vs. 60.5 years), somewhat less heavily pre-treated (median number of prior AMTs 5.0 vs. 6.0 and proportion of patients with at least one prior ASCT 70.5% vs. 93.8%) and had a lower degree of refractoriness to prior AMTs (53.7% vs. 89.1% were double-class refractory).

The eligible RRMM cohort were treated with currently available therapies as the next-line study treatment which typically consisted of combinations of immunomodulatory agents, PIs, monoclonal antibodies, corticosteroids, and cytotoxic agents. There were more than 90 different regimens and 74.7% were able to receive 3 or more drug combinations as their index therapy.

Based on the logistic regression equation, covariates that needed to be included in the stabilised inverse probability weighting and in the matched analysis are summarised in Table 18.

Table 18: Summary of Covariate Balance Adjusted for Trimmed Stabilised Inverse Probability of Treatment Weighting of Eligible RRMM and Ide-cel Cohorts

	Before Balancing			After Balancing		
Covariate	Eligible RRMM Cohort (N = 190)	Ide-cel Cohort (N = 128)	Standardized Mean Difference (Ide-cel -RW)	Eligible RRMM Cohort (N = 190)	Ide-cel Cohort (N = 128)	Standardized Mean Difference (Ide-cel -RW)
Age (years)	64.5	59.8	-0.5068	62.9	60.8	-0.2189
Sex (Male = 1, Female = 0)	0.6	0.6	0.0194	0.6	0.6	-0.0753
Albumin Serum (g/dL)	3.6	3.7	0.2709	3.6	3.7	0.0712
Corrected Calcium (mmol/L)	2.4	3.0	0.4302	2.5	2.8	0.2693
Years from initial diagnosis	4.9	6.9	0.5814	5.9	6.3	0.1289
Number of prior regimens	4.8	5.6	0.5288	5.1	5.1	0.0611
Number of prior regimens/year since diagnosis	1.3	1.2	-0.1423	1.2	1.1	-0.0770
Prior refractory to immuno-modulatory agent (Yes = 1, No = 0)	0.7	1.0	0.7418	0.8	0.9	0.1159
Refractory to a PI, an immuno-modulatory agent, and an anti-CD38 antibody (Yes = 1, No = 0)	0.4	0.8	0.9491	0.6	0.6	0.1268

PI = proteasome inhibitor; RRMM = relapsed and refractory multiple myeloma; RW = real-world.

Notes: Multiple imputation procedures created 30 datasets. Overall estimates were obtained using Rubin's rules to combine the individual estimates. Means are presented for continuous variables and proportions are presented for categorical variables. Standardised mean difference was obtained from the ide-cel cohort minus the Eligible RRMM cohort and used trimmed stabilised weights when combining the mean and standard deviation.A covariate was not included in the balancing if the covariate had more than 30% missing for the Eligible RRMM cohort. The stabilised inverse probability treatment weighting was trimmed at the maximum of the minimum weight and the minimum of the maximum weight for the ide-cel cohort and the Eligible RRMM cohort.

ORR and VGPR

A summary of ORR and VGPR rate adjusted for trimmed stabilised IPTW for subjects in the Eligible RRMM and ide-cel enrolled cohorts (Data cut off 16 Oct 2019) is presented in Table 19.

Table 19 :Overall Response Rate and VGPR or Better Rate Adjusted for Trimmed Stabilised IPTW for Subjects in the Eligible RRMM and Ide-cel Enrolled Cohorts

Method Response	Eligible RRMM Cohort[a] (N = 190)	Ide-cel Enrolled Cohort[a] (N = 140)
Trimmed Stabilized Inverse of Probability Treatment Weighting		
Overall Response Rate (%)	32.0	69.4
95% CI[b]	(24.1, 42.5)	(60.3, 80.0)
Relative risk (95% CI)	2.2 (1.5, 3.1)[c]	-
P-value[c]	< .0001	-
Very Good Partial Response (VGPR) Rate (%)	13.6	52.0
95% CI[b]	(8.5, 21.7)	(42.3, 63.9)
Relative risk (95% CI)	3.8 (2.2, 6.6)[c]	-
P-value[c]	< .0001	-

a Index date for ORR was start of new therapy for Eligible RRMM cohort and start of leukapheresis for ide-cel cohort.,b 2-sided 95% CI,c Relative risk, p-value, and CI are based on a Poisson regression with robust error variance, adjusted for theunbalanced covariates in the propensity score model. The primary analysis used a log link function and stabilisedIPTWs trimmed at the maximum of the minimum weight and the minimum of the maximum weight for the ide-cel cohort and Eligible RRMM cohort.

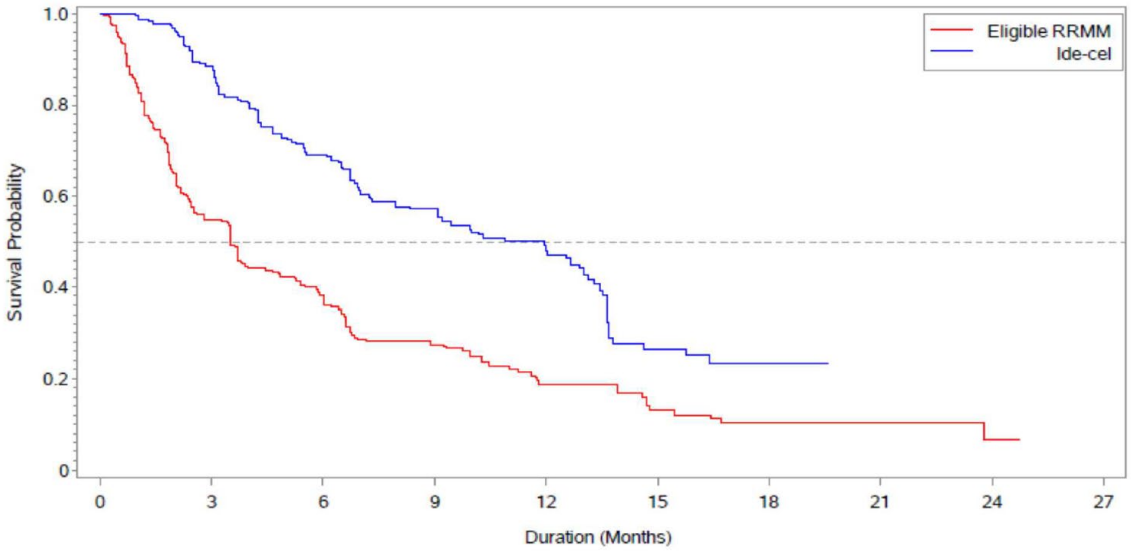
Note: Overall response rate: Rate of subjects who achieved a best response of partial response (PR) or better. VGPR or better response rate: Rate of subjects who achieved a best response of VGPR or better. Very good partial response for the RWE data may not have a bone marrow sample confirmation. Multiple imputation procedures created 30 datasets. Estimates were then obtained using Rubin's rules to combine the individual estimates from each dataset.

Duration of Response (DoR);

The median adjusted DoR by trimmed stabilised IPTW for subjects who achieved at least a PR was 9.0 months (95% CI: 7.5, 10.4) for 30.5% responders in the Eligible RRMM cohort versus 11.0 months (95% CI: 10.7, 11.3) for 73.4% responders in the ide-cel responder cohort.

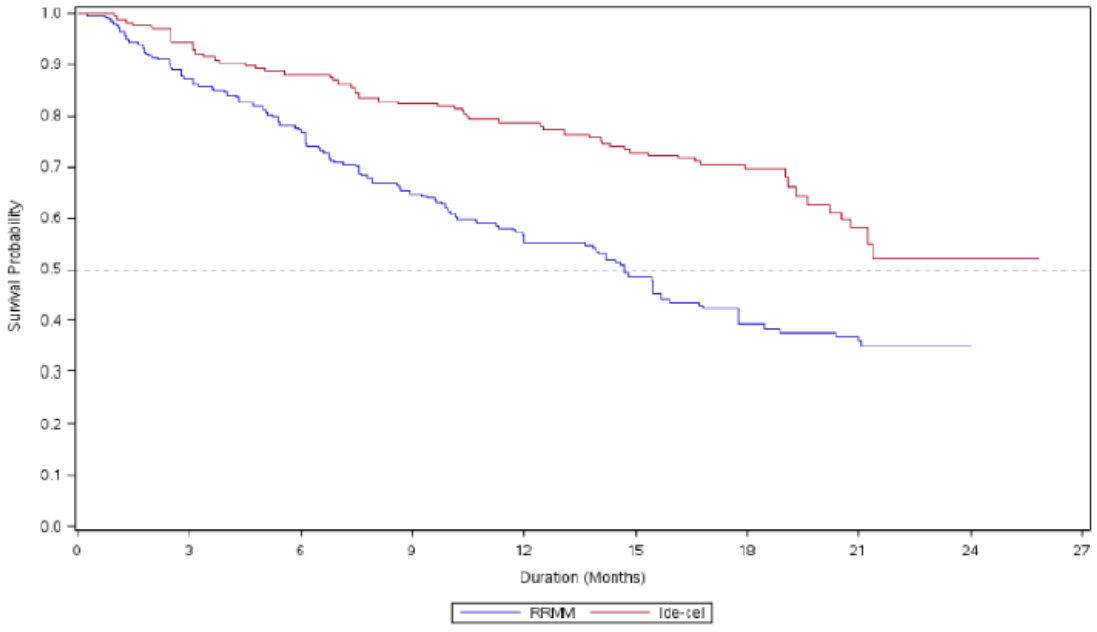
The median adjusted PFS was lower in the Eligible RRMM cohort compared with the ide-cel enrolled cohort (3.5 months versus 12.0 months, respectively). A comparison between the 2 groups yielded a PFS HR of 0.43 (95% CI: 0.30, 0.62, p < 0.0001), favouring the ide-cel enrolled cohort compared with the Eligible RRMM cohort (Figure 27).

Figure 27: PFS According to EMA Censoring Rules Adjusted for Trimmed Stabilised IPTW for Subjects in the Eligible RRMM and Ide-cel Enrolled Cohorts



The analyses for the Eligible RRMM cohort versus the ide-cel enrolled cohort has been updated. i.e. data from the ide- cel study at data cut off 7 Apr 2020 reporting an adjusted median PFS of 10.9 months. A updated comparison between 2 the groups yielded an HR of 0.45 (95% CI 0.32, 0.64, p < 0.0001)

Figure 28: Overall Survival Adjusted for Trimmed Stabilised IPTW for the Eligible RRMM Cohort and Ide-cel Enrolled Cohort



The median OS was 14.7 months (95% CI: 14.0, 15.4) for RW subjects in the Eligible RRMM cohort. The analyses for the Eligible RRMM cohort versus the ide-cel cohort has been updated with OS data from the MM-001 (Data cut off 4 Apr 2020), with the adjusted median OS Not Estimable (NE) (95% CI was not estimable) in the ide-cel enrolled population, relative to the start date of leukapheresis. A comparison between the 2 groups yielded an HR of 0.46 (95% CI 0.29, 0.73, p = 0.001).

Systematic Literature Review (SLR)

An SLR was conducted to identify clinical trials and real-world studies (RWS) of patients with RRMM who had received ≥3 prior lines of therapy including a PI, an immunomodulatory drug, and an anti-CD38 antibody. Studies that did not explicitly require previous anti-CD38 treatment but did report the proportion of patients who had received such an agent were also included. For further information, please refer to bb2121-mm-001-slr-protocol-original.docx.

Results

A total of 36 publications, representing 24 unique studies, were included in the SLR. Eleven were RW studies and 13 were clinical trials, evaluating approved (1) and unlicensed (12) therapies.

All RWS studies were conducted in the US, except for Brioli 2019 that was carried out in Germany. MAMMOTH (N=275) and Richardson 2019 (N=36) were multicentre studies, while the other studies were mostly small (sample size ranging from 9 to 126) and conducted in a single centre. All studies were similar to one another with regard to patient demographics, with median age ranging from 60 to 67 years and the populations being predominantly Caucasian. ORR ranged from 23% to 90%, median PFS (when reported) ranged from 2.2 months to 7 months, and OS (when reported) ranged from 5.6 to 16 months.

There were four clinical trials of CAR-T therapies, three trials of BCMA targeted agents and five trials of non-BCMA targeted agents, including the STORM part 1 and 2 trials, supporting the FDA approval of Selinexor combined with dexamethasone. ORR for the CAR-T therapies ranged from 27% to 100%, and for the non-CAR-T therapies ORRs of 21% to 48% were reported.

For further characteristics of the 11 RWS and 13 clinical trials identified by the systematic literature search, see summary tables below.

Table 20: Overview of real-world studies (RWS) included in the SLR (compiled by the assessor).

Category	Study /enrollment	Treatment	Sample size	No. of prior lines, median (range)	Refractory status	N (%)	ORR, n (%)	sCR + CR n (%)	DoR months (median)	PFS months (median)	OS months (median)
Pivotal trial	**MM001**	**BB2121**	**140**	**6 (3-17)**	**Double refractory (89%) Triple refractory (84%) Pentarefractory (26%)**	**140**	**94 (67)**	**40 (29)**	**10.6**	**9.4**	**19.3**
Multicentre	Mammoth /2017-2018	Various agents	275	4 (1-16) b	Refractory to daratumumab or isatuximab	249 (91)	78 (31)	5 (2)	-	3.4	9.3
					Penta-refractory	70 (26)	(30)	-	-	-	5.6
					Triple- or quad-refractory	148 (54)	(29)	-	-	-	9.2
					Not triple-refractory	57 (21)	(38)	-	-	-	11.2
	Richardson /-	Various agents	36	5 (2-7)	Penta-exposed, tripleclass Refractory	36	-	-	-	-	5.8
Single centre	Nooka /2015-2016	Daratumumab + pomalidomide + Dexamethasone	22c/12 d	5 (3-13)/ 6.5 (3-13)	Dual-class refractory (59% with prior exposure to daratumumab)	22	9 (40.9)	0 (0)	-	5.7	15.2
					Triple-class refractory	12	4 (33.3)	0 (0)	-	3.3	13.1
	Lakshman /2015-2016	Daratumumab+ Dexamethasone+	126	4 (1-14)	Penta-refractory	8	2 (25)	0 (0)	-	2.2	-

		pomalidomide or lenalidomide or bortezomib									
	Goldsmith BENDA /2013-2018	Bendamustine	27	8 (4-15)	Penta-refractory	22	5 (23)	0 (0)	-	-	-
	Goldsmith DCEP /2013-2018	Dexamethasone + cyclophosphamide + etoposide + cisplatin	31	-	Penta-refractory	23	7 (30)	0 (0)	-	-	-
	Kambhampat /-	Venetoclax + bortezomib	31	7 (2-13)	Relapsed	31	11 (35)	1 (3.2)	7.2	-	-
	Brioli /-	Pomalidomide + cyclophosphamide + Dexamethasone	9	4 (2-8)	Triple-class exposed	9	5 (56)	2 (22)	-	7	16
	Zhou /2016-2019	Pomalidomide + bortezomib + doxorubicin + dexamethasone + daratumumab	56	-	Penta-refractory	10	9 (90)	-	-	-	-
	Basali /-	Venetoclax-based regimens	10	6 (2-19)	All (≥80% refractory to daratumumab) t(11;14) cytogenetic abnormality only	10	7 (78)	1 (11.1)	-	-	-
	Sidiqi /2016-2019	Venetoclax as monotherapy or in combination	56	6 (1-15)	All (61% penta-refractory or penta-exposed)	52	23 (44)	11 (21)	-	5.6	NR

Table 21: Overview of clinical trials included in the SLR (compiled by the assessor)

Category	Trial	Treatment	Design	Sample size	Inclusion criteria		No. of prior lines, median (range)	ORR%	sCR + CR %	DoR months (median)	PFS months (median)	OS months (median)
					ECOG PS	Prior lines						
Pivotal trial	**MM001**	**BB2121**	**Phase II, single-arm**	**140**	**0-1**	**≥3 lines, refractory to last line**	**6 (3-17)**	**67**	**29 %**	**10.6**	**9.4**	**19.3**
Car-T	APRIL	Auto 2	Phase II single-arm	11	0-1	≥3 lines or dual-class refractory	5 (3-6)	27	0	-	-	-
	CARTITUDE -1	JNJ-4528	Phase Ib/II single-arm	29	0-1	≥3 lines or dual-class refractory	5 (3-16)	100	69	-	-	-
	Cohen 2019	CART-BCMA	Phase I single-arm	25	0-2	≥3 lines	7 (3-13)	48	8	4.1	-	16.5
	CRB-402	bb21217 + cyclophosphamide + fludarabine	Phase I single-arm	38	0-1	≥3 lines	6 (3-17)	61	15	-	-	-
BCMA-targeted	DREAMM-2	Belantamab mafodotin 3.4 mg/kg	Phase II RCT (open-label)	99	0-2	≥3 lines and triple-class refractory	6 (3-21)	34	-	NR	4.9	Data not mature
		Belantamab mafodotin 2.5 mg/kg		97			7 (3-21)	31	-	NR	2.9	Data not mature
	DREAMM-1	Belantamab mafodotin	Phase I single-arm	35	0-1	≥1 line	5 (1-10+)	29 (penta refractory) 38 (triple refractory)	-	-	6.2 (triple refractory)	-
	C1071001	PF-3135	Phase I	17	0-2	-	11	-	-	-	-	-

			single -arm									
Non-BCMA targeted	STORM part 1	Selinexor + dexamethasone	Phase II single -arm trial	79	0-2	≥3 lines	7 (3-17)	21	0	5.0	2.3	9.3
	STORM part 2	Selinexor + dexamethasone	Phase II single -arm trial	122	0-2	≥5 lines	7 (3-18)	26	2	4.4	3.7	8.6
	HORIZON	Melflufen + dexamethasone	Phase II single -arm	121	0-2	≥2 lines	5 (2-12)	21	-	3.6	-	8.5
	KEYNOTE-183	Pembrolizumab + pomalidomide + dexamethasone vs Pomalidomide + dexamethasone	Phase III RCT (open -label)	249	0-1	≥2 lines	-	34 (triple combination) 40 (double combination)	<1	8.2 (triple) Not reached (double)	5.6 (triple) 8.4 (double)	Not reached (triple) 15.2 (double)
	M13-367	Venetoclax + dexamethasone	Phase I/II single -arm	31	0-2	≥2 lines	5 (2-12)	48	6	Not reached	10.8	Not reached

Adjusted indirect treatment comparisons

Population Matching-adjusted indirect comparisons (MAICs), using PS weights to adjust for cross-study differences, were undertaken using individual subject-level data from Study MM-001 for ide-cel and aggregated summary data from STORM part 2 (selinexor) and DREAMM-2 (belantamab mafodontin) primary publications (MAIC – STORM-II; MAIC-DREAMM-2).

For the enrolled population, the effective sample size (ESS) was reduced by 56.3% and 57.7% for the Selinexor and Belantamab comparisons, respectively.

Table 22: Results for Matching-adjusted Indirect Comparison of Ide-cel Versus Selinexor and Versus Belantamab Mafodotin

Endpoint	Ide-cel Infused Population		Enrolled Population	
	Ide-cel vs selinexor + dexamethasone mITT	Ide-cel vs belantamab mafodotin, 2.5 mg/kg ITT	Ide-cel vs selinexor + dexamethasone mITT	Ide-cel vs belantamab mafodotin, 2.5 mg/kg ITT
ORR, OR (95% CI)	7.01 (3.46, 14.21)	5.12 (2.35, 11.13)	5.07 (2.63,9.78)	3.08 (1.57,6.06)
DoR, (months)	Median (95% CI) 10.68 (9.03, NE) vs 4.4 (3.7, 10.8)	HR (95% CI) 0.74 (0.30, 1.86)	Median (95% CI) 10.68 (9.03, NE) vs 4.4 (3.7, 10.8)	HR (95% CI) 0.74 (0.3,1.86)
PFS, HR (95% CI)	0.46 (0.28, 0.78)	0.45 (0.27, 0.76)	0.39 (0.24, 0.63)	0.44 (0.28, 0.69)
OS, HR (95% CI)	0.28 (0.16, 0.50)	0.36 (0.15, 0.86)	0.33 (0.19, 0.56)	0.59 (0.3, 1.16)

CI = confidence interval; DoR = duration of response; HR = hazard ratio; ITT = intention to treat; mITT = modified intention to treat; NE = not estimable; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; vs = versus.
Source: Study MAIC-STORM-2; Study MAIC-DREAMM-2

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23 : Summary of Efficacy for Study BB2121-MM-001

Title: A Phase 2, Multicenter Study to Determine the Efficacy and Safety of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma		
Study identifier	BB2121-MM-001 (MM-001; NCT03361748; U1111-1202-5554; EudraCT: 2017-002245-29)	
Design	Open-label, single-arm, multicentre, multinational, Phase 2 study	
	First subject's first ide-cel infusion:	05 Feb 2018
	Last subject's first ide-cel infusion:	20 Dec 2018
	Duration of main phase:	Pretreatment period: up to 28 days for screening prior to leukapheresis, followed by leukapheresis then approximately 4 to 5 weeks anticipated for ide-cel product to be manufactured. Treatment period: one 3-day cycle of LDC starting 5 days prior to the target ide-cel infusion date, followed by ide-cel infusion. Posttreatment period: a minimum of 24 months post-ide-cel infusion or until documented disease progression, whichever is longer, up to 5 years.
	Duration of run-in phase:	Not applicable
	Duration of extension phase:	Subjects will be monitored in a LTFU study for up to 15 years from the date of their last ide-cel infusion.
Hypothesis	The null hypothesis to be tested was that the ORR (primary efficacy endpoint) is ≤ 50%; the alternative hypothesis was that the ORR is > 50%. If the ORR tested positive, CR rate (key secondary efficacy endpoint) was to be tested using a stepdown approach. For CR rate, the null hypothesis was ≤ 10%.	

Treatments groups	This was a single-arm study. A leukapheresis collection was performed on each subject to obtain a sufficient quantity of PBMCs for the production of ide-cel. If necessary, per investigator discretion, subjects could have received bridging therapy for myeloma disease control while ide-cel was being manufactured. Subjects received one 3-day cycle of LDC starting 5 days prior to ide-cel infusion: • Cyclophosphamide 300 mg/m^2 IV infusion over 30 minutes on Days -5, -4, and -3 • Fludarabine 30 mg/m^2 IV infusion over 30 minutes administered immediately after cyclophosphamide on Days -5, -4, and -3 Ide-cel was administered IV at a target dose of 150, 300, or 450 x 10^6 CAR+ T cells. The clinical dose range was 150 to 540 x 10^6 CAR+ T cells. The maximum dose (540 x 10^6 CAR+ T cells) was defined by the upper limit of 450 x 10^6 CAR+ T cells plus 20%, as detailed in the study protocol.					
Endpoints and definitions	Primary endpoint	ORR	Percentage of subjects who achieved PR or better as assessed by an IRC according to IMWG uniform response criteria for multiple myeloma.			
	Key secondary endpoint	CR rate	Percentage of subjects who achieved CR or sCR as assessed by an IRC according to IMWG uniform response criteria for multiple myeloma.			
	Secondary endpoint	DoR	Time from first documentation of response of PR or better to first documentation of disease progression or death from any cause, whichever occurred first.			
	Secondary endpoint	TTR	Time from ide-cel infusion to first documentation of response of PR or better.			
	Secondary endpoint	MRD	Evaluation of subjects for MRD status using NGS. The primary analysis on MRD status was the proportion of subjects who achieved ≥ CR and MRD-negative status at a sensitivity of 10^{-5} at any timepoint within 3 months prior to achieving at least CR until the time of PD or death (exclusive) based on the ide-cel-treated population (also referred to as MRD-negative status and ≥ CR).			
	Secondary endpoint	PFS	Time from first ide-cel infusion to first documentation of PD, or death due to any cause, whichever occurred first.			
	Secondary endpoint	OS	Time from first ide-cel infusion to time of death due to any cause.			
Data cutoff dates	16 Oct 2019; 7 April 2020					
Results and Analysis						
Analysis description	**Primary Analysis of ORR, CR rate, MRD, and TTR (16 Oct 2019 Data Cutoff Date)**					
Analysis population and time point description	Enrolled population: all subjects who signed informed consent and underwent leukapheresis. Ide-cel-treated population: all subjects in the enrolled population who received ide-cel infusion. Endpoints were assessed throughout the posttreatment period.					
Descriptive statistics and estimate variability	Treatment group / target dose subgroup	Ide-cel-treated population Ide-cel (CAR+ T cells x 10^6) target dose				Enrolled population
		150	300	450	150 to 450	
	Number of subjects	4	70	54	128	140
	ORR (≥ PR), n (%)	2 (50.0)	48 (68.6)	44 (81.5)	94 (73.4)*	94 (67.1)
	95% CI[a]	6.8, 93.2	56.4, 79.1	68.6, 90.7	65.8, 81.1	59.4, 74.9
	CR rate (≥ CR), n (%)	1 (25.0)	20 (28.6)	19 (35.2)	40 (31.3)*	40 (28.6)

	95% CI[a]	0.6, 80.6	18.4, 40.6	22.7, 49.4	23.2, 39.3	21.1, 36.1
	MRD-negative status and ≥ CR, n (%)	1 (25.0)	17 (24.3)	13 (24.1)	31 (24.2)	☐
	95% CI[a]	0.6, 80.6	14.8, 36.0	13.5, 37.6	17.1, 32.6	☐
	TTR median (months)[b]	1.0	1.0	1.0	1.0	1.0
	Range	1.0, 1.0	0.5, 8.8	0.9, 2.0	0.5, 8.8	0.5, 8.8
	DoR[c] (≥ PR) events, n/N (%) – EMA censoring	½ (50.0)	35/48 (72.9)	18/44 (40.9)	54/94 (57.4)	54/94 (57.4)
	DoR[c] (≥ PR) median (months)[d] – EMA censoring	NE	8.5	11.3	10.5	10.5
	95% CI	2.8, NE	5.4, 10.9	9.2, 11.4	8.0, 11.3	8.0, 11.3
	PFS[e] events, n (%) – EMA censoring	3 (75.0)	57 (81.4)	27 (50.0)	87 (68.0)	95 (67.9)
	PFS[e,f] median (months)[d] – EMA censoring	2.8	5.9	11.3	8.2	8.3
	95% CI	1.0, NE	4.2, 8.9	7.5, 12.4	5.6, 11.0	6.7, 12.0
	OS events, n (%)	2 (50.0)	20 (28.6)	12 (22.2)	34 (26.6)	42 (30.0)
	OS[f] median (months)[d]	18.2	NE	NE	18.2	19.3
	95% CI	9.4, 18.2	16.8, NE	NE, NE	18.0, NE	17.9, NE
Notes	The primary analysis was performed using a data cutoff date of 16 Oct 2019, which is approximately 10 months after the last subject was infused with ide-cel. *p < 0.0001, 1-sample binomial test rejecting the null hypothesis of ≤ 50% for ORR and ≤ 10% for CR rate.					
Analysis description	**Updated Analyses of Endpoints (07 April 2020 Data Cutoff Date)**					
Analysis population and time point description	Enrolled population: all subjects who signed informed consent and underwent leukapheresis. Ide-cel-treated population: all subjects in the enrolled population who received ide-cel infusion. Endpoints were assessed throughout the posttreatment period.					
Descriptive statistics and estimate variability	Treatment group / target dose subgroup	Ide-cel-treated population Ide-cel (CAR+ T cells x 10^6) target dose				Enrolled population
		150	300	450	150 to 450	
	Number of subjects	4	70	54	128	140
	ORR (≥ PR), n (%)	2 (50.0)	48 (68.6)	44 (81.5)	94 (73.4)	94 (67.1)
	95% CI[a]	6.8, 93.2	56.4, 79.1	68.6, 90.7	65.8, 81.1	59.4, 74.9
	CR rate (≥ CR), n (%)	1 (25.0)	20 (28.6)	21 (38.9)	42 (32.8)	42 (30.0)
	95% CI[a]	0.6, 80.6	18.4, 40.6	25.9, 53.1	24.7, 40.9	22.4, 37.6
	MRD-negative status and ≥ CR, n (%)	1 (25.0)	17 (24.3)	15 (27.8)	33 (25.8)	☐
	95% CI[a]	0.6, 80.6	14.8, 36.0	16.5, 41.6	18.5, 34.3	☐

	TTR median (months)[b]	1.0	1.0	1.0	1.0	1.0
	Range	1.0, 1.0	0.5, 8.8	0.9, 2.0	0.5, 8.8	0.5, 8.8
	DoR[c] (≥ PR) events, n/N (%) – EMA censoring	2/2 (100.0)	37/48 (77.1)	25/44 (56.8)	63/94 (67.0)	64/94 (68.1)
	DoR[c] (≥ PR) median (months)[d] – EMA censoring	13	8.5	11.3	10.6	10.6
	95% CI	2.8, 23.3	5.4, 10.9	10.3, NE	8.0, 11.4	8.0, 11.3
	PFS[e] events, n (%) – EMA censoring	4 (100.0)	59(84.3)	34 (63.0)	97 (75.8)	105 (75.0)
	PFS[e,f] median (months)[d] – EMA censoring	2.8	5.9	12.1	8.2	8.3
	95% CI	1.0, 24.2	4.2, 8.9	7.5, 12.4	5.6, 11.1	6.7, 12.0
	OS events, n (%)	2 (50.0)	29 (41.4)	16 (29.6)	47 (36.7)	55 (39.3)
	OS[f] median (months)[d]	18.2	NE	NE	NE	21.4
	95% CI	9.4, NE	18.0, NE	NE, NE	18.9, NE	19.3, NE
Notes	The 07 April 2020 data cutoff date provides 6 months of additional follow-up for key efficacy data.					

CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response; DoR = duration of response; EMA = European Medicines Agency; ide-cel = idecabtagene vicleucel; IMWG = International Myeloma Working Group; IRC = Independent Response Committee; IV = intravenous; LDC = lymphodepleting chemotherapy; LTFU = long-term follow-up; MRD = minimal residual disease; NGS = next generation sequencing; ORR = overall response rate; OS = overall survival; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; TTR = time to response.

[a] Clopper-Pearson exact CI, except for ORR and CR rate for 150 to 450 x 10^6 CAR+ T cells, where Wald CI was used.

[b] Time to response of PR or better based on IRC review using IMWG criteria.

[c] Duration of response of PR or better based on IRC review using IMWG criteria.

[d] Median based on Kaplan-Meier estimation.

[e] Progression-free survival based on IRC review using IMWG criteria.

[f] Progression-free survival and OS were measured from the day of infusion for the ide-cel-treated population and from the day of enrollment (ie, leukapheresis) for the enrolled population, up to the time of event.

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analysis of data from MM-001 and CRB-401 is presented for the 150 x 106 CAR+ T cells dose in section Supportive studies.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Non Controlled trials MM-001 CBR-401	43/140 22/67	5/140 2/67	0/140 0/67

The results < 65-year-old subgroup and the 65- to < 75-year-old subgroup were stated to be generally consistent in the MM-001 and CBR-401 study, but due to small number of patients in the age group 75-84 years no firm conclusions can currently be drawn.

Supportive study

Study CRB-401 dose-escalation study

Methods

This was a first-in-human, 2-part, nonrandomised, open-label, multicentre, Phase 1 study in subjects with relapsed or refractory MM. The study included 2 parts i.e dose-escalation (Part A) and dose-expansion (Part B).

- The primary objective of Part A of the study (dose escalation) was to determine the MTD of ide-cel in subjects with multiple myeloma (MM) whose tumours expressed BCMA and to select a RP2D for future studies.
- The primary objective of the Part B of the study (dose expansion) was to confirm the safety of the doses chosen in Part A.
- The secondary objective of the study was to provide preliminary efficacy data on the antitumor effects of treatment with ide-cel in subjects with MM whose tumours expressed BCMA.
- Several exploratory objectives were defined including evaluation of OS and PFS and MRD.

For further information on the dose-escalation and dose-expansion part of the study, see section Dose response studies above.

Study participants

In Part A (dose escalation), subjects had been diagnosed with relapsed or refractory MM and received at least 3 different prior lines of therapy including an immunomodulatory agent (eg, lenalidomide or pomalidomide) and proteasome inhibitor (PI; eg, bortezomib or carfilzomib), or had double refractory disease to an immunomodulatory agent and PI. In Part B (dose expansion), subjects had been diagnosed with RRMM and had previous exposure to an immunomodulatory agent (eg, lenalidomide or pomalidomide), PI (eg, bortezomib or carfilzomib), and daratumumab, and were refractory to their last line of therapy.

A summary of key eligibility criteria and treatment by dose cohort is provided in Table 25.

Table 24:Summary of Key Eligibility Criteria and Treatment by Dose Cohort in Study CRB-401 (Ide-cel-treated Population)

	Part A (Dose Escalation) (N=21)	Part B (Dose Expansion)		
		Cohort 1 (N=12)	Cohort 2 (N=10)	Cohort 3 (N=19)
Target dose/ Target dose range ($\times 10^6$ CAR+ T cells)	50, 150, 450, 800 (50 to 800)	450 (150 to 450)	150 (150 to 300)	450 (150 to 450)
Manufacturing process	Process I/II	Process I/II	Process III/IV (Commercial)	Process III/IV (Commercial)
Bridging AMT restrictions	Any drug; stop ≥ 14 days prior to LDC	Any drug; stop ≥ 14 days prior to LDC	Any drug; stop ≥ 14 days prior to LDC	Restricted to therapies previously used by the subject; stop ≥ 14 days prior to LDC
Tumor BCMA expression (% BCMA+ PC)	≥ 50%	< 50% (9/12 subjects)	≥ 50%	No restriction
Measurable disease criteria	M-protein/FLC+ plasmacytoma only and nonsecretory MM allowed (>30% BM PC)	M-protein/FLC+ plasmacytoma only and nonsecretory MM allowed (>30% BM PC)	M-protein/FLC+ plasmacytoma only and nonsecretory MM allowed (>30% BM PC)	Only serum (>0.5g/dL) and urine (>200 mg/24 hr); M-protein/FLC (>100 mg/L)
Number of required prior lines and AMT	At least 3, including immunomodulatory agent and PI or double-refractory	Prior immunomodulatory agent, PI, and anti-CD38 antibody	Prior immunomodulatory agent, PI, and anti-CD38 antibody	Prior immunomodulatory agent, PI, and anti-CD38 antibody
Prior anti-CD38 antibody exposure	Not required	Required	Required	Required
Refractory to last regimen	Not required	Required	Required	Required

Outcomes/endpoints

- The primary endpoints of the study were the incidence of AEs and abnormal laboratory test results, including dose-limiting toxicities.
- The secondary endpoints of the study were disease-specific response criteria including ORR, CR, VGPR, and PR as assessed by the investigator according to the IMWG uniform response criteria for MM.
- The most relevant exploratory efficacy endpoints were DoR, PFS, OS, and MRD.

Results

Subject disposition: A total of 67 subjects were enrolled into Study CRB-401 (ie, underwent leukapheresis), including 24 subjects in Part A (dose escalation) and 43 subjects in Part B (dose expansion). Of the 67 subjects who underwent leukapheresis, 5 discontinued prior to LDC and ide-cel administration due to physician decision (n = 2), progressive disease (PD) (n =1), AE (n = 1), and withdrawal prior to ide-cel dosing (n = 1). No subjects discontinued after starting LDC but prior to receiving ide-cel.

The median follow-up duration for subjects who received ide-cel target doses of 150 and 450 × 10^6 CAR+ T cells was 14.47 months and 9.77 months, respectively. The median follow across the target doses at the latest data cut (7 April 2020) was 15.95 months (95% CI 1.5, 44.5)

Extent of exposure to bridging AMT, LCD and ide-cel:

The median time from leukapheresis to Abecma administration was 33.0 days, and approximately half of subjects (51.6%) in the treated population overall received bridging AMT for disease control during Abecma manufacturing. The most commonly received (≥ 5%) bridging AMTs in the Abecma-treated population included dexamethasone (46.8%), cyclophosphamide (14.5%), bortezomib (14.5%), carfilzomib (9.7%), pomalidomide (9.7%), and daratumumab (8.1%). A total of 3 (4.8%) subjects

overall no longer had measurable disease in the week prior to LDC. Such subjects were to be assessed by the IRC only for CR or disease progression in accordance with IMWG criteria.

All subjects received LDC (flu/cy) before ide-cel infusion as per protocol, except for 1 subject (Part B Cohort 1) who did not receive fludarabine due to inadequate renal function.

A total of 62 (92.5%) enrolled subjects received ide-cel infusion. Of the 62 ide-cel-treated subjects, 45 (72.6%) discontinued from study after receiving ide-cel, with the most common reasons being due to PD (32 subjects; 51.6%) and death (6 subjects; 9.7%).

Ide-cel was successfully manufactured and released for all enrolled subjects.

Recruitment:

The first subject signed ICF for the study on 22 Dec 2015, underwent leukapheresis on 14 Jan 2016, and was administered ide-cel on 16 Feb 2016. The last subject underwent initial ide-cel infusion on 07 Jan 2019. Enrolment in study CRB-401 is complete; a total of 62 subjects received ide-cel infusion, with 17 subjects ongoing and 8 subjects ongoing in Study GC-LTFU-001 for posttreatment follow-up. The data cutoff date for the results reported is 22 Jul 2019, approximately 7 months after the last subject was infused with ide-cel. An updated analyses for OS with data cut-off 7 April 2020 is reported.

Baseline characteristics:

In the enrolled population, across the target dose-levels, the median age of subjects was 61.0 years (range: 37 to 80) with more than half (64.2.%) being < 65 years of age. The majority of subjects were male (64.2%) and white (88.1%). Almost all subjects had a baseline ECOG PS of 0 (25.4%) or 1 (70.1%).

Approximately half (43.3%) were defined as having high tumour burden (≥ 50% BM CD138+ plasma cells) and 24 subjects (37.3%) had clinical and/or radiological extra medullary plasmacytomas (EMP). More than half (62.7%) were assessed as having R-ISS Stage II disease; 16.4% had R-ISS Stage III disease. Approximately one-fourth of the subjects (28.4%) had at least 1 high-risk cytogenetic abnormality (defined as del[17p], t[4;14], or t[14;16]), with cytogenetic risk unknown in 28.4% of the ide-cel-treated population overall, 46.3 % of subjects had received > 6 prior regimens. The baseline characteristics of the enrolled population were similar to the ide-cel-treated population (N=62).

Data on prior therapies and on refractory status was reported for the ide-cel treated population only. In these patients the median number of prior antimyeloma regimens was 6.0 (range: 3 to 18), 91.9% of subjects had received at least 1 prior ASCT (25.8% received at least 2 prior ASCTs) and the median time from initial diagnosis to ide-cel administration was 5.51 years (range: 0.8 to 35.7). Patients had a high degree of refractoriness to prior AMTs, with 88.7% being refractory to immunomodulatory agents, 83.9% being refractory to PIs, 80.6% being refractory to anti-CD38 antibody, 80.6% of subjects being double-refractory (ie, refractory to an IMiD and a PI) and 69.4% of subjects being triple-refractory (ie, refractory to an IMiD, a PI, and anti-CD38 antibody). Approximately 75% of subjects were refractory to their last prior therapy.

ORR: Results from response assessment for the ide-cel-treated and enrolled populations in CBR-401 are presented by ide-cel target doses, i.e. RP2D (150 to 450 × 10^6 CAR+ T cells) and in the enrolled population together with data from the MM-001 study. Due to limited number of patients in the 150 x 10^6 dose group a pooled analysis including results from the MM-001 (n=4) and CRB-401 (n=18) studies was performed (Table 26).

Table 25: Best Overall Response by IRC Review Based on IMWG Criteria - Studies MM-001 and CRB-401 (Ide-cel-Treated and Enrolled Populations)

	Pooled [a] 150x10^6 Ide-cel CAR+ T cells (N = 22)	Study MM 001 Ide-cel CAR+ T Cells					CRB 401 Escalation and Expansion Ide-cel CAR+ T Cells			
		Ide-cel-treated Population				Enrolled Population (N = 140)	Ide-cel-treated Population			Enrolled Population (N = 67)
		150x10^6 (N=4)	300x10^6 (N=70)	450x10^6 (N=54)	150 to 450x10^6 (N=128)		150x10^6 (N=18)	450x10^6 (N=38)	150 to 450x10^6 (N=56)	
Best Overall Response - n (%)										
sCR	7 (31.8)	1 (25.0)	19 (27.1)	19 (35.2)	39 (30.5)	39 (27.9)	6 (33.3)	13 (34.2)	19 (33.9)	21 (31.3)
CR	0	0	1 (1.4)	0	1 (0.8)	1 (0.7)	0	1 (2.6)	1 (1.8)	1 (1.5)
VGPR	2 (9.1)	1 (25.0)	10 (14.3)	15 (27.8)	26 (20.3)	26 (18.6)	1 (5.6)	13 (34.2)	14 (25.0)	15 (22.4)
PR	3 (13.6)	0	18 (25.7)	10 (18.5)	28 (21.9)	28 (20.0)	3 (16.7)	5 (13.2)	8 (14.3)	9 (13.4)
MR	1 (4.5)	0	2 (2.9)	0	2 (1.6)	2 (1.4)	1 (5.6)	1 (2.6)	2 (3.6)	2 (3.0)
SD	5 (22.7)	1 (25.0)	14 (20.0)	7 (13.0)	22 (17.2)	22 (15.7)	4 (22.2)	3 (7.9)	7 (12.5)	9 (13.4)
PD	4 (18.2)	1 (25.0)	6 (8.6)	1 (1.9)	8 (6.3)	8 (5.7)	3 (16.7)	2 (5.3)	5 (8.9)	5 (7.5)
NE [b]	0	0	0	1 (1.9)	1 (0.8)	14 (10.0)	0	0	0	5 (7.5)
Missing Response	0	0	0	1 (1.9)	1 (0.8)	0	0	0	0	0
ORR - n (%) [c]	**12 (54.5)**	**2 (50.0)**	**48 (68.6)**	**44 (81.5)**	**94 (73.4)**	**94 (67.1)**	**10 (55.6)**	**32 (84.2)**	**42 (75.0)**	**46 (68.7)**
95% CI [d]	(32.2, 75.6)	(6.8 , 93.2)	(56.4 , 79.1)	(68.6 , 90.7)	(64.9 , 80.9)	(59.4 , 74.9)	(30.8 , 78.5)	(68.7 , 94.0)	(61.6 , 85.6)	56.2, 79.4
95% Wald CI [e]	-	-	-	-	(65.8 , 81.1)	-	-	-	-	-
CR Rate - n (%) [c]	**7 (31.8)**	**1 (25.0)**	**20 (28.6)**	**19 (35.2)**	**40 (31.3)**	**40 (28.6)**	**6 (33.3)**	**14 (36.8)**	**20 (35.7)**	**22 (32.8)**
95% CI [d]	(13.9, 54.9)	(0.6 , 80.6)	(18.4 , 40.6)	(22.7 , 49.4)	(23.4 , 40.0)	(21.1 , 36.1)	(13.3 , 59.0)	(21.8 , 54.0)	(23.4 , 49.6)	21.8, 45.4
95% Wald CI [e]	-	-	-	-	(23.2 , 39.3)	-	-	-	-	-
Response Rate of VGPR or better - n (%) [c]	**9 (40.9)**	**2 (50.0)**	**30 (42.9)**	**34 (63.0)**	**66 (51.6)**	**66 (47.1)**	**7 (38.9)**	**27 (71.1)**	**34 (60.7)**	**37 (55.2)**
95% CI [d]	(20.7, 63.6)	(6.8 , 93.2)	(31.1 , 55.3)	(48.7 , 75.7)	(42.6 , 60.5)	(38.9 , 55.4)	(17.3 , 64.3)	(54.1 , 84.6)	(46.8 , 73.5)	42.6, 67.4
95% Wald CI [e]					(42.9 , 60.2)					

Table 26: Time to Response and Duration of Response (FDA censoring) for Subjects who Achieved at Least Partial Response by IRC Assessment Based on IMWG Criteria - Studies MM-001 and CRB-401 (Ide-cel-treated population)

Statistics	Pooled[a] 150x10^6 Ide-cel CAR+ T cells (N = 12)	Study MM 001 Ide-cel CAR+ T Cells				CRB 401 Escalation and Expansion Ide-cel CAR+ T Cells		
		Ide-cel-treated Population				Ide-cel-treated Population		
		150x10^6 (N=2)	300x10^6 (N=48)	450x10^6 (N=44)	150 to 450x10^6 (N=94)	150x10^6 (N=10)	450x10^6 (N=32)	150 to 450x10^6 (N=42)
Time-to-Response, n (months)[b,c]								
Mean	1.2	1.0	1.3	1.1	1.2	1.3	1.4	1.4
SD	0.68	0.05	1.19	0.30	0.88	0.75	0.96	0.90
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Min, Max	0.7, 3.1	1.0,1.0	0.5,8.8	0.9,2.0	0.5,8.8	0.7,3.1	1.0,5.8	0.7,5.8
Duration of Response[b, c, d]								
Censored, n (%)	4 (33.3)	1 (50.0)	15 (31.3)	26 (59.1)	42 (44.7)	3 (30.0)	11 (34.4)	14 (33.3)
Progressed/Died, n (%)	8 (66.7)	1 (50.0)	33 (68.8)	18 (40.9)	52 (55.3)	7 (70.0)	21 (65.6)	28 (66.7)
Median (95% CI)	10.8 (2.8, NE)	NE (2.8,NE)	9.9 (5.4,11.0)	11.3 (9.2,11.4)	10.6 (9.0,11.3)	10.8 (2.1,NE)	8.8 (6.2,14.8)	8.8 (7.4,13.6)

a Efficacy data for the target dose of 150 x 10^6 CAR+ T cells from both studies are pooled to provide a robust dataset in support of this target.b Response is defined as achieving sCR, CR, VGPR or PR.c Only subjects with a response (sCR, CR, VGPR or PR) are included in the analysis.d The median is based on the Kaplan-Meier estimate.

Data Cutoff: 16 Oct 2019 (Study MM-001) and 22 July 2019 (Study CRB-401)

PFS:

Table 27: Progression-free Survival by IRC Assessment Based on IMWG Criteria – FDA Censoring Rules - Studies MM-001 and CRB-401

Statistics	Pooled[a] 150x10^6 Ide-cel CAR+ T cells (N = 22)	Study MM 001 Ide-cel CAR+ T Cells					CRB 401 Escalation and Expansion Ide-cel CAR+ T Cells		
		Ide-cel-treated Population				Enrolled Population (N = 140)	Ide-cel-treated Population		
		150x10^6 (N=4)	300x10^6 (N=70)	450x10^6 (N=54)	150 to 450x10^6 (N=128)		150x10^6 (N=18)	450x10^6 (N=38)	150 to 450x10^6 (N=56)
Progression-free Survival									
Censored, n (%)	4 (18.2)	1 (25.0)	15 (21.4)	29 (53.7)	45 (35.2)	52 (37.1)	3 (16.7)	11 (28.9)	14 (25.0)
Progressed/Died, n (%)	18 (81.8)	3 (75.0)	55 (78.6)	25 (46.3)	83 (64.8)	88 (62.9)	15 (83.3)	27 (71.1)	42 (75.0)
Progression-free Survival									
Time (months)[b]									
Median (95% CI)	3.8 (1.9, 10.9)	2.8 (1.0, NE)	5.8 (4.2,8.9)	11.3 (8.8,12.4)	8.6 (5.6,11.3)	9.4 (6.7, 12.1)	4.5 (2.0,10.9)	9.0 (7.2,11.9)	8.8 (5.9,11.1)
Event-free rate									
3 Months Event-Free % (SE)	63.6 (10.26)	50.0 (25.00)	71.3 (5.43)	82.6 (5.27)	75.3 (3.85)	87.9 (2.84)	66.7 (11.11)	86.8 (5.52)	80.3 (5.33)
6 Months Event-Free % (SE)	40.9 (10.48)	25.0 (21.65)	49.1 (6.05)	70.8 (6.35)	57.4 (4.45)	64.6 (4.20)	44.4 (11.71)	72.6 (7.42)	63.5 (6.53)
9 Months Event-Free % (SE)	31.8 (9.93)	25.0 (21.65)	37.2 (5.87)	62.8 (6.77)	47.4 (4.51)	52.0 (4.41)	33.3 (11.11)	50.2 (8.73)	44.9 (6.98)
12 Months Event-Free % (SE)	27.3 (9.50)	25.0 (21.65)	26.1 (5.42)	49.0 (8.84)	34.3 (4.84)	42.1 (4.51)	27.8 (10.56)	29.2 (8.91)	29.9 (6.85)
15 Months Event-Free % (SE)	18.2 (8.22)	25.0 (21.65)	17.4 (4.81)	NE (NE)	20.3 (4.79)	23.4 (4.72)	16.7 (8.78)	29.2 (8.91)	24.5 (6.60)
18 Months Event-Free % (SE)	18.2 (8.22)	NE (NE)	17.4 (4.81)	NE (NE)	20.3 (4.79)	19.4 (4.69)	16.7 (8.78)	24.4 (8.65)	21.8 (6.40)
21 Months Event-Free % (SE)	18.2 (8.22)	NE (NE)	NE (NE)	NE (NE)	NE (NE)	NE (NE)	16.7 (8.78)	14.6 (7.44)	15.6 (5.89)

For subjects who were enrolled (ie, leukapheresed), but not infused, minimal efficacy assessment data following IMWG criteria were collected; therefore, PFS and OS was not analysed for the enrolled population in the CBR-401 study.

In the CBR-401 study the analyses of PFS as assessed by the IRC using the EMA censoring rules the KM estimate for median PFS in subjects who received the ide-cel i.e. RP2D population was 8.8 months (95% CI: 5.9, 11.1), identical to the median PFS as assessed using FDA censoring rules.

Overall survival (OS)

A summary of OS is presented by ide-cel target dose, RP2D (150 to 450 × 10^6 CAR+ T cells), and overall in shown in

Table 28. OS was not calculated for the enrolled population in study CRB-401.

Table 28 : Overall Survival - Studies MM-001 and CRB-401

Statistics	Pooled[a] 150x10^6 Ide-cel CAR+ T cells (N = 22)	Study MM 001 Ide-cel CAR+ T Cells					CRB 401 Escalation and Expansion Ide-cel CAR+ T Cells		
		Ide-cel-treated Population				Enrolled Population (N = 140)	Ide-cel-treated Population		
		150 x 10^6 (N=4)	300 x 10^6 (N=70)	450 x 10^6 (N=54)	150 to 450 x 10^6 (N=128)		150 x 10^6 (N=18)	450 x 10^6 (N=38)	150 to 450 x 10^6 (N=56)
Overall Survival									
Censored, n (%)	13 (59.1)	2 (50.0)	50 (71.4)	42 (77.8)	94 (73.4)	98 (70.0)	11 (61.1)	31 (81.6)	42 (75.0)
Died, n (%)	9 (40.9)	2 (50.0)	20 (28.6)	12 (22.2)	34 (26.6)	42 (30.0)	7 (38.9)	7 (18.4)	14 (25.0)
Overall Survival Time (months)									
Median (95% CI)	19.1 (10.8, NE)	18.2 (9.4,18.2)	NE (16.8, NE)	NE (NE, NE)	18.2 (18.0, NE)	19.3 (17.9, NE)	19.1 (10.8,NE)	NE (15.9,NE)	NE (19.1,NE)
3 Months Event-Free, % (SE)	90.9 (6.13)	100 (0.00)	95.7 (2.44)	92.6 (3.56)	94.5 (2.02)	94.9 (1.86)	88.9 (7.41)	97.3 (2.67)	94.5 (3.06)
6 Months Event-Free, % (SE)	86.4 (7.32)	100 (0.00)	89.6 (3.71)	86.9 (4.61)	88.8 (2.82)	87.4 (2.85)	83.3 (8.78)	91.5 (4.71)	88.9 (4.29)
9 Months Event-Free, % (SE)	81.8 (8.22)	100 (0.00)	86.6 (4.16)	79.1 (5.62)	83.9 (3.31)	81.3 (3.38)	77.8 (9.80)	91.5 (4.71)	86.8 (4.66)
12 Months Event-Free, % (SE)	71.6 (9.88)	75.0 (21.65)	78.6 (5.09)	76.8 (5.92)	76.9 (3.96)	75.5 (3.78)	71.3 (10.92)	87.3 (6.06)	81.2 (5.80)
15 Months Event-Free, % (SE)	71.6 (9.88)	75.0 (21.65)	72.7 (5.73)	NE (NE)	71.6 (4.72)	67.3 (4.70)	71.3 (10.92)	87.3 (6.06)	81.2 (5.80)
18 Months Event-Free, % (SE)	64.4 (11.19)	75.0 (21.65)	52.4 (13.04)	NE (NE)	54.5 (11.16)	61.8 (5.75)	61.1 (13.28)	73.9 (10.13)	69.1 (8.15)
21 Months Event-Free, % (SE)	38.7 (15.63)	0 (NE)	NE (NE)	NE (NE)	NE (NE)	NE (NE)	45.8 (16.56)	73.9 (10.13)	64.1 (8.93)

a Efficacy data for the target dose of 150 x 106 CAR+ T cells from both studies are pooled to provide a robust dataset in support of this target.

Note: For the ide-cel-treated population, OS was defined as time from ide-cel infusion to death due to any cause. Overall survival for the enrolled population was calculated from the date of enrolment (ie, leukapheresis).

Data Cutoff: 16 Oct 2019 (Study MM-001) and 22 July 2019 (Study CRB-401)

In updated analyses (Data cut off 7 Apr 2020) in the total study population in CBR-401 (across the dose groups) a median OS of 36.6 months (23.2, NE) was reported with a median follow-up of 15.95 months (95% CI 1.5, 44.5).

In updated analyses in the pooled 150 x 10^6 dose cohort (N=22) across the studies (Data cut off 7 Apr 2020 for both studies) the ORR, DoR and PFS did not change. At the last data cut-off, the median OS was Not Estimable (NE) (95%CI 10.8, NE) with an event-free rate at 36 months of 50.6% (SE 12.39)

Efficacy following retreatment with ide-cel

Of the total 62 subjects included in CBR-401, 17 (35.5%) did receive ide-cel retreatment at target dose levels ranging from 150 to 450 × 106 CAR+ T cells. As of the 22 Jul 2019 data cutoff date, the ORR (ie, best confirmed response of PR or better) as determined by the investigator was 11.8% (2/17) (95% CI: 1.5, 36.4) for subjects retreated with ide-cel, the subjects confirmed best overall response of VGPR. After first infusion of ide-cel the two patient achieved sCR and SD. The median duration from initial infusion to retreatment was 8.31 months (range: 2.8, 18.7).

Comparison of Efficacy for Ide-cel and Other Therapies for the Treatment of RRMM

The efficacy of an ide-cel target dose of 150 × 10^6 CAR+ T cells was compared to that from other therapies tested in subjects with RRMM who had been previously exposed to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody using a systematic literature review.

Table 29: Comparison of Efficacy of an Ide-cel Target Dose of 150 × 10^6 CAR+ T Cells With Benchmark Data

	Systemic Literature Review			External Control	Pooled MM-001 and CRB-401
	CD-38 mAb (MAMMOTH retrospective)[a]	Selinexor (STORM Part 2)[b]	Belantamab mafodotin (DREAMM-2)[c]	RWE NDS-MM-003	Ide-cel 150 × 10^6 CAR+ T cells[d]
ORR, %	31.3	26.2	30.9	32.2	54.5
≥ VGPR rate, %	10.8	6.6	18.6	13.7	40.9
≥ CR rate, %	2.0	1.6	3.1	—	31.8
Median DoR, mo	—	4.4	11[e]	9.0	10.8
Median PFS, mo	3.4	3.7	2.9	3.5	3.8
Median OS, mo	9.3	8.6	13.7[e]	14.7	NE

CAR = chimeric antigen receptor; CR = complete response; DoR = duration of response; mAb = monoclonal antibody; mo = month; ide cel = idecabtagene vicleucel; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RWE = real world evidence; VGPR = very good partial response.

[a] Gandhi, 2019.

[b] Chari, 2019.

[c] Lonial, 2020. Data at 2.5 mg/kg dose; DoR, PFS, and OS were derived from Kaplan-Meier curves.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The primary evidence of efficacy comes from an ongoing, open-label, uncontrolled, multicentre, multinational, Phase 2 study, BB2121-MM-001 (MM-001), based on a primary data cut-off of 16th Oct 2019. More mature data based on two updated cut-offs (14th Jan 2020 and 07th April 2020) have also been provided.

The uncontrolled study design was the subject of Scientific Advice where concerns were raised that the target population was not representative of a "last line population", for which an uncontrolled trial approach would be acceptable. In the current MAA, the lack of alternative therapies to provide a SOC control arm in an RCT has not been justified. Nevertheless, in light of the rather compelling efficacy data, further substantiated by adjusted indirect comparisons to external controls, the provided clinical data package is considered sufficient to allow a benefit/risk assessment.

The main uncertainties relate to the single arm study design, the limited sample size in addition to a rather short duration of follow-up, especially for OS. Furthermore, the robustness of the adjusted indirect treatment comparison based on the RWS is difficult to verify, considering the rather selected study population, and the missing data of several important prognostic factors. Thus, although the ORR/DoR benefit is considered sufficiently compelling in the context of a single arm trial, the true magnitude of the treatment effect, including to what extent the observed responses will be reflected in long term benefit in OS, cannot be reliably ascertained. The patient population in the pivotal MM-001 study was heterogenous.

Per inclusion criteria, patients had received at least 3 prior regimens including an immunomodulatory agent, a PI, and an anti-CD38 antibody, and had to be refractory to their last treatment regimen. Data on the less refractory patients are limited i.e only 16.4% (n=23) were mono or double refractory. The greater availability and benefit of SOC options in these less refractory patients, introduces uncertainty as to the true magnitude of the effect size, as robust comparative data on the benefit of ide-cel vs SOC options in this population are lacking. Due to these deficiencies, the clinical data package was not

considered comprehensive to fulfil the requirements for a full MA, and the applicant submitted a formal request for conditional marketing authorisation. More comprehensive data in the less refractory patients will be part of the obligations for a full MA i.e. results from the MM-003 study comparing ide-cel to SOC triplet regimes in patients with 2-4 prior anti-myeloma therapies.

Further key eligibility criteria included PS of 0-1 and no major co-morbidities or organ dysfunction. Although exclusion of patients with significant comorbidities is understood from the safety perspective, the criteria applied selected untypically healthy patients, and thus tolerability of the treatment, ability of the patients to withstand the delay from treatment decision to ide-cel infusion, and the extent of clinical benefit in a less fit, older patient population is not known. Rephrasing the indication is unlikely to be sufficient to ensure that clinical use is restricted to a similarly fit patient population for which a positive benefit/risk has been demonstrated. However, patient populations that were excluded from the clinical study are described in the Product Information.

The primary efficacy endpoint was ORR according to the IMWG criteria (Kumar, 2016) assessed by an IRC. This is acceptable in the context of an uncontrolled trial. CR rate was defined as a key secondary endpoint. The remaining secondary outcomes included endpoints conventional for oncology trials such as DOR, PFS and OS and are considered acceptable.

As per Scientific Advice, a global, non-interventional, retrospective study (NDS-MM-003) was set up to generate an external comparison arm for study MM-001 including patient level data from 190 eligible RRMM subjects treated with currently available therapies. Propensity score methodology was used to ensure that RW subjects were comparable to the ide-cel cohort. A SLR was also performed to further understand the efficacy of ide-cel in the context of the current treatment landscape. Two studies from the SLR were selected for MAIC comparisons (selinexor and belantamab mafodontin).

Study CRB-401 investigated the efficacy of ide-cel in a similar patient population and at the same target dose levels as those used in study MM-001, and it's use as a supportive study for the MAA is considered acceptable.

Efficacy data and additional analyses

Of the total 140 subjects enrolled in MM-001, 128 subjects received ide-cel infusion and were included in the ide-cel-treated population. This was defined as the primary efficacy population by the applicant. However, for the purpose of this assessment, the analyses based on the ITT (enrolled) population is considered the main efficacy analyses.

The drop-out rate of 8.5% from enrolment to infusion was lower than the anticipated 15%, indicating the majority of patients are able to tolerate the treatment delay required for product manufacturing and LDC.

Included patients were young (median age 60.5 years), and heavily pre-treated (median of 6 (range 3-17) previous lines of therapy) with 83.6% being triple refractory. As expected in this advanced patient population, participants with ISS stage III disease, extramedullary disease, and high-risk cytogenetic features were well represented. The European population is represented by the inclusion of 33 patients from several EU countries.

The majority of subjects (87.5%) received bridging therapy, to which only five subjects achieved a response (i.e. "unconfirmed" PR (4 subjects) or VGPR (1 subject)) prior to LDC. A total of 6 (4.7%) subjects in the pivotal study and three patients in the CRB-401 no longer had measurable disease at baseline prior to LDC after bridging. Pre-lymphodepletion disease status indicate that these patients were responders to bridging chemotherapy. For the purpose of the efficacy analyses, these subjects were to be assessed by the IRC only for at least a CR or disease progression in accordance with IMWG 2016 guidelines. Three CR/sCR responses after ide-cel infusion were observed in these patients,

indicating that deep responses were not disproportionally driven by patients who did not have measurable disease at baseline. Thus, bridging therapy is considered to have had a limited impact on the efficacy outcomes.

The study met its primary endpoint for ORR as assessed by IRC; In the enrolled population, the ORR across the target dose levels of 150 to 450 x 10^6 CAR+T cells was 67.1%, 95% CI: 59.4, 74.9 ($p < 0.0001$) (Data Cut Off day 7 April 2020), statistically significantly higher than the pre-specified 50% cut-off. After 3 months further follow-up, two additional subjects received stringent complete response (sCR) (previously with PR and VGPR) and MRD negative status, with the ORR unchanged.

The CR rate (CR or better) in the enrolled population was 28.6% (95% CI: 21.1, 36.1), rejecting the null hypothesis of $\leqslant$ 10%. At a later data cut-off date (7 April 2020) the result has been confirmed being 30.0% (95% CI: 22.4, 37.6).

The majority of the subgroups evaluated achieved a response rate in line with the ORR of the overall patient population.

The benefit of ide-cel was supported by secondary endpoints. At the primary data cut off (16 October 2019), across the three dose levels, a median DoR of 10.5 months (95% CI: 8.0, 11.3) was reported among the 94 ide-cel responders. This DoR was confirmed at the latest data-cuf off (i.e median DoR of 10.6 months (95% CI: 8.0, 11.4, 07 April 2020). The DoR is over twice as long as the TTP on previous treatment regimen received (4.6 months), and comparable to that observed for belantamab mafodotin (11 months) and the RWD Eligible RRMM cohort (9.0 months). This is considered clinically relevant, especially in the context that approximately 2/3 of the patients respond to the treatment.

At the latest data cut-off (07 April 2020) the median PFS was 8.3 months (95% CI: 6.7, 12.0) and 75.0% of the subjects had progressed/died. At the target dose of 450 x 10^6 CAR+ T cells, the median PFS was 12.1 months (95% CI: 7.5, 12.4) with a 63.0% event rate. The median OS was 21.4 months (95% CI: 19.3, NE; 39.3% of subjects had died), and the estimated survival rate at 18 months from leukapheresis was 64%. At the target dose of 450 x 10^6 CAR+ T cells, the median OS was NE (95% CI: NE, NE) and the survival rate at 18 months from infusion was 69%.

No curative potential can be concluded based on available data. Thus, the duration of response has to be weighed against the long delay from treatment decision to administration of therapy, and risks associated with the relatively harsh treatment procedures including bridging therapies likely required and the LDC.

The adjusted indirect comparisons to the NDS-MM-003 study demonstrated a clinically relevant and statistically significant benefit for ide-cel across all pre-defined efficacy endpoints, with an ORR of 69.4% (95% CI: 60.3, 80.0) for the ide-cel enrolled population vs 32.0% (95% CI: 24.1, 42.5) for the RW eligible cohort. The HR for PFS (0.43 (95% CI: 0.30, 0.62, $p < 0.0001$) was also compelling in favour of ide-cel. However, despite extensive efforts to match the patient populations, the comparisons are limited by several factors including the rather long time period (up to 60 days from the index date) allowed for the collection of baseline data, the overlapping recruitment periods for the RWS and the MM-001 at the same study centres, the large proportion of missing data (up to 30%) for some included co-variates and several co-variates excluded from the PS model due to >30% missing data.

The SLR mostly identified studies that were small, single centre and/or Phase I/II. Across the RWS (n=11), ORR ranged from 23% to 90%, probably reflective of the heterogeneity of the included patient populations and the small sample sizes. With the exception of belantamab mafodotin and selinexor the clinical trials (n=13) reported outcomes for unapproved therapies, and are as such not considered immediately relevant for the current application. For the two MAIC comparisons, the study populations were generally more heavily pre-treated and more refractory than that of the MM-001 study, leading to a substantial reduction in the ESSs (close to 60%). Results following matching showed a benefit of ide-

cel in terms of ORR, PFS and OS (Selinexor only). However, the unanchored comparisons may produce biased estimates, due to the lack of adjustment for all important co-variates and the inability to adjust for unknown confounders.

Nevertheless, despite the limitations of the indirect treatment comparisons, the results indicate that ide-cel treatment is associated with responses that are well above those reported with current standard of care. The durability of responses is confirmed, with ongoing responses observed in 29 of the 94 responders (30.9%) at the last data cut off. Results from PFS and OS also appear compelling in the context of the external data provided, lending further support for the sustained benefit of ide-cel. To what extent the observed responses will be reflected in long term benefit in OS is not known. The follow-up for OS is short (i.e. the median follow-up duration for all surviving subjects in the ide-cel enrolled population was only 17 months at the latest DCO) and the OS estimates especially beyond median follow-up are considered to be encumbered with high uncertainty.

The proposed ide-cel dose range was 150 to 540 x 10^6 CAR+ T cells. The actual ide-cel dose administered to the patient will be driven by feasibility (ie, the success of leukapheresis and manufacturing), with a target dose for all patients of 450 x 10^6 CAR+ T cells. To support the approval of this dose range, pooled efficacy results from study MM-001 and from study CRB-401 were provided.

Compared to MM-001, fewer subjects in CBR-401 were triple-refractory (75.0% vs 84.4%), were refractory to anti-CD 38 antibodies (87.5% vs 93.5% and had received AMT bridging therapy for disease control during ide-cel manufacturing (53.6% vs 87.5%). Otherwise, the baseline characteristics of the patient populations were relatively well aligned across the two studies. In both studies, allocation to the dose-groups was not randomised and some imbalances in prognostic factors hampers the comparison across the dose categories both within and across the studies.

In both study MM-001 and CRB-401, there was a numerically increase in response rates for each dose level. The highest response rates were observed at the target dose of 450 x 10^6 CAR T+ cells, with consistent results across the two studies (ORR of 81.5 %, CR rate of 35.2% in study MM-001 compared to ORR of 84.2% and CR of 36.8% in CBR-401). The dose of 300 x 10^6 CAR+ T cells was only investigated in study MM-001 with response rates close to those observed for the 450 x 10^6 CAR+ T cell target dose (ORR 68.6%, 95%CI:56.4, 79.1) and the lower bound of the 95% CI above the pre-specified cut off of ORR >50%. For the 150 x 10^6 CAR+ T cells dose level, however, the pooled analysis indicate substantially lower response rates of 54.5% with the lower bound of the 95% CI below the pre-specified cutoff of 50% (95% CI: 32.2, 75.6) for ORR an 31% (95% CI: 13.9, 54.9) for CR or better. A similar trend for dose response was observed for PFS, with the median PFS time at the lowest dose level of only 3.8 months (95% CI: 1.9, 10.9). The dose response relationship is further supported by the PK data as well as by the multivariate analyses.

Thus, the limited data provided indicates reduced clinical responses at the 150 x 10^6 dose level across both the supportive and the pivotal study, and a positive benefit/risk for the 150 x10^6 dose level in the context of the external data cannot be concluded. Therefore, the dose-range was restricted to 300 to 450 x 10^6 CAR+ T cells corresponding to 260 to 420 x 10^6 viable CAR+T cells (with the allowance of 20% over the target dose of 420 x 10^6 viable CAR+ T cells). The data on the lowest dose level will be kept under the summary of efficacy in section 5.1 SmPC as the data was part of the primary efficacy analysis and as it is considered the information may be useful for the prescriber (i.e. in case administration of an out of specification dose is considered).

In both the pivotal and supportive studies retreatment was allowed for eligible subjects (achieving a best response to initial ide-cel infusion of SD or better). Responses reported in the re-treated population in study MM-001 were infrequent i.e. only 5 PRs (17.2%) and one VGPR (3.4%) reported in the 29 retreated patients, and a limited PFS was observed (1.0 month, 95% CI: 0.95, 1.97). In the supportive study (CRB-401) 17 patients received retreatment with a reported ORR of 11.8% (2/17)

(95% CI: 1.5, 36.4), both subjects confirmed with VGPR as best overall response. In study MM-001, all patients who achieved a response were ADA negative before retreatment (6/12 ADA negative patients) while none of the 17 ADA positive patients achieved a response. Adverse events leading to death were reported in 9 (31.0%) subjects. Considering the safety profile, and lack of responses in ADA positive patients, a warning is included in the SmPC.

Additional efficacy data needed in the context of a conditional MA

The original MAA was for a full MA. However, the clinical data package consisting of one uncontrolled pivotal trial (MM-001 n=140) and one uncontrolled Phase 1 supportive study (CRB 401, n=67) was not considered to provide comprehensive data to fulfil the requirements for a full MA. Although the size of the clinical efficacy and safety database as well as the duration of follow up were considered adequate, there are outstanding uncertainties; The patient population in the pivotal MM-001 study was highly selected in terms of performance status and co-morbidities, and can thus not be considered representative of a "real world" RRMM patient population. The main concern, therefore, is related to the lack of a concurrent control arm to establish the magnitude of the PFS and OS gain, in this highly selected study population. The external data provides contextualisation of the study results, however, there are several limitations impacting on the validity of the indirect treatment comparisons. Furthermore, the limited sample size hampers the subgroup analyses. Data on less refractory (i.e. mono- or double-refractory) patients are limited and robust comparative data on the benefit of SOC options in this population are lacking.

The applicant therefore requested consideration of its application for a Conditional Marketing Authorisation:

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Furthermore, it is considered that the product fulfils the requirements for a conditional marketing authorisation:

The benefit/risk is considered to be positive in a patient population consistent with the MM-001 study population. Ide-cel has a mechanism of action that is different from that of authorised treatments and has shown to be associated with a 67.1% objective response rate and a median duration of response of 11 months in this group of highly pre-treated patients. The toxicity profile of ide-cel is largely in line with the known adverse effect profile of CAR T cell therapies. The main safety concerns are cytokine release syndrome, cytopaenias and neurotoxicity, and the treatment is tolerated when adverse effects are closely monitored and actively managed.

It is likely that the applicant will be able to provide comprehensive data by post-approval specific obligations. The ongoing randomised study (MM-003) comparing ide-cel with SOC and conducted in an overlapping patient population (received 2-4 prior anti-myeloma regimens) is considered to be suitable as a specific obligation to the MA. These data will be provided by June 2023. Updated efficacy and safety data (24 months after the last subject has received ide-cel) from the ongoing Study BB2121-MM-001 will also be provided as a SOB to the CMA. These data will be provided by December 2021.

An unmet medical need exists in the target MM population, as available therapies in this setting offer limited clinical benefit. Almost all patients eventually relapse and become resistant to available treatments, where the remission duration generally decreases with each subsequent treatment regimen, and where the toxicity of different regimens is significant and quite different between products. In this context, medicinal products with a positive benefit-risk balance and new mechanism of action can provide a major therapeutic advantage to patients if they offer possible alternative or additional treatment options based on a different safety profile, or based on therapeutic efficacy.

Recently approved products for RRMM include lenalidomide, pomalidomide, bortezomib, carfilzomib, ixazomib, panobinostat, daratumumab, isatuximab, and elotuzumab. All of these treatments are set from first line to second line or beyond also in different combinations. Belantamab mafodotin and selinexor have been recently granted authorisation for treatment of multiple myeloma in adult patients in forth line and beyond.

Refractoriness to prior therapies largely defines the available treatment options for RRMM patients in late line setting in which several different treatment combinations may be used. Although indirect comparisons of efficacy are challenging in this heterogeneous population, based on high response rate, durability of responses and manageability of the safety profile, ide-cel can be considered to address the unmet medical need to a similar or greater extent than other approved medicinal products.

Therefore, Abecma can be considered to represent a major therapeutic advantage vis-à-vis existing treatments and fulfil an unmet medical need in the approved indication as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least three prior therapies including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy.

2.5.4. Conclusions on the clinical efficacy

In this heavily pre-treated RRMM population ide-cel showed response rates considered clinically meaningful and well above those reported with current standard of care. The durability of the responses is confirmed, with still ongoing responses observed in 29 of the 94 responders at the last data cut off (07 April 2020).

Results for the secondary endpoints were consistent with the primary endpoint, and overall the results compare favourably to those observed in the matched real world (RW) historical cohort as well as those reported in the literature.

Concerning the proposed ide-cel dose range (a target dose of 450 x 10^6 CAR+ T cells, within the dose range of 150 to 540 x 10^6 CAR+ T cells), the limited data for the 150 x 10^6 dose indicates efficacy may be substantially reduced, and a positive B/R for this dose level cannot be concluded. Therefore, the dose-range was restricted to 300 to 450 x 10^6 CAR+ T cells corresponding to 260 to 420 x 10^6 viable CAR+T cells (with the allowance of 20% over the target dose of 420 x 10^6 CAR+ T cells).

The CAT considers the following measures necessary to ensure the follow-up of efficacy:

- In order to further characterise the long-term efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol. Interim reports to be submitted in accordance with the RMP. Final report expected by 30 September 2042.

The CAT considers the following measures necessary to address the missing efficacy data in the context of a conditional marketing authorisation:

- In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH should submit 24 months post-Abecma infusion follow-up data (in the enrolled and treated population) of the pivotal study KarMMa (MM-001). Expected date for submission is 31 December 2021.

- In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH should submit the results of the Phase 3 study KarMMa-3 (MM-003) comparing the efficacy and safety of Abecma vs. standard triplet regimens in subjects with relapsed and refractory multiple myeloma. Expected date for submission is 30 June 2023.

The CHMP endorse the CAT conclusion on clinical efficacy as described above

2.6. Clinical safety

Patient exposure

The evaluation of safety includes data from 7 ongoing clinical studies (5 interventional studies and 2 LTFU studies). The primary focus of the safety analysis is on the pivotal Study MM-001 (Phase 2, N=128) with supportive safety data from the dose escalation Study CRB-401 (Phase 1, N=56), in total 184 patients (pooled analysis). Based on cut-off date 07 Apr 2020, the follow-up time is 15.5 months across the target dose levels of 150 to 450 x 10^6 CAR+ T cells and 15.2 months for the target dose of 450 x 10^6 CAR+ T cells in the pooled analysis of the pivotal study MM-001 and the supportive study CRB-401. Part of the patients in both studies have been re-exposed by one additional treatment consisting of LDC followed by one dose of ide-cel; 27 retreated patients in the pivotal study and 17 in the supportive study.

The following subject populations (i.e., analysis sets) were evaluated and used for presentation of the safety data:

- Enrolled population: All subjects who signed informed consent and underwent leukapheresis.
- Abecma-treated population.

The patient population consists of heavily pretreated patients with relapsed/refractory MM and who had been previously exposed to a wide range of available therapies. Based on baseline characteristics the patients can be considered to represent of very special population of MM patients being younger and having good performance status.

The exclusion criteria include several criteria to mitigate the risk of neurotoxicity. Patients with CNS involvement or CNS pathologies were excluded from the study. No contraindications are currently proposed.

Adverse events

Adverse events are presented from the pivotal study MM-001 and the supportive phase 1 study CRB 401 in tables below. The safety data are also presented as pooled analysis. In addition, AEs have been presented by target doses and time period (≤ 8 weeks and > 8 weeks after infusion). In general, the frequencies presented from the pivotal study and pooled analysis, are quite similar for most variables. The frequencies from the pivotal study are presented in the product information.

Table 30: Overview of Adverse Events – Study MM-001, and Pooled Analysis (Ide-cel-treated Population)

Subject with ≥ 1:	Study MM-001				Pooled Analysis (Studies MM-001 and CRB-401)			
	MAA		Safety Update		MAA		Safety Update	
	Ide-cel (CAR+ T Cells) Target Dose							
	450 × 10^6 (N = 54) n (%)	150 to 450 × 10^6 (N = 128) n (%)	450 × 10^6 (N = 54) n (%)	150 to 450 × 10^6 (N = 128) n (%)	450 × 10^6 (N = 92) n (%)	150 to 450 × 10^6 (N = 184) n (%)	450 × 10^6 (N = 92) n (%)	150 to 450 × 10^6 (N = 184) n (%)
AE	54 (100)	128 (100)	54 (100)	128 (100)	92 (100)	184 (100)	92 (100)	184 (100)
Grade 3 or 4 AE[a]	54 (100)	127 (99.2)	54 (100)	127 (99.2)	91 (98.9)	182 (98.9)	91 (98.9)	182 (98.9)
Serious AE	38 (70.4)	86 (67.2)	38 (70.4)	87 (68.0)	66 (71.7)	127 (69.0)	67 (72.8)	129 (70.1)
AE leading to death (Grade 5 AE)[a]	8 (14.8)	22 (17.2)	9 (16.7)	27 (21.1)	11 (12.0)	29 (15.8)	12 (13.0)	34 (18.5)

AE = adverse event; CAR = chimeric antigen receptor; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; ide-cel = idecabtagene vicleucel; MAA = Marketing Authorisation Application.
[a] Graded using CTCAE Version 4.03.
Data cutoff date = 16 Oct 2019 (Study MM-001) and 22 Jul 2019 (Study CRB-401) for the MAA; 07 Apr 2020 for the Safety Update.
Sources: MAA – SCS Table 3.1.1, SCS Table 3.3.1, SCS Table 3.4.1.1, and SCS Table 3.8.1;
Safety update (data cutoff date of 07 Apr 2020) – D120 Pooled Table 3.1.1, D120 Pooled Table 3.3.1, D120 Pooled Table 3.4.1.1, and D120 Pooled Table 3.8.1

The most common adverse reactions included neutropenia (91.3%), CRS (81.0%), anaemia (70.7%), thrombocytopenia (66.8%), Infections – Pathogen Unspecified (53.8%), leukopenia (48.4%), fatigue (39.1%), diarrhoea (36.4%), hypokalaemia (34.2%), hypophosphatemia and nausea (32.6% each), lymphopenia (31.5%), pyrexia (28.8%), cough (27.2%), hypocalcaemia (26.6%), Infections – Viral (26.1%), headache (23.9%), hypomagnesemia (22.3%), upper respiratory tract infection (21.7%), arthralgia (20.7%), oedema peripheral (20.1%), decreased appetite and hypogammaglobulinaemia (19.6%), and febrile neutropenia (16.3%). Other common adverse reactions occurring at lower frequency and considered clinically important included pneumonia (10.3%); tremor (8.2%); somnolence (5.4%); and aphasia, encephalopathy, and syncope (4.3% each).

Grade ≥3 AEs

The most common Grade 3 or 4 adverse reactions were neutropenia (88.6%); anaemia (58.2%); thrombocytopenia (53.3%); leukopenia (45.1%); lymphopenia (30.4%); Infections – Pathogen Unspecified (17.9%); hypophosphatemia (17.4%); febrile neutropenia (14.7%); hypocalcaemia and Infections – Viral (7.1% each); pneumonia (6.0%); and CRS, hypertension, and hyponatremia (5.4% each). Grade 3 or 4 adverse reactions were more often observed within the initial 8 weeks postinfusion (97.8%) compared to after 8 weeks postinfusion (60.8%).

Grade 3 or 4 Adverse Events in the First 8 Weeks Across Target Dose Levels by Period

The most frequently reported Grade 3 or 4 adverse reactions reported within the first 8 weeks after infusion were neutropenia (87.0%), anaemia (56.0%), thrombocytopenia (48.4%), leukopenia (44.0%), and lymphopenia (27.7%), and hypophosphatemia (16.3%).

The majority of Grade 3 or 4 AEs were hematologic events, and the frequency of all Grade 3 or 4 AEs increased slightly across the cumulative periods, which is not unanticipated as any subject with data for the first period would also be included throughout the other 3 periods.

Grade 5 adverse events

In the pooled analysis, ≥ 1 Grade 5 AE was reported in 34 (18.5%) subjects who received ide-cel across the target dose levels of 150 to 450 x10^6 CAR+ T cells. The most frequently reported Grade 5 AE was general physical health deterioration (19 [10.3%] subjects), followed by pneumonia and respiratory failure (2 [1.1%] subjects each). All other Grade 5 AEs were reported for 1 (0.5%) subject each: bronchopulmonary aspergillosis, cardiac failure congestive, cardio-respiratory arrest, cerebral haemorrhage, CRS, death, gastrointestinal haemorrhage, lung adenocarcinoma, pneumonia cytomegaloviral, sepsis, and toxicity to various agents. In the interval between the MAA and the updated data cutoff date, 2 additional subjects (1 subject in Study MM-001 and 1 subject in Study CRB-401) had a Grade 5 AE (general physical health deterioration and disease progression, respectively) reported after ide-cel retreatment. The majority of the verbatim terms for the Grade 5

AEs that were mapped to the PT of general physical health deterioration were related to the worsening of the subjects' health or general condition due to multiple myeloma (MM).

Among the 34 subjects with grade 5 AEs, five cases were considered related to ide-cel infusion: bronchopulmonary aspergillosis, cytokine release syndrome [CRS], death [from an unknown cause], and gastrointestinal [GI] haemorrhage and pneumonia cytomegaloviral one case each. CRS and infections are well known serious adverse events that can be potential fatal. The SmPC gives recommendation to minimise the risk for these AEs. Gastrointestinal haemorrhage is listed as a common AE in SmPC section 4.8; it is considered related to thrombocytopenia and in section 4.4 it is said that blood counts should be monitored prior to and after Abecma infusion. Cytopenias should be managed with myeloid growth factor and blood transfusion support according to institutional guidelines.

Deaths

In the pooled analysis, deaths from all causes were reported for 64 (34.8%) of 184 subjects who received ide-cel (including initial treatment and retreatment) across the target dose levels of 150 to 450 x 106 CAR+ T cells. Of the 64 deaths, 45 occurred after initial ide-cel infusion and 19 deaths occurred after ide-cel retreatment. For more information, see separate section below.

Serious AEs

In the pooled analysis, serious adverse reactions were reported in 70.1% of subjects. The most common serious adverse reactions included CRS (17.4%), pneumonia (7.1%), and febrile neutropenia and pyrexia (6.0% each). Other serious adverse reactions occurring at lower frequency and considered clinically important included neutropenia (4.3%); sepsis and thrombocytopenia (3.8% each); confusional state and dyspnoea (2.2% each); and encephalopathy, hypoxia, and mental status changes (1.6% each). For more information, see separate section below.

- *Adverse Events of Special Interest*

The table below gives the frequencies of AESIs seen in the pivotal study, the supportive study and the pooled analysis.

Table 31: Adverse Events of Special Interest/Selected Adverse Events by Category – Study MM-001 and Pooled Analysis (Ide-cel-treated Population)

AESI/Selected AE Category[a]	Study MM-001				Pooled Analysis (MM-001 and CRB-401)			
	MAA		Safety Update		MAA		Safety Update	
	Ide-cel (CAR+ T Cells) Target Dose							
	450×10^6 (N = 54) n (%)	150 to 450×10^6 (N = 128) n (%)	450×10^6 (N = 54) n (%)	150 to 450×10^6 (N = 128) n (%)	450×10^6 (N = 92) n (%)	150 to 450×10^6 (N = 184) n (%)	450×10^6 (N = 92) n (%)	150 to 450×10^6 (N = 184) n (%)
Cytokine release syndrome	52 (96.3)	107 (83.6)	52 (96.3)	107 (83.6)	87 (94.6)	149 (81.0)	87 (94.6)	149 (81.0)
Macrophage activation syndrome	3 (5.6)	4 (3.1)	3 (5.6)	4 (3.1)	3 (3.3)	4 (2.2)	3 (3.3)	4 (2.2)
iiNT[b]	11 (20.4)	23 (18.0)	11 (20.4)	23 (18.0)	NA	NA	NA	NA
Neurologic Toxicity – Focused[c]	21 (38.9)	50 (39.1)	21 (38.9)	52 (40.6)	40 (43.5)	74 (40.2)	41 (44.6)	77 (41.8)
Neurologic Toxicity – Broad[d]	30 (55.6)	87 (68.0)	30 (55.6)	88 (68.8)	63 (68.5)	134 (72.8)	63 (68.5)	135 (73.4)
Cytopenia – Overall	53 (98.1)	124 (96.9)	53 (98.1)	124 (96.9)	88 (95.7)	176 (95.7)	88 (95.7)	176 (95.7)
Cytopenia – Neutropenia	51 (94.4)	121 (94.5)	51 (94.4)	121 (94.5)	86 (93.5)	173 (94.0)	86 (93.5)	173 (94.0)
Cytopenia – Anemia	34 (63.0)	89 (69.5)	34 (63.0)	89 (69.5)	64 (69.6)	130 (70.7)	64 (69.6)	130 (70.7)
Cytopenia – Thrombocytopenia	35 (64.8)	84 (65.6)	35 (64.8)	84 (65.6)	64 (69.6)	126 (68.5)	64 (69.6)	126 (68.5)
Cytopenia – Lymphopenia	16 (29.6)	38 (29.7)	16 (29.6)	38 (29.7)	32 (34.8)	62 (33.7)	32 (34.8)	62 (33.7)
Cytopenia – Pancytopenia	0	2 (1.6)	1 (1.9)	3 (2.3)	0	2 (1.1)	1 (1.1)	3 (1.6)
Infections – Overall	38 (70.4)	88 (68.8)	39 (72.2)	89 (69.5)	67 (72.8)	130 (70.7)	68 (73.9)	131 (71.2)
Infections – Bacterial	13 (24.1)	19 (14.8)	14 (25.9)	20 (15.6)	19 (20.7)	25 (13.6)	20 (21.7)	26 (14.1)
Infections – Viral	15 (27.8)	35 (27.3)	16 (29.6)	36 (28.1)	23 (25.0)	45 (24.5)	26 (28.3)	48 (26.1)
Infections – Fungal	4 (7.4)	10 (7.8)	4 (7.4)	10 (7.8)	4 (4.3)	11 (6.0)	4 (4.3)	11 (6.0)
Infections – Pathogen Unspecified	25 (46.3)	62 (48.4)	26 (48.1)	63 (49.2)	49 (53.3)	98 (53.3)	50 (54.3)	99 (53.8)
Secondary malignancy[e]	4 (7.4)	8 (6.3)	5 (9.3)	9 (7.0)	9 (9.8)	15 (8.2)	10 (10.9)	16 (8.7)

AE = adverse event; AESI = adverse event of special interest; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; ide-cel = idecabtagene vicleucel; iiNT = investigator-identified neurotoxicity; MAA = Marketing Authorisation Application; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SCS = Summary of Clinical Safety; SMQ = standardized MedDRA query; SOC = system organ class.

[a] The AESI/selected AE categories were defined using MedDRA Version 22.0 (SMQ, sub-SMQ, or SOC hierarchy terms, and/or individual PTs) and medical judgement. The protocol-defined AESIs are encompassed in the AESI/selected AE analysis, which includes all grades (ie, not limited to ≥ Grade 3) of CRS, macrophage activation syndrome, neurologic toxicity (Broad or Focused), cytopenia, rheumatologic or other autoimmune disorders, infection, and secondary malignancy. A subject is counted only once for multiple events within each AESI/selected AE category. The groupings of AESI/selected AEs are determined by Celgene.

[b] Events that investigators identified as neurotoxicity; reported only in Study MM-001. Note that while iiNT was not specified as an AESI/selected AE in the protocol or SCS, iiNT was one of the 3 approaches used to assess neurologic toxicity and thus is included in this table for completeness.

[c] Neurologic Toxicity – Focused included selected PTs of neurologic toxicity events as determined by Celgene with consideration of biological/pharmacological plausibility for a drug-event relationship, known neurologic toxicities reported with this class of drug and consistent with published guidelines for CAR T cell-associated encephalopathy, and clinical judgement.

[d] Neurologic Toxicity – Broad included all PTs within the primary and secondary SOCs of nervous system disorders and psychiatric disorders.

[e] Two subjects who developed secondary malignancies after ide-cel retreatment, including 1 subject with plasmablastic lymphoma in Study MM-001 and 1 subject with Bowen's disease in Study CRB-401, are not counted in this table.

Note: Only AEs which occurred on or after ide-cel infusion are included in the table.

Data cutoff date = 16 Oct 2019 (Study MM-001) and 22 Jul 2019 (Study CRB-401) for the MAA; 07 Apr 2020 for the Safety Update.

Sources: MAA – SCS Table 3.5.1.1, CSR MM-001 Table 14.3.2.8.2.1, CSR MM-001 Listing 16.2.7.2, and CSR CRB-401 Listing 16.2.7.1.7;
Safety update (data cutoff date of 07 Apr 2020) – D120 Pooled Table 3.5.1.1, D120 MM-001 Table 14.3.2.8.2.1, D120 MM-001 Listing 16.2.7.2, and D120 CRB-401 Listing 16.2.7.1.7

Cytokine release syndrome (CRS)

At cutoff date 16 Oct 2019 CRS was seen in 83.6% of subjects in the pivotal study, with increasing frequency with increasing dose: 50.0%, 75.7%, and 96.3% of subjects at a target dose of 150, 300, and 450 x 10^6 CAR T cells, respectively. In the pooled analysis the frequency of CRS was 81.0% of subjects with increasing frequency with increasing dose: 40.9%, 75.7% and 94.6% of subjects at a target dose of 150, 300, and 450 x 10^6 CAR T cells, respectively. Overall there were no obvious differences in those patients who developed CRS compared to those who did not, except the exposure to ide-cel treatment. The increased frequency of CRS (any grade) was observed with increasing ide-cel dose and that was considered consistent with the mechanism of action and the expected effect of ide-cel, which was already reported in the original submission. No obvious predisposing factors concerning CRS development was thus observed. Most subjects with CRS had a maximum Grade 1 (47.4%) or 2 (30.5%) event, 5 (3.9%) subjects had a maximum Grade 3 CRS, and 1 (0.8%) subject each had a maximum Grade 4 or Grade 5 event. There was a higher frequency in Grade ≥3 with the higher dose levels of 300 and 450 x 10^6 CAR+T cells compared to 150 x 10^6 CAR+T cells (pivotal study:0%, 5.7%, and 5.6% with 150, 300 and 450 x 10^6 CAR+T cells respectively), but the frequencies at the highest

dose levels are indeed low. The frequencies of CRS in the dose escalation study confirmed the lower frequency at the lowest dose of 150 x 10^6 CAR+ T cells seen in the pivotal study.

In study MM-001 CRS was reported as an SAE for 22 (17.2%), and in CRB-401, CRS was reported as an SAE for 10 (17.9%) subjects. In MM-001 study, hospitalisation was required for 20 (15.6%) of subjects. There was one (0.8%) death due CRS SAE at a dose of 300 x 10^6 CAR+T cells.

In the pooled analysis, based on cutoff date 07 Apr 2020, CRS occurred in 81.0% of subjects receiving ide-cel. Grade 3 or higher CRS occurred in 10 (5.4%) subjects, with fatal CRS reported in 1 (0.8%) subject. The median time to onset of CRS, any grade, was 1 day (range: 1 to 17) and the median duration of CRS was 5 days (range: 1 to 63). The most common manifestations of CRS included pyrexia (78.3%), hypotension (32.1%), tachycardia (25.5%), chills (23.4%), hypoxia (16.3%), C-reactive protein increased (16.3%), headache (14.7%) and fatigue (10.9%). Grade 3 or higher events that may be observed in association with CRS included atrial fibrillation, capillary leak syndrome, hypotension, hypoxia and HLH/MAS. Of the 184 subjects, 45.1% of subjects received tocilizumab for treatment of CRS; 32.6% received a single dose while 12.5% received > 1 dose of tocilizumab. Overall, across the target dose levels, 15.8% of subjects received ≥ 1 dose of corticosteroids for treatment of CRS. Of 92 subjects at the target dose of 450 x 10^6 CAR+ T cells, 54.3% of subjects received ≥1 dose of tocilizumab and 22.8% received ≥1 dose of corticosteroids for treatment of CRS.

Neurologic toxicology

Neurologic AEs in the pivotal study were reported in 18.0%, 39.1% and 68.0% of subjects (almost the same in the pooled analysis, see table above) as reflected with three methods of reporting, respectively (cutoff date 16 Oct 2019):

- Investigator-identified neurotoxicity (iiNT) - included only the single AE PT of "neurotoxicity" as identified by the investigator in Study MM-001. In Study MM-001, iiNT was the primary safety assessment for neurotoxicity.
- Neurotoxicity focused - included selected PTs of neurologic toxicity events as determined by the sponsor with consideration of biological/pharmacological plausibility for a drug-event relationship. This is consistent with published guidelines for CAR T cell-associated encephalopathy (Lee DW et al , Biol Blood Marrow Transplant 25 (2019) 625-638).
- Neurotoxicity broad - In addition to reporting the AE term of "neurotoxicity" in Study MM-001, the investigators were instructed to report individual signs and symptoms associated with the iiNT separately. The individual signs or symptoms of iiNT were converted to AEs, and these PTs were combined with all AEs and replaced the AE PT of "neurotoxicity". Included all PTs within the primary or secondary MedDRA SOCs of nervous system disorders and psychiatric disorders.

iiNT method:

In the pivotal study the frequency of neurotoxicity was 18%, time to onset was 2.0 days (range: 1 to 10), duration was 3.0 days (range: 1-26), frequency of Grade≥3 neurotoxicity was 3.1%, time to onset was 4.0 days (range: 2-5) and duration was 4.0 days (range: 2-5).

Focused method:

Pivotal study: The frequency of neurotoxicity was 39.1%, time to onset was 4.0 days (range: 1 to 282), duration was 4.0 days (range: 1-242), frequency of Grade≥3 neurotoxicity was 5.5%, time to onset was 4.0 days (range: 2-226) and duration was 2.0 days (range: 2-26).

Pooled analysis: The frequency of neurotoxicity was 40,2%, time to onset was 4.5 days (range: 1 to 481), duration was 4.0 days (range: 1-360), frequency of Grade≥3 neurotoxicity was 4.8%, time to onset was 6.0 days (range: 2-226) and duration was 3.5 days (range: 2-32).

Broad method:

Frequency of neurotoxicity in the pivotal study was 68.0%, in the pooled analysis the frequency was 72.8%

"Neurotoxicity focused" seems to reflect study drug related AEs and is highlighted in this assessment. A comparison has been presented by the applicant of the iiNT method and "focused method" which concluded that the median onset time was longer (4.0 versus 2.0 days) with Neurologic Toxicity – Focused compared with iiNT. The severity, median duration, and management of these events (including the use of corticosteroids) were similar. The time to first onset of neurologic toxicity event was shorter with the higher doses. The median time to onset of the first Neurologic Toxicity – Focused AE was 4.5 days (range: 1 to 481) and the median duration was 4.0 days (range: 1 to 360), thus there are clearly patients with long-term neurological toxicity. However, only 9 subjects (4.8%) had Grade 3 or Grade 4 AE.

In the pooled analysis 33 (19.5%) subjects have neurological events lasting > 10 days, and the event was ongoing at data cut-off in 18 (10.7%) subjects.

The applicant has presented detailed analysis of Neurologic Toxicity – Focused AE in relation to AE duration, comorbidities or other predisposing factors (such as demographics or baseline disease characteristics). In general, the demographic and baseline disease characteristics were similar among the subjects regardless of the duration of neurologic toxicity.

Table 32:

Table 1: Summary of Neurologic Toxicity – Focused Events Lasting Greater Than 10 Days Across the Target Dose Levels in Study MM-001, Study CRB-401, and Pooled Analysis (Ide-cel-treated Population)

	Ide-cel CAR+ T cells (150 to 450 × 10^6)								
	Study MM-001 (N = 14)			CRB-401 (Parts A and B) (N = 7)			Pooled Analysis (MM-001 and CRB-401) (N = 21)		
	> 10 to ≤ 30 days	> 30 days	> 10 days	> 10 to ≤ 30 days	> 30 days	> 10 days	> 10 to ≤ 30 days	> 30 days	> 10 days
Subjects with ≥ 1 NT-F event lasting > 10 days, n[a]	7	7	14	3	7	7	10	14	21
Maximum reported grade, n (%)									
1	3 (42.9)	6 (85.7)	9 (64.3)	2 (66.7)	6 (85.7)	6 (85.7)	5 (50.0)	12 (85.7)	15 (71.4)
2	1 (14.3)	1 (14.3)	2 (14.3)	0	0	0	1 (10.0)	1 (7.1)	2 (9.5)
3	3 (42.9)	0	3 (21.4)	1 (33.3)	0	0	4 (40.0)	0	3 (14.3)
4	0	0	0	0	1 (14.3)	1 (14.3)	0	1 (7.1)	1 (4.8)
Time to first onset of NT-F event (days)[b]									
n	7	7	14	3	7	7	10	14	21
Median	6.0	42.0	11.0	13.0	30.0	11.0	6.0	36.0	11.0
Min, Max	1, 226	3, 246	1, 246	6, 374	1, 269	1, 269	1, 374	1, 269	1, 269
Total number of NT-F events	13	7	20	4	9	13	17	16	33
Subjects received steroids for NT-F, n (%)	4 (57.1)	0	4 (28.6)	1 (33.3)	1 (14.3)	1 (14.3)	5 (50.0)	1 (7.1)	5 (23.8)
NT-F AEs lasting > 10 days, n (%)[c]									
Tremor	1 (7.7)	2 (28.6)	3 (15.0)	1 (25.0)	2 (22.2)	3 (23.1)	2 (11.8)	4 (25.0)	6 (18.2)
Insomnia	0	2 (28.6)	2 (10.0)	2 (50.0)	1 (11.1)	3 (23.1)	2 (11.8)	3 (18.8)	5 (15.2)
Lethargy	2 (15.4)	0	2 (10.0)	1 (25.0)	1 (11.1)	2 (15.4)	3 (17.6)	1 (6.3)	4 (12.1)
Somnolence	1 (7.7)	1 (14.3)	2 (10.0)	0	1 (11.1)	1 (7.7)	1 (5.9)	2 (12.5)	3 (9.1)

A total of 21 subjects had at least 1 Neurologic Toxicity – Focused AE that lasted > 10 days in the pooled analysis, of which 14 in the pivotal Study MM-001. The only notable differences were that for those events lasting > 30 days, there was a lengthier time to onset from ide-cel infusion, with a median time to onset of 36 days, compared to a median time to onset of 6 days for those events with a duration of > 10 to ≤ 30 days.

A greater percentage of subjects who had Neurologic Toxicity - Focused AEs lasting > 10 to ≤ 30 days received steroid treatment compared to those subjects with events lasting > 30 days (50.0% versus 7.1%, respectively). However, as the numbers are small, no meaningful conclusions can be drawn on these observations at this stage.

Independent of the method approach, the frequencies were similar at the target doses of 300 and 450 x 10^6 CAR+ T cells, and higher than with the target dose of 150 x 10^6 CAR+ T cells (17.1% and 20.4% versus 0%, respectively, for iiNT; 40.0% and 38.9% versus 25.0% for Neurologic Toxicity – Focused). The frequency of "focused AEs" was 39.1% across the target doses in the pivotal study, but only 5.5% of subjects had AEs of maximum Grade 3, and none with Grade 4 or 5. There was an increase in frequency of Grade 3 or higher events with increased dose levels; 0%, 2.9%, and 9.3% across the target dose levels of 150, 300, and 450 x 10^6 CAR+ T cells, respectively. The frequencies of neurological AEs were a bit higher in the supportive study (42.9% overall "focused AEs"), than in the pivotal study (39.1%). Neurological AEs reported for ≥ 5% of subjects according to "focused AEs" were confusional state and dizziness (13.3%), insomnia (8.6%), tremor (7.8%), somnolence and encephalopathy (6.3% each), and aphasia (5.5%). In the non-focused, broader analysis of neurologic AEs the most frequently reported events were headache (28.8%), dizziness (15.2%), and confusional state (13.0%). Overall, there was no dose-dependent toxicity, and the Broad toxicity took place in 64.1% of subjects within the first 8 weeks.

Independent of investigator attribution of neurotoxicity, the most frequent neurologic or psychiatric adverse reactions included headache (28.8%), dizziness (15.2%), confusional state (13.0%), insomnia (9.8%), anxiety and tremor (8.2% each), and somnolence (6.5%). Other neurological reactions occurring at a lower frequency and considered clinically important included aphasia and encephalopathy (4.3% each).

The biomarker analyses suggested that the iiNT method may provide better specificity of neurotoxicity events in comparison to the Neurologic Toxicity – Focused and Neurologic Toxicity – Broad methods.

The iiNT method, the primary safety assessment for neurotoxicity in Study MM-001, is the same approach being used for ongoing ide-cel clinical studies.

Cytopenias

Almost all patients in the pivotal study (96.9%, 95.7% in the pooled analysis), had cytopenia (anaemia, lymphopenia, neutropenia, thrombocytopenia or pancytopenia) first 8 weeks and most of them were of Grade 3 or 4, none of Grade 5. After first 8 weeks, 50% still had cytopenias, of which 35.2% were of Grade 3 or 4. No cases of Grade 5 cytopenia were reported, but several subjects had persistent neutropenia and/or thrombocytopenia at death or loss of follow-up (cutoff date 16 Oct 2019). There was no clear dose dependent increase in frequency of cytopenia with increasing dose across the targeted dose levels of 300 and 450 x 10^6. The frequency was in general higher for the lowest dose of 150 x 10^6, but there were few subjects treated with this dose, so the interpretation of safety profile at this dose level is uncertain. The frequency of cytopenia overall was a bit lower in the supportive study (92.9%).

In the pooled analysis, **Neutropenia** AEs were reported for 94.0% subjects, and almost all (169 [91.8%]) had ≥ 1 Grade 3 or 4 Cytopenia. Roughly one third (34.8%) of these subjects had persistent neutropenia, where the median time to recovery in these subjects was 1.9 months (range: 1.2 to 5.6). For 11 of 62 subjects, their persistent Grade 3 or 4 neutropenia did not recover. Of these patients, 9/11 died and 2/11 were lost to follow-up. It is likely that the cytopenias are derived from the LDC, and therefore it is difficult to compare the frequencies between other CAR-T therapies due to differences in patient populations and different treatments.

Based on cutoff date 07 Apr 2020, the pooled analysis, 34.8% of the 178 subjects who had Grade 3 or 4 neutropenia and 72.7% of the 110 subjects who had Grade 3 or 4 thrombocytopenia during the first month following ide-cel infusion had not resolved by last assessment during the first month. Among the 62 subjects with neutropenia not resolved by Month 1, 82.3% recovered from Grade 3 or 4 neutropenia with a median time to recovery from ide-cel infusion of 1.9 months. Of the 80 subjects with thrombocytopenia not resolved by Month 1, 71.3% recovered from Grade 3 or 4 thrombocytopenia with the median time to recovery of 2.2 months.

Febrile neutropenia (Grade 3 or 4) was observed in 14.7% of subjects after ide-cel infusion and may be concurrent with CRS.

Cytopenias were the most frequently reported AESI that the investigators considered related to both LDC or ide-cel on or after ide-cel infusion, though the frequency was higher for those related to LDC compared to those related to ide-cel. Cytopenias are common in advanced MM patients, especially a heavily pretreated population and as such, it is difficult to ascertain the relative effect of LDC and ide-cel on cytopenias. In patients treated with CAR T cell therapy and LDC, both can impact early and late cytopenia. Though LDC is one of the contributing factors to early and late cytopenias, they are likely driven by multiple aetiologies based on data from CAR T cell products in other malignancies (Fried,

2019; Munshi, 2012; Brudno, 2016; Schaefer, 2019). The high frequency of cytopenias and persistent cytopenias can be considered expected in this heavily pre-treated patient population with several previous treatment modalities.

Cytopenias were managed primarily with the use of colony-stimulating factors (CSFs), RBC transfusions, and platelet transfusions. Most subjects (87.5%) received CSFs (e.g., filgrastim and pegfilgrastim) during the study for management of neutropenia.

Infections

Infections are usually a complication to cytopenias and was observed in 68.8% in the pivotal study, in 70.7% in pooled analysis. The most frequently (≥ 5% of subjects) reported infections in the pooled analysis were upper respiratory tract infection (20.7%), pneumonia (9.8%), urinary tract infection (9.2%), influenza (6.5%), sinusitis (6.0%), and nasopharyngitis (5.4%) (cutoff date 16 Oct 2019) . The frequencies were almost the same across the dose levels, but highest at dose 150 x 10^6 CAR+ T cells (75.0%, in the pivotal study, 72.7% in the pooled analysis. The frequencies of infections did not change much over time: 39.1% of subjects within the first 8 weeks, 24.6% of subjects > 8 to ≤ 16 weeks after infusion, and 30.1% of subjects > 16 weeks to ≤ 6 months after infusion. Nor did the frequency of Grade 3 or 4 infections change much over time: 6.0% in the first 8 weeks, 9.1% of subjects > 8 to ≤ 16 weeks, and 6.2% of subjects > 16 weeks to ≤ 6 months, and 7.7% of subjects > 6 months after infusion. Five (2.7%) subjects had Infection AEs that led to death (Grade 5). These were pneumonia (2 [1.6%] subjects) and bronchopulmonary aspergillosis, pneumonia cytomegaloviral, and sepsis, (1 [0.5%] subject each). In Study MM-001, bacterial infections were reported for 14.8% of subjects, viral infections for 27.3%, fungal infections for 7.8% of subjects and Infections with unspecified pathogen were reported for 48.4% of subjects.

Almost all subjects (99.5%) received anti-infectives for systemic use as concomitant therapy, primarily antibiotics (96.2%) and antivirals (95.7%) with 54.3% of subjects receiving antimycotics.

Data based on cutoff date 07 Apr 2020: Infections (overall) occurred in 71.2% of subjects. Grade 3 or 4 infections with an unspecified pathogen occurred in 17.9%, viral infections in 7.1%, bacterial infections in 3.8%, and fungal infections in 0.5% of subjects; no subject had a Grade 3 or 4 fungal infection. Fatal (Grade 5) infections of unspecified pathogen were reported in 1.6% of subjects, and 0.5% of subjects had a fatal fungal or viral infection.

Overall, the observed high frequency of infections - including even opportunistic infections as seen in the treated patients - are expected in subjects with MM who have been heavily pre-treated and have received LDC prior to Abecma treatment. The similar frequencies of infections and Grade 3-5 infections across different Abecma doses can be considered expected, as all the patients have received the same LDC.

Macrophage activation syndrome (PT of haemophagocytic lymphohistiocytosis) was reported for 4 subjects in in study MM-001: 1 (1.4%) subject who received ide-cel at a target dose of 300 x 10^6 CAR+ T cells and 3 (3.3%) subjects who received ide-cel at a target dose of 450 x 10^6 CAR+ T cells. Two of the 4 subjects had a Grade 4 MAS. All 4 events were reported within the first 8 weeks after infusion. No cases were seen in the supportive study.

Hypogammaglobulineaemia was reported in 26 subjects (20.3%) in study MM-001. The frequency was 25.0%, 20.0% and 20.4% across the target dose levels 150, 300, and 450 x 10^6 CAR+ T cells, respectively. The frequencies were a bit lower in the supportive study, but also in this study it was highest at the lowest dose. Hypogammaglobulinaemia was reported in 19.6% of patients treated with Abecma in the pooled studies with a median time to onset of 100 days (range 15 to 326). Monitoring and management guidance on this adverse event is included in the SmPC.

Tumour lysis syndrome (TLS) was reported for 1 (0.5%) subject in the supportive Study CRB-401 following a dose of 450 x 10^6 CAR+ T cells.

The presence of **Replication Competent Lentivirus** was not detected.

Secondary malignancies

In the pooled analysis (N =184), across the target dose levels of 150 to 450 × 10^6 CAR+ T cells, no secondary malignancies from insertional oncogenesis have been reported after ide-cel infusion, including initial infusion and retreatment, as of the data cutoff date of 07 Apr 2020.

Other secondary malignancies (not of T cell origin) were reported for 17 (9.2%) of 184 ide-cel-treated subjects after ide-cel infusion, including initial infusion and retreatment. These secondary malignancies were basal cell carcinoma (6 subjects); myelodysplastic syndrome (3 subjects); Bowen's disease (2 subjects); and anal cancer, bladder cancer, breast cancer, lung adenocarcinoma, malignant melanoma, plasmablastic lymphoma, and squamous cell carcinoma (1 subject each). One subject in Study CRB-401 had multiple malignancies of both basal cell skin carcinoma and bladder cancer.

Secondary malignancies were reported for 2 subjects within the first 8 weeks after initial infusion and for 15 subjects > 8 weeks after initial infusion.

Except for plasmablastic lymphoma and myelodysplastic syndrome (1 subject each), other secondary malignancies were considered unrelated to ide-cel. The investigator assessed the plasmablastic lymphoma (Grade 4 with an onset 110 days after ide-cel retreatment [250 days after initial ide cel infusion]) and myelodysplastic syndrome (Grade 4 with an onset 369 days after initial ide-cel infusion) as possibly related to ide-cel.

Secondary malignancies were reported more frequently in subjects who were ADA positive after initial ide-cel infusion (8/68 subjects [11.8%]), primarily basal cell carcinoma (5/68 subjects [7.4%]), compared to ADA negative subjects (1/59 subjects [1.7%]). All subjects with secondary malignancies in Study MM-001 had at least 9 months of follow-up from ide-cel infusion independent of ADA status. Based on the longer follow-up observed in these subjects, the likelihood of falling in the ADA-positive group was higher, consistent with the observed data.

Ide-cel manufacturing leads to high vector copy number (VCN) / cell as compared to approved CAR T cell products. The release criteria for VCN are proposed to be broad, allowing a VCN of up to 15. High VCN may be a potential concern for insertional mutagenicity resulting in development of secondary malignancies in subjects with long-term survival. The applicant has indicated that based on the published literature, *in vitro* characterisation studies, clinical manufacturing data, nonclinical studies, and available updated clinical safety data in 184 subjects from Studies MM-001 and CRB-401 who received ide-cel therapy across the target dose levels of 150 to 450 × 10^6 CAR+ T cells, VCN does not appear to be a risk factor for the development of secondary malignancies, which is the key AE mediated by insertional oncogenesis. With the more recent data cutoff date of 07 Apr 2020, 6 tumour samples sufficient for evaluation were available and received from 5 of the 17 subjects who reported secondary malignancies. All 6 tumour samples were negative for CAR transgene in Studies MM-001 and CRB-401.

AEs in retreated subjects

For subjects who received ide-cel retreatment, AEs that occurred following lymphodepleting chemotherapy (LDC) for retreatment and after ide-cel retreatment were analysed separately from those following initial treatment and thus were not included in the primary safety analyses.

There was a trend in lower frequency of AEs in the retreated subjects. In the pivotal study a total of 23 (85.2%) subjects had at least 1 AE assessed by the investigator as related to ide-cel following the

retreatment infusion. The most frequently reported related events after ide-cel retreatment (≥ 20% of subjects) were neutropenia (59.3%), CRS (51.9%), anaemia (44.4%), thrombocytopenia (29.6%), and leukopenia (22.2%). Similar frequencies were observed in the supportive study where 70.6% of retreated subjects had at least 1 AE considered related to the ide-cel retreatment, CRS in 35.3% of subjects and neurological toxicity ("focused") in 41.2% of subjects.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

A summary of SAEs reported for ≥ 2% of subjects on or after Abecma infusion in Studies MM-001 and CRB-401 is presented by SOC and PT in Table below (cuttoff date 16 Oct 2019).

Table 33: Serious Adverse Events by System Organ Class and Preferred Term Reported for at Least 2% of Subjects

System Organ Class Preferred Term[a]	Study MM-001				Study CRB-401 (Parts A and B)			Pooled Analysis (MM-001 and CRB-401)			
	Ide-cel (CAR+ T Cells) Target Dose										
	150 x 10^6 (N = 4) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 54) n (%)	150 to 450 x 10^6 (N = 128) n (%)	150 x 10^6 (N = 18) n (%)	450 x 10^6 (N = 38) n (%)	150 to 450 x 10^6 (N = 56) n (%)	150 x 10^6 (N = 22) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 92) n (%)	150 to 450 x 10^6 (N = 184) n (%)
Subjects with ≥ 1 serious AE	4 (100)	44 (62.9)	38 (70.4)	86 (67.2)	13 (72.2)	28 (73.7)	41 (73.2)	17 (77.3)	44 (62.9)	66 (71.7)	127 (69.0)
Infections and infestations	**1 (25.0)**	**15 (21.4)**	**15 (27.8)**	**31 (24.2)**	**4 (22.2)**	**9 (23.7)**	**13 (23.2)**	**5 (22.7)**	**15 (21.4)**	**24 (26.1)**	**44 (23.9)**
Pneumonia	0	5 (7.1)	6 (11.1)	11 (8.6)	0	1 (2.6)	1 (1.8)	0	5 (7.1)	7 (7.6)	12 (6.5)
Sepsis	0	4 (5.7)	2 (3.7)	6 (4.7)	0	0	0	0	4 (5.7)	2 (2.2)	6 (3.3)
General disorders and administration site conditions	**1 (25.0)**	**12 (17.1)**	**9 (16.7)**	**22 (17.2)**	**6 (33.3)**	**7 (18.4)**	**13 (23.2)**	**7 (31.8)**	**12 (17.1)**	**16 (17.4)**	**35 (19.0)**
General physical health deterioration	1 (25.0)	9 (12.9)	3 (5.6)	13 (10.2)	2 (11.1)	2 (5.3)	4 (7.1)	3 (13.6)	9 (12.9)	5 (5.4)	17 (9.2)
Pyrexia	0	1 (1.4)	4 (7.4)	5 (3.9)	2 (11.1)	4 (10.5)	6 (10.7)	2 (9.1)	1 (1.4)	8 (8.7)	11 (6.0)
Immune system disorders	**2 (50.0)**	**11 (15.7)**	**10 (18.5)**	**23 (18.0)**	**3 (16.7)**	**7 (18.4)**	**10 (17.9)**	**5 (22.7)**	**11 (15.7)**	**17 (18.5)**	**33 (17.9)**
Cytokine release syndrome	2 (50.0)	11 (15.7)	9 (16.7)	22 (17.2)	3 (16.7)	7 (18.4)	10 (17.9)	5 (22.7)	11 (15.7)	16 (17.4)	32 (17.4)
Blood and lymphatic system disorders	**2 (50.0)**	**7 (10.0)**	**10 (18.5)**	**19 (14.8)**	**3 (16.7)**	**2 (5.3)**	**5 (8.9)**	**5 (22.7)**	**7 (10.0)**	**12 (13.0)**	**24 (13.0)**
Febrile neutropenia	2 (50.0)	5 (7.1)	2 (3.7)	9 (7.0)	0	2 (5.3)	2 (3.6)	2 (9.1)	5 (7.1)	4 (4.3)	11 (6.0)
Neutropenia	0	2 (2.9)	4 (7.4)	6 (4.7)	2 (11.1)	0	2 (3.6)	2 (9.1)	2 (2.9)	4 (4.3)	8 (4.3)
Thrombocytopenia	0	2 (2.9)	4 (7.4)	6 (4.7)	1 (5.6)	0	1 (1.8)	1 (4.5)	2 (2.9)	4 (4.3)	7 (3.8)

System Organ Class Preferred Term[a]	Study MM-001				Study CRB-401 (Parts A and B)			Pooled Analysis (MM-001 and CRB-401)			
	Ide-cel (CAR+ T Cells) Target Dose										
	150 x 10^6 (N = 4) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 54) n (%)	150 to 450 x 10^6 (N = 128) n (%)	150 x 10^6 (N = 18) n (%)	450 x 10^6 (N = 38) n (%)	150 to 450 x 10^6 (N = 56) n (%)	150 x 10^6 (N = 22) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 92) n (%)	150 to 450 x 10^6 (N = 184) n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**5 (7.1)**	**4 (7.4)**	**9 (7.0)**	**3 (16.7)**	**5 (13.2)**	**8 (14.3)**	**3 (13.6)**	**5 (7.1)**	**9 (9.8)**	**17 (9.2)**
Basal cell carcinoma	0	1 (1.4)	4 (7.4)	5 (3.9)	0	1 (2.6)	1 (1.8)	0	1 (1.4)	5 (5.4)	6 (3.3)
Respiratory, thoracic and mediastinal disorders	**0**	**6 (8.6)**	**3 (5.6)**	**9 (7.0)**	**2 (11.1)**	**1 (2.6)**	**3 (5.4)**	**2 (9.1)**	**6 (8.6)**	**4 (4.3)**	**12 (6.5)**
Dyspnoea	0	2 (2.9)	2 (3.7)	4 (3.1)	0	0	0	0	2 (2.9)	2 (2.2)	4 (2.2)
Investigations	**0**	**5 (7.1)**	**0**	**5 (3.9)**	**0**	**1 (2.6)**	**1 (1.8)**	**0**	**5 (7.1)**	**1 (1.1)**	**6 (3.3)**
C-reactive protein increased	0	3 (4.3)	0	3 (2.3)	0	1 (2.6)	1 (1.8)	0	3 (4.3)	1 (1.1)	4 (2.2)
Psychiatric disorders	**0**	**2 (2.9)**	**3 (5.6)**	**5 (3.9)**	**0**	**0**	**0**	**0**	**2 (2.9)**	**3 (3.3)**	**5 (2.7)**
Confusional state	0	2 (2.9)	2 (3.7)	4 (3.1)	0	0	0	0	2 (2.9)	2 (2.2)	4 (2.2)

AE = adverse event; CAR = chimeric antigen receptor; CSR = clinical study report; ide-cel = idecabtagene vicleucel; incl = including; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.

[a] Coded using MedDRA Version 22.0. A subject is counted only once for multiple events within PT/SOC. Adverse events are sorted by descending frequency of SOCs and then by descending frequency of PTs within each SOC for AEs reported with a ≥ 2% frequency across the target dose levels of 150 to 450 x 10^6 CAR+ T cells for the pooled analysis.

Note: The target dose levels of 150 to 450 x 10^6 CAR+ T cells in Study MM-001 includes target doses of 150, 300, and 450 x 10^6 CAR+ T cells and in Study CRB-401 includes the target doses of 150 and 450 x 10^6 CAR+ T cells; results for the individual doses of 50 and 800 x 10^6 CAR+ T cells are presented within the CRB-401 CSR. In Study MM-001, 1 subject dosed at 339 × 10^6 CAR+ T cells is included under the target dose of 450 × 10^6 CAR+ T cells, and 1 subject dosed at 192 × 10^6 CAR+ T cells is included under the target dose of 150 × 10^6 CAR+ T cells. In Study CRB-401, 1 subject dosed at 205 × 10^6 CAR+ T cells and 1 subject dosed at 305 × 10^6 CAR+ T cells are included under the target dose of 450 × 10^6 CAR+ T cells. For the 300 x 10^6 target dose level, the pooled column is identical to the Study MM-001 column, as there is no contribution from Study CRB-401. Only AEs which occurred on or after ide-cel infusion are included in the table.

Data cutoff dates = 16 Oct 2019 (Study MM-001) and 22 Jul 2019 (Study CRB-401).

Source: SCS Table 3.4.1.1

In the pivotal study 67.2% (69.0% in the pooled analysis) of subjects across the targeted dose levels had ≥1 SAE. The most frequently reported (≥ 5%) SAE was CRS (17.2%, 17.4% in pooled analysis), followed by general physical health deterioration (10.2%, 9.2% in pooled analysis), pneumonia (8.6%, 6.5% in pooled analysis) and febrile neutropenia (7.0%, 6.0% in pooled analysis). Overall, the frequencies of subjects with SAEs were high (100%, 62.9% and 70.4% in the pivotal study, 77.3%, 62.9% and 71.7% in the pooled analysis) across the target dose levels 150, 300 and 450 x106 CAR+ T cells respectively.

In the pivotal study a total 44.5% (44.6% pooled analysis) of subjects had SAEs reported within the first 8 weeks and 43.4% (45.5% in pooled analysis) of subjects had SAEs reported > 8 weeks after infusion. All SAEs of CRS and C-reactive protein (CRP) increased were reported within the first 8 weeks after infusion.

Serious Adverse Events in the First 8 Weeks Across the Target Dose Levels by Period

An analysis of SAEs reported within the first 8 weeks by discrete time period (≤ 1 week, > 1 week to ≤ 2 weeks, > 2 weeks to ≤ 4 weeks, and > 4 weeks to ≤ 8 weeks after ide-cel infusion) is presented in table below. As noted above there were no SAEs reported from the infections and infestations SOC within the first week, while 2 subjects (1.1%) experienced an infection and infestation SAE between > 1 to ≤ 2 weeks, and 7 subjects each (3.8%) experienced an infection and infestation SAE during the latter 2 time periods. Otherwise, there were no consistent trends of SAEs occurring during the discrete time periods, and no clinically meaningful conclusions of SAE occurrence by discrete time period can be made.

Table 34

Table 4: Serious Adverse Events by System Organ Class and Preferred Term Reported for at Least 2% of Subjects Across the Target Dose Levels of 150 to 450 × 10^6 CAR+ T Cells, by Cumulative Period during the First 8 Weeks – Study MM-001, Study CRB-401, and Pooled Analysis (Ide-cel-treated Population)

System Organ Class Preferred Term[a]	Study MM-001 (N = 128)				Study CRB-401 (Parts A and B) (N = 56)				Pooled Analysis (MM-001 and CRB-401) (N= 184)			
	Within 1 week n (%)	Within 2 weeks n (%)	Within 4 weeks n (%)	Within 8 weeks n (%)	Within 1 week n (%)	Within 2 weeks n (%)	Within 4 weeks n (%)	Within 8 weeks n (%)	Within 1 week n (%)	Within 2 weeks n (%)	Within 4 weeks n (%)	Within 8 weeks n (%)
Subjects with ≥ 1 serious AE	23 (18.0)	31 (24.2)	51 (39.8)	57 (44.5)	5 (8.9)	11 (19.6)	21 (37.5)	25 (44.6)	28 (15.2)	42 (22.8)	72 (39.1)	82 (44.6)
Immune system disorders	**16 (12.5)**	**21 (16.4)**	**23 (18.0)**	**23 (18.0)**	**5 (8.9)**	**7 (12.5)**	**9 (16.1)**	**10 (17.9)**	**21 (11.4)**	**28 (15.2)**	**32 (17.4)**	**33 (17.9)**
Cytokine release syndrome	15 (11.7)	20 (15.6)	22 (17.2)	22 (17.2)	5 (8.9)	7 (12.5)	9 (16.1)	10 (17.9)	20 (10.9)	27 (14.7)	31 (16.8)	32 (17.4)
Infections and infestations	**0**	**1 (0.8)**	**7 (5.5)**	**11 (8.6)**	**0**	**1 (1.8)**	**1 (1.8)**	**2 (3.6)**	**0**	**2 (1.1)**	**8 (4.3)**	**13 (7.1)**
Pneumonia	0	0	2 (1.6)	4 (3.1)	0	0	0	0	0	0	2 (1.1)	4 (2.2)
Sepsis	0	0	1 (0.8)	1 (0.8)	0	0	0	0	0	0	1 (0.5)	1 (0.5)
General disorders and administration site conditions	**2 (1.6)**	**2 (1.6)**	**5 (3.9)**	**6 (4.7)**	**0**	**1 (1.8)**	**4 (7.1)**	**6 (10.7)**	**2 (1.1)**	**3 (1.6)**	**9 (4.9)**	**12 (6.5)**
Pyrexia	0	0	2 (1.6)	2 (1.6)	0	0	3 (5.4)	3 (5.4)	0	0	5 (2.7)	5 (2.7)
General physical health deterioration	0	0	0	1 (0.8)	0	0	0	1 (1.8)	0	0	0	2 (1.1)
Blood and lymphatic system disorders	**1 (0.8)**	**3 (2.3)**	**10 (7.8)**	**10 (7.8)**	**0**	**1 (1.8)**	**1 (1.8)**	**1 (1.8)**	**1 (0.5)**	**4 (2.2)**	**11 (6.0)**	**11 (6.0)**
Thrombocytopenia	1 (0.8)	1 (0.8)	5 (3.9)	5 (3.9)	0	0	0	0	1 (0.5)	1 (0.5)	5 (2.7)	5 (2.7)
Neutropenia	1 (0.8)	2 (1.6)	4 (3.1)	4 (3.1)	0	0	0	0	1 (0.5)	2 (1.1)	4 (2.2)	4 (2.2)
Febrile neutropenia	0	0	2 (1.6)	2 (1.6)	0	1 (1.8)	1 (1.8)	1 (1.8)	0	1 (0.5)	3 (1.6)	3 (1.6)
Respiratory, thoracic and mediastinal disorders	**2 (1.6)**	**3 (2.3)**	**5 (3.9)**	**7 (5.5)**	**0**	**0**	**0**	**0**	**2 (1.1)**	**3 (1.6)**	**5 (2.7)**	**7 (3.8)**
Dyspnoea	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.6)	0	0	0	0	1 (0.5)	1 (0.5)	1 (0.5)	2 (1.1)
Investigations	**1 (0.8)**	**2 (1.6)**	**3 (2.3)**	**3 (2.3)**	**0**	**0**	**1 (1.8)**	**1 (1.8)**	**1 (0.5)**	**2 (1.1)**	**4 (2.2)**	**4 (2.2)**
C-reactive protein increased	1 (0.8)	2 (1.6)	3 (2.3)	3 (2.3)	0	0	1 (1.8)	1 (1.8)	1 (0.5)	2 (1.1)	4 (2.2)	4 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**2 (1.6)**	**2 (1.6)**	**0**	**1 (1.8)**	**2 (3.6)**	**2 (3.6)**	**0**	**1 (0.5)**	**4 (2.2)**	**4 (2.2)**
Basal cell carcinoma	0	0	1 (0.8)	1 (0.8)	0	0	0	0	0	0	1 (0.5)	1 (0.5)
Psychiatric disorders	**4 (3.1)**	**4 (3.1)**	**4 (3.1)**	**4 (3.1)**	**0**	**0**	**0**	**0**	**4 (2.2)**	**4 (2.2)**	**4 (2.2)**	**4 (2.2)**
Confusional state	3 (2.3)	3 (2.3)	3 (2.3)	3 (2.3)	0	0	0	0	3 (1.6)	3 (1.6)	3 (1.6)	3 (1.6)

AE = adverse event; CAR = chimeric antigen receptor; ide-cel = idecabtagene vicleucel; incl = including; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SCS = Summary of Clinical Safety; SOC = system organ class.

[a] Coded using MedDRA Version 22.0. A subject is counted only once for multiple events within PT/SOC. Adverse events are sorted by descending frequency of SOCs and then by descending frequency of PTs within each SOC for the last column of the pooled analysis.

Note: Only AEs which occurred on or after ide-cel infusion, but before retreatment lymphodepleting chemotherapy are included in the table. The 2% cutoff is applied to the target dose levels of 150 to 450 × 10^6 CAR+ T cells for the pooled analysis in SCS Table 23.

Data cutoff date = 16 Oct 2019 (Study MM-001) and 22 Jul 2019 (Study CRB-401).

Source: D120 Pooled Table 3.2.3.1.3.

With few exceptions, most AEs and Grade 3 or 4 AEs are reported during the first week following ide-cel infusion. A notable exception was hypogammaglobulinaemia, which has a later onset beyond the

first 2 weeks. The majority of events of CRS occurred within the first week. In the analysis of events reported in the first 8 weeks after ide-cel infusion, the cumulative frequency of events across time periods generally remains the same or slightly increases, as any subject with data for the first period is also included throughout the other 3 periods.

The updated data presented with a cutoff date of 07 Apr 2020, confirm that the majority of hospitalisations happen during the early postinfusion period, and adverse events were reported as the main reason for most hospitalisations. Within the seriousness criteria of inpatient hospitalisation or prolongation of existing hospitalisation, the most commonly reported AEs were CRS (15.6%), pneumonia (9.4%), and febrile neutropenia (7.0%).

The results of subgroup analyses of hospitalisation (including those for target dose, ECOG PS, and age subgroups) were generally consistent with those of the overall MM-001 ide-cel-treated population. The median duration of hospitalisation for the subgroups generally ranged from 4 to 6 days.

The results of these analyses did not show any unexpected findings, and the data presented do not have any implications for SmPC

Serious AEs in retreated subjects

In total 44 subjects in the pivotal study and the supportive study were retreated (cutoff date 16 Oct 2019) Serious adverse events occurred in 11 (64.7%) retreated subjects, but only 3 (17.6%) subjects had SAEs considered related to ide-cel by the investigator (cough, pyrexia, neurotoxicity, and CRS in 1 subject each).

Death /grade 5 AEs

In Study MM-001, 34 (26.6%) deaths (all causes) were reported for subjects who received Abecma (including treatment and retreatment), see table below. Of the 34 deaths, 25 deaths occurred after initial Abecma infusion and 9 deaths occurred after retreatment. The investigator attributed most of the 34 deaths to the primary cause of death category of malignant disease under study or complication due to malignant disease under study (24 [18.8%] subjects), and most of these deaths were due to plasma cell myeloma (21 [16.4%] subjects).

In Study CRB-401, 14 (25.0%) deaths were reported (including initial treatment and retreatment). Of the 14 deaths, 8 occurred after initial infusion and 6 occurred after retreatment. Thus, in the pooled analysis, 33/48 deaths occurred after initial Abecma infusion and 15 deaths occurred after retreatment.

Table 35: Grade 5 Adverse Events by System Organ Class and Preferred Term – Study MM-001, Study CRB-401, and Pooled Analysis (Ide-cel-treated Population)

System Organ Class Preferred Term [a]	Study MM-001				Study CRB-401 (Parts A and B)			Pooled Analysis (MM-001 and CRB-401)			
	Ide-cel (CAR+ T Cells) Target Dose										
	150 x 10^6 (N = 4) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 54) n (%)	150 to 450 x 10^6 (N = 128) n (%)	150 x 10^6 (N = 18) n (%)	450 x 10^6 (N = 38) n (%)	150 to 450 x 10^6 (N = 56) n (%)	150 x 10^6 (N = 22) n (%)	300 x 10^6 (N = 70) n (%)	450 x 10^6 (N = 92) n (%)	150 to 450 x 10^6 (N = 184) n (%)
Subjects with ≥ 1 AE leading to death	1 (25.0)	13 (18.6)	8 (14.8)	22 (17.2)	4 (22.2)	3 (7.9)	7 (12.5)	5 (22.7)	13 (18.6)	11 (12.0)	29 (15.8)
General disorders and administration site conditions	**1 (25.0)**	**10 (14.3)**	**3 (5.6)**	**14 (10.9)**	**3 (16.7)**	**1 (2.6)**	**4 (7.1)**	**4 (18.2)**	**10 (14.3)**	**4 (4.3)**	**18 (9.8)**
General physical health deterioration	1 (25.0)	9 (12.9)	3 (5.6)	13 (10.2)	2 (11.1)	1 (2.6)	3 (5.4)	3 (13.6)	9 (12.9)	4 (4.3)	16 (8.7)
Death	0	0	0	0	1 (5.6)	0	1 (1.8)	1 (4.5)	0	0	1 (0.5)
Disease progression	0	1 (1.4)	0	1 (0.8)	0	0	0	0	1 (1.4)	0	1 (0.5)
Infections and infestations	**0**	**2 (2.9)**	**3 (5.6)**	**5 (3.9)**	**0**	**0**	**0**	**0**	**2 (2.9)**	**3 (3.3)**	**5 (2.7)**
Pneumonia	0	0	2 (3.7)	2 (1.6)	0	0	0	0	0	2 (2.2)	2 (1.1)
Bronchopulmonary aspergillosis	0	0	1 (1.9)	1 (0.8)	0	0	0	0	0	1 (1.1)	1 (0.5)
Pneumonia cytomegaloviral	0	1 (1.4)	0	1 (0.8)	0	0	0	0	1 (1.4)	0	1 (0.5)
Sepsis	0	1 (1.4)	0	1 (0.8)	0	0	0	0	1 (1.4)	0	1 (0.5)
Cardiac disorders	**0**	**0**	**0**	**0**	**0**	**2 (5.3)**	**2 (3.6)**	**0**	**0**	**2 (2.2)**	**2 (1.1)**
Cardiac failure congestive	0	0	0	0	0	1 (2.6)	1 (1.8)	0	0	1 (1.1)	1 (0.5)
Cardio-respiratory arrest	0	0	0	0	0	1 (2.6)	1 (1.8)	0	0	1 (1.1)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (1.9)**	**1 (0.8)**	**1 (5.6)**	**0**	**1 (1.8)**	**1 (4.5)**	**0**	**1 (1.1)**	**2 (1.1)**
Respiratory failure	0	0	1 (1.9)	1 (0.8)	1 (5.6)	0	1 (1.8)	1 (4.5)	0	1 (1.1)	2 (1.1)
Gastrointestinal disorders	**0**	**0**	**1 (1.9)**	**1 (0.8)**	**0**	**0**	**0**	**0**	**0**	**1 (1.1)**	**1 (0.5)**
Gastrointestinal haemorrhage	0	0	1 (1.9)	1 (0.8)	0	0	0	0	0	1 (1.1)	1 (0.5)
Immune system disorders	**0**	**1 (1.4)**	**0**	**1 (0.8)**	**0**	**0**	**0**	**0**	**1 (1.4)**	**0**	**1 (0.5)**
Cytokine release syndrome	0	1 (1.4)	0	1 (0.8)	0	0	0	0	1 (1.4)	0	1 (0.5)

AE = adverse event; CAR = chimeric antigen receptor; CSR = clinical study report; ide-cel = idecabtagene vicleucel; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.

[a] Coded using MedDRA Version 22.0. A subject is counted only once for multiple events within PT/SOC at the maximum severity. Adverse events are sorted by descending frequency of SOCs and then by descending frequency of PTs within each SOC for AEs reported across the target dose levels of 150 to 450 x 10^6 CAR+ T cells for the pooled analysis.

Note: The target dose levels of 150 to 450 x 10^6 CAR+ T cells in Study MM-001 includes target doses of 150, 300, and 450 x 10^6 CAR+ T cells and in Study CRB-401 includes the target doses of 150 and 450 x 10^6 CAR+ T cells; results for the individual doses of 50 and 800 x 10^6 CAR+ T cells are presented within the CRB-401 CSR. In Study MM-001, 1 subject dosed at 339 × 10^6 CAR+ T cells is included under the target dose of 450 × 10^6 CAR+ T cells, and 1 subject dosed at 192 × 10^6 CAR+ T cells is included under the target dose of 150 × 10^6 CAR+ T cells. In Study CRB-401, 1 subject dosed at 205 × 10^6 CAR+ T cells and 1 subject dosed at 305 × 10^6 CAR+ T cells are included under the target dose of 450 × 10^6 CAR+ T cells. For the 300 x 10^6 target dose level, the pooled column is identical to the Study MM-001 column, as there is no contribution from Study CRB-401. Only AEs which occurred on or after ide-cel infusion are included in the table.

Data cutoff date = 16 Oct 2019 (Study MM-001) and 22 Jul 2019 (Study CRB-401).

Source: SCS Table 3.8.1

Grade 5 (fatal) AEs were reported in 22 (17.2%, 15.8% in the pooled analysis) subjects. The most frequently reported Grade 5 AEs in the pivotal study was general physical health deterioration (13 [10.2%] subjects), followed by pneumonia (2 [1.6%] subjects). All other Grade 5 AEs were reported for 1 [0.8%] subject each: bronchopulmonary aspergillosis, CRS, disease progression, gastrointestinal haemorrhage, pneumonia cytomegaloviral, respiratory failure, and sepsis. The one subject with Grade 5 CRS (fatal) had been treated with a dose of 300 x 10^6 CAR+T cells.

Death in retreated subjects

As of 07 Apr 2020, 47 subjects received ide-cel retreatment, which includes 29 subjects from Study MM-001 and 18 subjects from Study CRB-401. All but 1 subject were initially treated with ide-cel at target dose levels of 150 to 450 x 10^6 CAR+ T cells; 1 subject in Study CRB-401 initially received ide-cel at a target dose of 800 x 10^6 CAR+ T cells. Of all of those that were retreated at target dose levels of 150 to 450 x 10^6 CAR+ T cells, 20 subjects have died. Nineteen of the 20 subjects who died

following ide-cel retreatment had documented disease progression following ide-cel retreatment; 13 of these 20 subjects received at least 1 subsequent AMT following documented disease progression and prior to death.

The investigators attributed the primary cause of death category as due to adverse event (AE) in 4 retreated subjects, of which 1 each was due to PTs of fungal infection, mucormycosis, respiratory tract infection, and subdural hematoma.

In review of the 20 deaths in retreated subjects by time period, 3 subjects died within the first 8 weeks after the retreatment infusion (all due to malignant disease under study/plasma cell myeloma), 8 subjects died after 8 weeks through 6 months, 8 died after 6 months through 24 months, and 1 died after 24 months.

There were no new safety signals identified regarding deaths after retreatment compared to deaths after initial infusion based on updated data with cutoff date 07 Apr 2020.

Laboratory findings

Shifts in haematology, blood chemistry, and coagulation laboratory parameters were generally consistent with the reported AE profile of Abecma across the target dose levels of 150 to 450 x 10^6 CAR+ T cells.

The most frequently reported shifts from baseline in the haematology laboratory parameters were to low values post-baseline (decrease). The shifts in haematology laboratory parameters were generally consistent with the reported hematologic AEs, except for leukopenia, which was reported as a Grade 4 AE for 32.6% of subjects.

Shifts in chemistry laboratory parameters from Grade 0 to 2 at baseline to Grade 3 post-baseline were reported for < 10% of subjects, most frequently reported for Hb (73.4%). Shifts from Grade 0 to 3 at baseline to Grade 4 were reported for < 4% of subjects, most frequently reported for lymphocytes (99.2%), leukocytes and neutrophils (86.5% each), and platelets (49.2%).

Shifts in hepatic and renal function, electrolytes, and metabolic laboratory parameters were generally consistent with the reported AE profile:

- Hepatic function: Increased: Alanine aminotransferase (ALT increased) 8.7%, Alkaline phosphatase (ALP increased) 5.4%, Aspartate aminotransferase (AST increased) 5.4% and Bilirubin (hyperbilirubinaemia) 4.9%. Decreased: Albumin (hypoalbuminaemia): 7.1%
- Renal function: Creatinine (creatinine increased) 1.1%.
- Electrolytes: Increased: Magnesium (hypermagnesemia) 2.8%. Decreased: Calcium corrected (hypocalcaemia) 2.3%, Phosphate (hypophosphataemia) 37.4%, Potassium (hypokalaemia) 7.6% and Sodium (hyponatremia) 10.5%.
- Metabolism: Increased: Creatine kinase (CK increased) 1.1% and Glucose (hyperglycaemia) 7.1%. Decreased: Glucose (hypoglycaemia) 0.5%.

Inflammatory Markers: Mean CRP levels were increased at baseline, continued to increase to Day 2 (consistent with the median time to onset for CRS), and then decreased steadily thereafter. Mean ferritin levels were increased at baseline, continued to increase until Day 7, and then decreased steadily thereafter.

Coagulation: Increase: Activated partial thromboplastin time (aPTT increased) in 10.6%, INR increased 1.6% and Fibrinogen (hyperfibrinogenaemia) none subjects. Decrease: Fibrinogen (hypofibrinogenaemia) 2.7%.

Safety in special populations

Age: The specified AE categories (all grades) reported on or after initial ide-cel infusion across the target dose levels of 150 to 450 x 10^6 CAR+ T cells are presented by the requested age subgroups in Table below. Of the 184 subjects included in the pooled analysis, the majority (118 [64.1%]) were < 65 years old, 61 (33.2%) were 65 to < 75 years old, and 5 (2.7%) were 75 to < 85 years old. No subjects 85 years of age or older were enrolled in Studies MM-001 or CRB-401; therefore, this age subgroup is not relevant for inclusion in this analysis.

Table 36: Summary of Adverse Events by Criteria or MedDRA Terms and Age Subgroups – Studies MM-001 and CRB-401 (Ide-cel-treated Population)

Criteria or MedDRA Terms	< 65 years (N = 118) n (%)	65 to < 75 years (N = 61) n (%)	75 to < 85 years (N = 5) n (%)	≥ 85 years (N = 0) n (%)
Total AEs[a]	118 (100)	61 (100)	5 (100)	0
Serious AEs – Total[b]	77 (65.3)	49 (80.3)	3 (60.0)	0
Resulted in death	23 (19.5)	11 (18.0)	0	0
Inpatient hospitalization or prolongation of existing hospitalization	68 (57.6)	42 (68.9)	3 (60.0)	0
Life threatening	12 (10.2)	9 (14.8)	0	0
Persistent or significant disability/incapacity	2 (1.7)	0	0	0
Other medically important event	26 (22.0)	17 (27.9)	0	0
AE leading to treatment discontinuation[c]	NA	NA	NA	NA
Psychiatric disorders (SOC)	50 (42.4)	29 (47.5)	2 (40.0)	0
Nervous system disorders (SOC)	82 (69.5)	44 (72.1)	4 (80.0)	0
Accidents and injuries[d]	14 (11.9)	10 (16.4)	0	0
Cardiac disorders (SOC)	62 (52.5)	37 (60.7)	4 (80.0)	0
Vascular disorders (SOC)	62 (52.5)	36 (59.0)	4 (80.0)	0
Cerebrovascular disorders[e]	3 (2.5)	3 (4.9)	0	0
Infections and infestations (SOC)	88 (74.6)	40 (65.6)	3 (60.0)	0
Anticholinergic syndrome (PT)	0	0	0	0
Quality of life decreased[f]	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, and fractures[g]	27 (22.9)	18 (29.5)	3 (60.0)	0
Other AEs appearing more frequently in older patients[h]				
Pyrexia	30 (25.4)	22 (36.1)	1 (20.0)	0
Oedema peripheral	18 (15.3)	18 (29.5)	1 (20.0)	0
Hypertension	11 (9.3)	13 (21.3)	0	0

AE = adverse event; CAR = chimeric antigen receptor; CNS = central nervous system; HLGT = high-level group term; HLT = high-level term; ide-cel = idecabtagene vicleucel; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; PT = preferred term; SMQ = standardized MedDRA query; SOC = system organ class.

[a] Subjects with ≥ 1 event.

[b] Subjects may have met more than 1 serious AE criterion.

[c] As also discussed in the Response to Question 183, ide-cel was intended for administration as a single dose in Studies MM-001 and CRB-401, and follow-up continued for survival and long-term safety. In addition, as defined in the protocol, subjects could not discontinue treatment due to an AE because no subjects in the studies met the protocol-mandated minimum follow-up period, considering the single-dose treatment regimen. Thus, an analysis of AEs leading to treatment discontinuation from Studies MM-001 and CRB-401 is not applicable.

[d] Narrow scope of SMQ Accidents and injuries.

[e] Narrow scope of Central nervous system vascular disorders; Narrow scope of Sub-SMQ CNS vascular disorders, not specified as hemorrhagic or ischemic; Narrow scope of Sub-SMQ Conditions associated with central nervous system hemorrhages and cerebrovascular accidents, Narrow scope of Sub-SMQ Hemorrhagic central nervous system vascular conditions; and Narrow scope of Sub-SMQ Ischemic central nervous system vascular conditions.

[f] Search includes PTs of impaired quality of life and quality of life decreased.

[g] Search includes PTs of blood pressure orthostatic decreased, dizziness, dizziness exertional, dizziness postural, fall, loss of consciousness, orthostatic hypotension, persistent-postural perceptual dizziness, procedural dizziness, and syncope; HLT Gait disturbances and HLT Coordination and balance disturbances; and HLGT Fractures.

[h] The PTs in this category are those with a higher frequency (≥ 10% difference) in the 65- to < 75-year-old subgroup compared to the < 65-year-old subgroup. Due to the small sample size of the 75- to < 85-year-old subgroup (N = 5), a meaningful comparison could not be performed.

Notes: Data are shown across the target dose levels of 150 to 450 × 10^6 CAR+ T cells. Only AEs that occurred on or after ide-cel infusion are included.

Data cutoff date: 07 Apr 2020.

Sources: D120 Pooled Table 3.1.1.74.1.1, D120 Pooled Table 3.1.1.74.1.2, D120 Pooled Table 3.1.1.74.1.3, D120 Pooled Table 3.1.1.74.2.1, D120 Pooled Table 3.1.1.74.2.2, D120 Pooled Table 3.1.1.74.2.3, D120 Pooled Table 3.1.1.74.3.1, D120 Pooled Table 3.1.1.74.3.2, and D120 Pooled Table 3.1.1.74.3.3

The only difference among age categories <65 and 65- to < 75-year-old subgroup were seen in AEs in SOC Cardiac disorders (PT oedema peripheral) and SOC Vascular disorders (hypertension) and for the PT pyrexia.

From the table overview based on SOCs, it can be seen an overall small increased frequency in AEs in almost all SOCs in the subgroups 65 to <75 years of age and 75 to <85 years of age compared to the age group <65 years old..

No consistent trends in the AE profile were observed that would suggest clinically meaningful effect by age group. Adverse events reported with ≥ 10% higher frequency for subjects ≥ 65 compared with subjects < 65 years were fatigue (47.0% versus 34.7%), oedema peripheral (28.8% versus 15.3%), and hypertension (19.7% versus 8.5%). Grade 3 or 4 AEs reported with ≥ 5% higher frequency for subjects ≥ 65 compared with subjects < 65 years were Grade 3 or 4 hematologic AEs of anaemia (66.7% versus 53.4%), leukopenia (50.0% versus 42.4%), lymphopenia (36.4% versus 27.1%), and neutrophil count decreased (6.1% versus 0.8%) and non-hematologic AEs of fatigue (7.6% versus 0.8%) and hypertension (10.6% versus 2.5%). Serious AEs: Confusional state was the only serious AE reported with ≥ 5% higher frequency for subjects ≥ 65 compared with subjects < 65 years (6.1% versus 0%). Overall, SAEs were reported with ≥ 5% higher frequency for subjects ≥ 65 years compared with subjects < 65 years (77.3% versus 64.4%, pooled analysis). However, no dose adjustment has been suggested for patients over 65 years of age.

AESIs/Selected AEs: Infections - Pathogen Unspecified AEs were reported with ≥ 10% higher frequency for subjects < 65 years compared with subjects ≥ 65 years (58.5% versus 43.9%, pooled analysis).

Sex: There was a higher frequency of CRS reported as an SAE for female compared with male subjects (23.6% versus 13.4%).

Race: Most subjects (83.2%, 153/184 subjects) were white.

Ethnicity: Most subjects (84.8%, 156/184 subjects) were not Hispanic/Latino. The data available is too small to look at trends in other ethnic groups.

Anti-CD38 Antibody Refractory: Most subjects (91.8%, 169/184) subjects were anti-CD38 antibody refractory.

Tumour BCMA Expression at Baseline: There were 22 subjects with < 50% BCMA+ expression and 139 subjects with ≥ 50% BCMA+ expression at baseline. Although numerical differences in the frequencies of subjects with AEs, Grade 3 or 4 AEs, SAEs, and AESIs/selected AEs were observed, no consistent trends in the AE profile were observed that would suggest a clinically meaningful effect by baseline tumour BCMA+ expression.

Tumour Burden at Baseline: There were 88 subjects with low tumour burden (BM CD138+ plasma cells < 50%) and 89 subjects with high tumour burden (BM CD138+ plasma cells ≥ 50%) at baseline. Serious AEs were reported for 61.4% of subjects with low tumour burden at baseline and for 76.4% of subjects with high tumour burden at baseline. Adverse events, Grade 3 or 4 AEs, and AESI/selected AEs of thrombocytopenia and serious CRS were reported more frequently for subjects with high tumour burden compared with subjects with low tumour burden at baseline.

Bridging Antimyeloma Therapies (AMT): Different AMTs used are well known for a wide spectrum of AEs. It will in general be difficult to differ or interpret what AEs are related to the bridging/LDP therapy and ide-cel infusion. There was no clear trend, but leucopenia and transaminases increased were among AEs more frequent in those not being exposed for bridging AMT. There were no notable differences in the overall frequency of Grade 3 or 4 AEs between subjects who received and those who had not received bridging AMTs. Serious AEs were reported for 71.8% of subjects who received bridging AMTs and 59.5% of subjects who had not received bridging AMTs.

Use in pregnancy and lactation: There are no available data with ide-cel use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with idecabtagene vicleucel to assess whether it can cause foetal harm when administered to a pregnant woman. It is not known if idecabtagene vicleucel has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including plasma cell aplasia or hypogammaglobulinaemia. Relevant warnings on this matter are

reflected in the SmPC. There is no information regarding the presence of ide-cel in human milk, the effect on the breastfed infant, and the effects on milk production. Relevant warnings are included in the SmPC.

Immunological events

Idecabtagene vicleucel construct

The CAR is comprised of a BCMA-specific murine extracellular single-chain variable fragment followed by a human CD8α hinge and transmembrane domain fused to the cytoplasmic signalling domains of CD137 (4-1BB) and CD3ζ chain, in tandem. Autologous T cells transduced ex vivo with the anti-BCMA02 CAR LVV express the anti-BCMA CAR on the T cell surface (see illustration of construct below).

C11D5.3 = anti-BCMA monoclonal antibody; TM = transmembrane; V_H = heavy chain variable domain; V_L = light chain variable domain.

Sampling

Potential immunogenicity to ide-cel was evaluated by determining both humoral as well as cell-mediated responses. Serum samples collected from subjects post-infusion were evaluated for the formation of antidrug antibodies (ADAs) using an immunoassay designed and validated to detect antibodies to the extracellular CAR domain. Cell-mediated immune responses were evaluated using an Interferon-gamma ELISPOT assay that was performed on PBMCs derived from subjects.

Antidrug antibody formation

In both studies, the proportion of ADA-evaluated subjects who were ADA-positive increased over time from month 3.

Table 37: Summary of Antidrug Antibodies by visit – Study MM-001 and Study CRB-401 (ide-cel-treated population)

Visit	Antidrug Antibodies Status	Study MM-001	Study CRB-401 (Part A and B)
		Ide-cel (CAR+ T cells) Target Dose (150 to 450 x 10^6)	
		(N = 128)	(N = 56)
Month 1	N	123	52
	Positive, n (%)	0	2 (3.8)
	Negative, n (%)	123 (100.0)	50 (96.2)
Month 3	N	102	44
	Positive, n (%)	21 (20.6)	18 (40.9)
	Negative, n (%)	81 (79.4)	26 (59.1)
Month 6	N	80	34
	Positive, n (%)	35 (43.8)	21 (61.8)
	Negative, n (%)	45 (56.3)	13 (38.2)
Month 9	N	64	23
	Positive, n (%)	37 (57.8)	15 (65.2)
	Negative, n (%)	27 (42.2)	8 (34.8)
Month 12	N	29	15
	Positive, n (%)	18 (62.1)	12 (80.0)
	Negative, n (%)	11 (37.9)	3 (20.0)

CAR = chimeric antigen receptor; ide-cel = idecabtagene vicleucel. Note: N is the number of subjects with antidrug antibody data record. Data cutoff dates = 16 Oct 2019 (Study MM-001) and 22 Jul 2019 (Study CRB-401). Source: CSR MM-001 Table 14.2.9.1.1 and CSR CRB-401 Table 14.2.9.4.1.

Effect of antidrug antibody on pharmacokinetics – MM-001 study

Of 127 subjects evaluable for PK, exposure parameters for five subjects who were ADA-positive prior to ide-cel infusion, were generally comparable to the PK parameters of all subjects treated at the respective dose level.

A total of 65 subjects had at least one sample with detectable ADAs post-infusion. The geometric mean C_{max} and $AUC_{0\text{-}28}$ days for subjects who had at least one visit with detectable ADA post-infusion (pooled across dose levels) was 280,862 (131%) copies/µg and 3,433,112 (141%) copies*days/µg, respectively. These values are comparable to the overall geometric mean C_{max} of 231,278 (178%) copies/µg and $AUC_{0\text{-}28days}$ of 2,860,340 (197%) copies*days/µg, respectively, observed in subjects irrespective of ADA status.

ADA formation versus selected efficacy endpoints in study MM-001

Among the 65 subjects in the ide-cel-treated population who were post-positive for ADAs (these include also the five subjects who were pre-positive as of the 16 Oct 2019 data cut-off date), the ORR based on IRC assessments was 89.2% (95% CI: 79.1, 95.6) and the CR rate was 41.5% (95% CI: 29.4, 54.4). Among the 62 subjects who were post-negative for ADAs, the ORR was 58.1% (95% CI: 44.8, 70.5) and the CR rate was 21.0% (95% CI: 11.7, 33.2). Median TTR was 1.0 month regardless of whether or not ADAs developed after ide-cel infusion.

A KM estimate for median PFS was 11.3 months (95% CI: 8.9, 12.2) among subjects who were post-positive for ADAs versus 4.9 months (95% CI: 2.9, 8.2) among subjects who were post-negative for ADAs.

The KM estimate for median DoR was 10.7 months (95% CI: 9.2, 11.3) among responders who were post-positive for ADAs versus 10.3 months (95% CI: 5.0, NE) among responders who were post-negative for ADAs.

Antidrug Antibody formation versus selected safety endpoints in study MM-001

Among the 65 subjects in the ide-cel-treated population who were post-positive for ADAs, 59 (90.8%) had CRS on or after ide-cel infusion. Among the 62 subjects in the ide-cel-treated population who were post-negative for ADAs, 47 (75.8%) had CRS on or after ide-cel infusion.

Among subjects who were post-positive for ADAs, the frequency of CRS AEs was 100% at the target dose of 450 x 10^6 CAR+T cells versus 84.2% at the target dose of 300 x 10^6 CAR+T cells. Among subjects who were post-negative for ADAs, the frequency of CRS AEs was 92.9% at the target dose of 450 x 10^6 CAR+T cells versus 64.5% at the target dose of 300 x 10^6 CAR+T cells.

Among the 65 subjects in the ide-cel-treated population who were post-positive for ADAs, 9 (13.8%) had iiNT events on or after ide-cel infusion. Among the 62 subjects in the ide-cel-treated population who were post-negative for ADAs, 13 (21.0%) had iiNT events on or after ide-cel infusion.

Among subjects who were post-positive for ADAs, the frequency of iiNT events was 11.5% at the target dose of 450 x 10^6 CAR+T cells versus 15.8% at the target dose of 300 x 106 CAR+ T cells.

Among subjects who were post-negative for ADAs, the frequency of iiNT events was 28.6% at the target dose of 450 x 10^6 CAR+T cells versus 16.1% at the target dose of 300 x 10^6 CAR+T cells.

Development of positive ADA post-ide-cel infusion did not increase the frequency or severity of CRS or iiNT.

Immunogenicity in study CRB-401

In Study CRB-401, there were 5.4% subjects across the target dose levels of 150 to 450 x 10^6 CAR+T cells who had pre-existing ADAs before infusion of ide-cel. The immunogenicity analyses were performed using a data cut-off date of 22 Jul 2019.

The proportion of subjects who were ADA-positive increased over time: 5.2% at Month 1, 39.6% at Month 3, 64.9% at Month 6, 69.2% at Month 9, and 83.3% at Month 12.

PK–data from the CRB-401 study, indicated that ADA development is not going to impact cellular expansion of ide-cel, since the majority of which occurred in the first month after infusion, and the ADAs developed firstly after about three months. These results are supporting data from the MM-001 study.

Safety related to drug-drug interactions and other interactions

Ide-cel is a cellular product that is not cleared by the usual mechanisms that apply to small molecules or antibodies. No drug-drug interaction studies have been performed.

Discontinuation due to adverse events

As ide-cel is a single-dose treatment, no adverse events (AEs) leading to treatment discontinuation were reported. Therefore, an analysis of AEs leading to treatment discontinuation in these studies was

not conducted. Reasons for discontinuing study participation (rather than treatment discontinuation) were recorded. No ide-cel-treated subjects in Studies MM-001 or CRB-401 discontinued the studies due to an AE after starting lymphodepleting chemotherapy (LDC) but prior to receiving ide-cel, and no ide-cel-treated subjects discontinued the studies due to an AE.

In study MM-001 a total of 58 (45.3%) of the 128 ide-cel-treated subjects discontinued from different phases of the study after initial infusion. The most common reasons were reported as death (31 subjects [24.2%]) and withdrawal by subject (26 subjects [20.3%]). Of the 27 subjects who discontinued the study due to reasons other than death, 5 subjects entered the LTFU study (GC-LTFU-001) for continued follow-up.

Although there were 26 withdrawals by subject, only 2 subjects were censored for PFS due to discontinuing study without PD/death. Of the 27 subjects who discontinued the study due to reasons other than death, 5 subjects entered the LTFU study (GC-LTFU-001) for continued follow-up.

In study CRB-401 Forty (71.4%) subjects discontinued the study. The most commonly reported reason for discontinuation was PD (27 [48.2%] subjects); 6 (10.7%) subjects died, 6 (10.7%) subjects withdrew consent, and 1 (1.8%) subject discontinued due to other reasons. Of the 34 subjects who discontinued the study due to reasons other than death, 21 subjects entered the LTFU study (GC-LTFU-001 or LTF-305) for continued follow-up.

Post marketing experience

No post-marketing data are available at this time

2.6.1. Discussion on clinical safety

Overall, the AEs observed are anticipated toxicities consistent with the mechanism of action of CAR T cell therapies with main safety concerns related to CRS, neurological toxicity and cytopenias. With proper use of management guidance and use of proposed additional risk minimisation measures (controlled distribution programme including HCP educational programme and a patient educational programme), these safety concerns should be manageable across all dose levels. The safety looks in general similar to the safety profile known for other CAR-T products.

The safety assessment is based on 184 subjects and the majority of subjects included are <65 years of age. Based on the number of subjects exposed, only common AEs have been detected. In addition, the single arm study brings uncertainties in the safety assessment and does not allow separation of AEs attributable to Abecma vs. e.g., lymphodepleting chemotherapy (LDC).

A non-interventional, post authorisation, registry-based study (BB2121-MM-006) is proposed to further characterise the incidence and severity of ADRs.

The patient population consists of heavily pre-treated patients with relapsed/refractory MM and who have previously been exposed to a wide range of available therapies. Based on baseline characteristics the patients can be considered to represent a very special population of MM patients being younger and having good performance status.

The short follow-up time (15.5 months for the pooled analysis of the pivotal study and the supportive study) means that long-term safety cannot be assessed, and therefore more long-term follow-up data from other studies are required to be able to assess long-term safety of the product**.** Particular concerns in this respect are secondary malignancies and long-term neurological AEs, many of which were still ongoing at the data cut-off date. A 15 years follow-up of patients that have been included in

the clinical trials (Long-term follow-up study GC-LTFU-001) are proposed together with the registry study (BB2121-MM-006) to monitor long-term safety.

General description of the safety data

AEs were generally similar across the target dose levels. The frequency of subjects with SAEs and AEs leading to death varied across the target dose levels, although no dose-response is evident. However, regarding doses, in the pivotal study there were only 4 (and in the pooled dataset 22) subjects in the 150 x 10^6 CAR+ T dose group. Therefore, it is impossible to make conclusions for the B/R for the lower dose.

Cytokine Release Syndrome and Macrophage Activation Syndrome

CRS was seen in 81.0% in the pooled analysis of subjects with increasing frequency with increasing dose. CRS occurs in the first days following treatment, median time to onset was 1.0 day (range: 1 to 17 days) and the median duration was 5.0 days (range: 1 to 63). The median time to onset was shorter and the median duration was longer for the highest dose level. All cases were observed within first 8 weeks following ide-cel infusion. CRS was the most common SAE reported, 17.2% and 17.9% of subjects in study MM 001 and CRB-401, respectively. No clear predisposing or preventive medications or conditions concerning CRS could be identified by the applicant, except the Abecma dose. Further investigations on this topic are considered important in context of ongoing and planned clinical studies. A proper management guide, including treatment with tocilizumab and/or corticosteroids, was used in the clinical trials and is also included in the SmPC.

MAS is a very rare and potentially life-threatening condition. MAS was reported for 4 (3.1%) subjects in MM-001 study: 1 (1.4%) subject at a target dose of 300x 106 CAR+ T cells and 3 (3.3%) subjects at a target dose of 450x 106 CAR+ T cells. Two of the 4 subjects had a Grade 4 MAS.

Neurologic toxicity

Neurologic AEs were reported in 18.0% (iiNT), 39.1% (focused method) and 68.0% (broad method) of subjects as reflected by the three different methods of reporting. It is not clear what method of reporting neurotoxicity is the most optimal or what method is most comparable to how neurotoxicity is reported in other CAR-T products. However, as the iiNT method is the approach being used for ongoing ide-cel clinical studies with ide-cel, it will be useful to have these data from the pivotal study available in the SmPC and RMP documents. Nevertheless, independent of investigator attribution of neurotoxicity, neurologic or psychiatric adverse reactions have been reported as indicated by the data in the safety section above.

The exclusion criteria include several criteria to mitigate the risk of neurotoxicity. Patients with CNS involvement or CNS pathologies were excluded from the study. No contraindications are currently proposed.

Overall, based on limited data and a different target patient population, the neurological events reported with ide-cel are comparable to those reported with other products in the same class. Neurological events were also long-lasting, or ongoing at the data cut-off, which emphasises the need for follow-up of these events in long-term studies.

A proper management guide including treatment with tocilizumab or corticosteroids, was used in the clinical trials and is also included in the SmPC.

Cytopenias

Almost all patients in 95,7% in the pooled analysis had cytopenia first 8 weeks and most of them were of Grade 3 or 4, none of Grade 5. Patients may exhibit prolonged cytopenias following lymphodepleting chemotherapy and ide-cel infusion.

There was no clear dose dependent increase in frequency of cytopenia with increasing dose across the dose levels of 300 and 450 x 10^6. The frequency was in general higher for the lowest dose of 150 x 10^6. Cytopenias were managed primarily with the use of CSFs, RBC transfusions, and platelet transfusions.

It is likely that the cytopenias are derived from the LDC, and therefore it is difficult to compare the frequencies between other CAR-T therapies due to differences in patient populations and different treatments. This persistent neutropenia needs to be further followed up in further studies and also in other lines of treatment outside R/R MM.

The high frequency of cytopenias and persistent cytopenias can be considered expected in this heavily treated patient population. As LDC was an instrumental part of the treatment, given only few days before ide-cel-treatment, it is obviously impossible to evaluate, how much these cytopenia (or other AEs) were related to ide-cel and how much to LDC.

Infections

Overall, the observed high frequency of infections - including the opportunistic infections - as seen in the treated patients - are expected in subjects with MM who have been heavily pretreated and have received LDC prior to ide-cel treatment. Further, the similar frequencies of infections and Grade 3-5 infections across different ide-cel doses can be considered expected, as all the patients have received the same LDC.

Secondary malignancies

In the pooled analysis (N =184), across the target dose levels of 150 to 450 × 106 CAR+ T cells, no secondary malignancies from insertional oncogenesis have been reported after ide-cel infusion as of the data cutoff date of 07 Apr 2020.

Other secondary malignancies (not of T cell origin) were reported for 17 (9.2%) of 184 ide-cel-treated subjects after ide-cel infusion, including initial infusion and retreatment.

Secondary malignancies were reported more frequently in subjects who were ADA positive after initial ide-cel infusion, compared to ADA negative subjects (1/59 subjects [1.7%]). Outside of the confounding effect of follow-up times, no other biologic casual explanation for clustering of subjects with secondary malignancies in the ADA positive group was found. In addition to postmarketing surveillance, subjects in all ide-cel clinical studies will be monitored for potential delayed toxicities of gene therapy, which includes ADRs of secondary malignancies, for up to 15 years from last ide-cel infusion.

Secondary malignancies are a well-known risk in MM patients. It has to be considered that patients treated in Study MM-001 have been exposed to a median of 6 previous treatments each potentially carrying attributable risk for secondary malignancies. Secondary malignancies from ide-cel are considered an important potential risk based on the theoretical risk of vector insertional mutagenesis leading to oncogenesis (Risk Management Plan). Importantly, no insertional mutagenesis or malignancies of T cell origin have been reported or identified to date in the clinical study setting.

All ide-cel-treated subjects will be asked to enrol in a separate LTFU study (GC-LTFU-001) to be monitored for survival and long-term safety effects, including secondary malignancies, for up to 15 years from the last ide-cel infusion, as per health authority guidelines. In both the parent study or the LTFU study protocol, testing for ide-cel transgene will be conducted on all secondary malignancies where tissue is available.

A post-authorisation safety study (PASS), BB2121-MM-006, is planned to be conducted following the grant of the MAA. This registry based study will characterise the incidence and severity of selected

adverse drug reactions, including secondary malignancies, in patients treated with ide-cel in the postmarketing setting and monitor for potential clinically important adverse events that have not yet been identified as part of the ide-cel safety profile. The applicant has informed that in the planned postmarketing surveillance study (PASS BB2121-MM-006) only secondary malignancies of T cell origin will be tested for ide-cel transgene, whereas in previous and ongoing clinical studies testing for ide-cel transgene is performed for all secondary malignancies. This is acceptable, as there would be no biological rational for how malignant cells of non T-cell origins could be positive for ide-cell transgene. In Study BB2121-MM-006, if a secondary malignancy of T cell origin occurs, testing for ide-cel transgene will be conducted on all secondary malignancies of T cell origin where tissue is available.

Furthermore, SmPC Section 4.4 specifies that in the event that a secondary malignancy of T cell origin occurs, the company should be contacted to obtain instructions on the collection of patient samples for testing.

Upon receipt of a report of secondary malignancy, a questionnaire directed to assist in characterizing the event will be sent to healthcare professionals.

For the post-authorisation safety Study BB2121-MM-006, and postmarketing commercial use, transgene testing will be conducted for all secondary malignancies of T cell origin where a tissue sample is available. The reporting health care professional will be asked for additional information to help characterize the report of secondary malignancy, including, but not limited to, history of prior malignancies, previous cancer therapies or radiotherapy, other relevant exposures, family history, and biopsy report. The applicant will assist prescribers in coordinating transfer of tumour tissue samples from patients for ide-cel transgene testing.

Deaths

Overall, the incidence of deaths during the study was high. However, the death rate is understandable taking into account the heavily treated patient population with no further treatment options. In most cases, the cause of death was related to the baseline disease condition, one patient died due to CRS and few patients due to infections.

Other safety findings

Shifts in haematology, blood chemistry, and coagulation laboratory parameters were generally consistent with the reported AE profile of ide-cel across the target dose levels of 150 to 450 x 10^6 CAR+ T cells and were also generally consistent with the reported frequencies of hematologic AEs, except for leukopenia, which was reported as a Grade 4 AE for 28.1% of subjects. These laboratory findings can be considered expected in the current study population consisting of heavily pre-treated patients. There was no specific safety concern related to laboratory data presented.

No relevant pharmacodynamic biomarkers for safety have been identified. However, the development of PD biomarkers for safety and efficacy is considered to be of prime importance and further work on this recommended.

Except for CRS (female 23.6% versus 13.4% in male), there were no notable differences in the frequency of subjects with Grade 3 or 4 AEs and SAEs for female and male subjects. In general, based on the experiences so far, there seems to be no specific safety concern related to age groups. It is agreed though, that the number in subgroup ≥85 is very limited. Furthermore, the interpretation of safety in subjects in the 75- to < 85-year-old subgroup (N = 5) is limited, and it is difficult to make meaningful comparisons with the other age subgroups; thus, the results in this specific age subpopulation should be interpreted with caution.

The data set available is too small to look for trends in other race groups. As well, data are too few to look for trends in subjects being not anti-CD38 antibody refractory at baseline.

Human immunodeficiency virus (HIV) and the lentivirus used to make ide-cel have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received ide-cel. This is reflected in the SmPc section 4.4 with the subheading "Interference with serological testing".

The SmPC includes: *The safety of immunisation with live vaccines during or following Abecma treatment has not been studied. Vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during ide-cel treatment, and until immune recovery following treatment with ide-cel.*

AEs in retreated subjects

There is limited experience of retreating patients with a second dose of Abecma. Responses after Abecma retreatment were infrequent and less durable when compared to initial treatment. Additionally, fatal outcomes were observed in retreated patients. this has been added as a warning in the SmPC.

Immunogenicity

ADAs are likely to be induced by the ide-cel construct in patients, since a murine BCMA-binding site is a central part.

Available data suggest that the impact of pre-existing ADAs on cellular expansion is limited. However, a substantial number of patients generated post-infusion ADAs towards ide-cel (after three and monitored up to twelve months). At month 12, the fraction of patients present with ADAs were 62.1% in the MM-001 study and 80% in the CRB-401-study.

Results showed that exposures (AUC0-28days; AUC0-3 months) were very similar between ADA-positive and ADA-negative subjects. In addition, most antibodies were generated after about three months (both studies) and the majority of CAR+T cell expansion occurred in the first month after infusion. This may suggest that formation of ADAs following ide-cel infusion has limited impact on CAR+T cell expansion after the first infusion.

Potential impact of ADA's on efficacy is not clear. Particularly since there is a substantial time lag from administration to onset of immunresponses, impact on cellular expansion would be limited. However, negative impact on ide-cell persistence and long-term outcome cannot be ruled out. Furthermore, updated analysis indicate blunting of ide-cell expansion and tumour response in subjects that are ADA positive when receiving a second administration of ide-cell.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

In conclusion, the patient population consists of heavily pre-treated R/R MM patients who have previously been exposed to a wide range of available therapies. The efficacy assessment mainly relies on one pivotal single arm study with 128 ide-cel-treated patients. Based on baseline characteristics, the patients represent a very special population of MM patients being younger and having good performance status and hence the representativeness of the safety data for the actual, less fit and older patient population remain unknown. The long term follow up study GC-LTFU-001 together with post-authorisation safety study (PASS), BB2121-MM-006 will collect relevant data on safety to complete the safety profile of the product.

Additional safety data needed in the context of a conditional MA

The imposed specific obligations in the frame of the conditional Marketing Authorisation will provide further efficacy data and will also collect further long-term safety data for the product.

2.6.2. Conclusions on the clinical safety

The safety profile is consistent with the mechanism of action and what is known for other CAR+ T cell products. The main concerns are CRS, neurotoxicity, cytopenias and infections. The overall frequency of CRS increased with increasing dose, the frequency of Grade 3 or higher CRS was low and similar across the target dose levels of 300 to 450 x 10^6 CAR+ T cells. The frequency of subjects with neurologic toxicity (focused) Grade 3 or 4 was also low, and dose-dependent. In general, AEs were reported at higher frequencies in the first 8 weeks after ide-cel infusion compared with > 8 weeks after ide-cel infusion, with some exceptions such as infections and hypogammaglobulinaemia.

Overall, the AEs were generally manageable across the dose range of 150 to 450 x 10^6 CAR+ T cells with management guidelines proposed for the SmPC and additional risk minimisation measures in the RMP for CRS and neurotoxicity including a controlled distribution programme with educational programme at all treatment sites and a patient educational programme.

The CAT considers the following measures necessary to address issues related to safety:

- In order to further characterise the long-term efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol. Interim reports to be submitted in accordance with the RMP. Final report expected by 30 September 2042.

The CAT considers the following measures necessary to address the missing safety data in the context of a conditional MA under exceptional circumstances:

- In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH should submit 24 months post-Abecma infusion follow-up data (in the enrolled and treated population) of the pivotal study KarMMa (MM-001). Expected date for submission is 31 December 2021.
- In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH should submit the results of the Phase 3 study KarMMa-3 (MM-003) comparing the efficacy and safety of Abecma vs. standard triplet regimens in subjects with relapsed and refractory multiple myeloma. Expected date for submission is 30 June 2023.

The CHMP endorse the CAT conclusion on clinical safety as described above.

2.7. Risk Management Plan

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Cytokine release syndrome	**Routine Risk Minimisation Activities:** SmPC Sections 4.2 and 4.4, PL Sections 2 and 3 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** • Educational programme for HCPs and patients • Controlled distribution programme	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire **Additional pharmacovigilance activities:** Post-authorisation safety study (BB2121-MM-006)
Neurologic toxicity	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 and 4.7, PL Section 2– warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** • Educational programme for HCPs and patients • Controlled distribution programme	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire **Additional pharmacovigilance activities:** Post-authorisation safety study (BB2121-MM-006)
Cytopenias	**Routine Risk Minimisation Activities:** SmPC Section 4.4, PL Sections 2 and 4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Post-authorisation safety study (BB2121-MM-006)
Hypogammaglobulinaemia	**Routine Risk Minimisation Activities:** SmPC Sections 4.4 and 4.6 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Post-authorisation safety study (BB2121-MM-006)

Infections	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 and PL Sections 2, 3 and 4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** • Educational programme for HCPs (need to coordinate ide-cel thawing and its infusion) • Controlled distribution programme	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Post-authorisation safety study (BB2121-MM-006)
Important Potential Risk		
Secondary malignancies	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings, advice and management discussed Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire. **Additional pharmacovigilance activities:** Post-authorisation safety study (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable
Tumour lysis syndrome	**Routine Risk Minimisation Activities:** Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Post-authorisation safety study (BB2121-MM-006)
Aggravation of graft versus host disease	**Routine Risk Minimisation Activities:** SmPC Section 4.4 and PL Section 2 – warnings, advice and management discussed Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Included under the category of Other AEs considered related to ide-cel treatment in PASS (BB2121-MM-006)
Generation of replication competent lentivirus	**Routine Risk Minimisation Activities:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

	Additional Risk Minimisation Activities: None proposed	None proposed. **Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001)
Immunogenicity	**Routine Risk Minimisation Activities:** SmPC Section 4.2 and PL Section 3 – premedication with paracetamol and diphenhydramine or another H_1-antihistamine SmPC Section 4.8 – listed as an ADR **Additional Risk Minimisation Activities:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** None proposed.
Missing Information		
Impact on pregnancy and lactation	**Routine Risk Minimisation Activities:** SmPC Section 4.6 and PL Section 2 – warnings, advice and management discussed Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Post-authorisation safety study (BB2121-MM-006) for pregnancy events
Long-term safety	**Routine Risk Minimisation Activities:** SmPC Annex II – long-term registry discussed Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Post-authorisation safety study (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001)
Safety in elderly patients (≥ 75 years)	**Routine Risk Minimisation Activities:** SmPC Section 4.2 – No dose adjustment necessary Ide-cel is administered by an HCP **Additional Risk Minimisation Activities:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** None proposed.

The CHMP, CAT and PRAC considered that the risk management plan version 0.9 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP and CAT considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26 March 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that idecabtagene vicleucel has not been previously authorised in a medicinal product in the European Union.

The CAT/CHMP, based on the available data, considers idecabtagene vicleucel to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons.

The applicant requested the omission of certain particulars on the outer (metal cassette) and immediate (infusion bag) packaging. On the outer packaging the Group accepted omissions pertaining to the statements to keep the medicinal product out of the sight and reach of children, and to see the leaflet for further information, the inclusion of the strength as part of the active substance, and the pharmaceutical form. The omissions of strength and pharmaceutical form could be accepted as both elements can be found as part of section 1 of the labelling. The Group accepted omissions on the immediate packaging related to the active substance, excipients, pharmaceutical form and warning statements in line with the omissions on the outer packaging, in addition to a warning on irradiating the product. The Group did not accept requests to omit warnings on the use of leukodepleting filters, and the special precautions for disposal which reflect the need to comply with the local guidelines on handling of waste of human-derived material.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The applicant requested the Release for infusion certificate (RFI), which is part of Annex IIIA, to be provided in English only. The QRD group concluded that the proposal was acceptable based on the orphan status of the product, operational challenges linked to the translation the document into multiple languages, and the fact that the product will only be administered in qualified treatment centres by specialised and trained healthcare professionals.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Abecma (idecabtagene vicleucel) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is a biological product that is not covered by the previous category and authorised after 1 January 2011;
- It has a PASS imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)];
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The present application concerns the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

MM is a incurable blood cancer characterised by the clonal proliferation of malignant plasma cells both within the bone marrow (BM) and at localised extramedullary sites. Despite progress in its current treatment, MM remains largely incurable and in a such multiple relapsed disease, refractoriness to several drug classes represents a major therapeutic challenge. The aim of the treatment is to achieve deep and durable responses that extend patient survival and afford the opportunity for treatment-free intervals and improved quality of life.

3.1.2. Available therapies and unmet medical need

The treatment landscape for relapsed/refractory MM has changed in recent years. Since the beginning of 2015, 8 relapsed/refractory MM indications (all for regimens evaluated in second or third line) have been approved for 6 products (including panobinostat, carfilzomib, ixazomib, daratumumab, pomalidomide, and elotuzumab) through the centralised procedure. In addition, an MA has recently been granted for Blenrep and for Nexpovio in the 5th line RRMM indication.

For relapsed/refractory MM patients with second or subsequent relapses, ESMO-recommended options are a triplet regimen based on a backbone of pomalidomide and dexamethasone (Pd) (plus bortezomib, cyclophosphamide, daratumumab, elotuzumab, or ixazomib), daratumumab (single agent or in combination), or enrollment in a clinical trial.

In relapsed/refractory MM patients exposed to multiple prior AMTs, or refractory to major classes of AMT, the disease is life threatening and is associated with low response rates, short DoR, and poor survival. Thus, there is an unmet medical need for more treatment options capable of achieving deep and durable responses.

3.1.3. Main clinical studies

The pivotal data comes from an open-label, uncontrolled, multicentre, multinational, Phase 2 study (MM-001), evaluating the efficacy and safety of ide-cel in subjects with RRMM who had received at least 3 prior regimens including an immunomodulatory agent, a PI, and an anti-CD38 antibody, and who were refractory to their last prior treatment regimen (N=140). The study consisted of 3 stages: pre-treatment (screening, leukapheresis, and bridging therapy [if administered]), treatment (LDC and ide-cel infusion) and posttreatment (post-ide-cel infusion). Experimental agents and myeloma therapies to which the subject had not been previously exposed were not to be used as bridging therapy. A new baseline evaluation including disease restaging was performed within 72 hours of initiating LDC. Ide-cel was administered across a dose range of 150 (N=4), 300 (N=70) and 450 (N=54) x 10^6 CAR+ T cells, with the highest dose level being added through a protocol amendment, due to emerging dose response data in the dose finding study, CRB-401.

The primary endpoint was ORR per IRC according to the IMWG response criteria. Secondary endpoints included CR rate (key secondary), TTR, DoR, PFS, OS, MRD and HRQoL. The applicant defined the ide-cel infused patient population as the primary analyses population, whereas for the purpose of this assessment the main focus was put on the enrolled (ITT) population. Data were reported based on a primary data cutoff of 16th Oct 2019. Two updates based on later data cutoffs were also provided (14th Jan 2020 and 7th April 2020).

The cut-off defining study success was set at ORR >50%, based on the observed activity of daratumumab in triple exposed/double refractory RRMM patients, reporting response rates ranging from 29% to 36%. Contextualisation of the data was provided in terms of an adjusted, indirect treatment comparisons to an external control arm, based on a global, non-interventional, retrospective study (NDS-MM-003, N=190). In addition, a SLR was provided to further understand the efficacy of ide-cel in the context of the current treatment landscape.

The supportive Study CRB-401 was nonrandomised, open-label, multicentre Phase 1 study. Part A (dose escalation) enrolled subjects who had received at least 3 prior lines of AMT, including an immunomodulatory agent and a PI, or were double-refractory to an immunomodulatory agent and a PI (N=24). Part B (expansion) the ide-cel target dose levels were from 150 to 450 x 10^6 CAR+ T cells and the enrolled subjects had received an immunomodulatory agent, a PI, and daratumumab, and were refractory to their last line of therapy (N=43).

3.2. Favourable effects

The pivotal study (MM-001) met its primary endpoint with an ORR of 67.1% (95% CI: 59.4, 74.9 ($p < 0.0001$)) across the target dose levels in the enrolled population. For the individual doses, the point estimate for ORR increased with each dose level, with an ORR of 50% (95% CI: 6.8, 93.2) for the 150 x 10^6 dose, 68.6% (95% CI: 56.4, 79.1) for the 300 x 10^6 dose, and 81.5% (95% CI: 68.6, 90.7) for the 450 x 10^6 dose.

The benefit of ide-cel was supported by the secondary endpoints, with a CR rate in the enrolled population (CR or better, key secondary endpoint) of 28.6% (95% CI: 21.1, 36.1), rejecting the null hypothesis of $\leq$ 10%.

At the latest data cut off (07 April 2020), across the three dose levels, the median DoR was 10.6 months (95% CI: 8.0, 11.4) among the 94 ide-cel responders. The median PFS was 8.3 months (95% CI: 6.7, 12.0) in the overall population and 12.1 months at the target dose of 450 x 10^6 CAR+ T cells). The median OS was 21.4 months (95% CI: 19.3, NE) in the overall population, and at the target dose of 450 x 10^6 CAR+ T cells, the median OS was NE (95% CI: NE, NE).

The response rates were generally consistent across various evaluable subgroups, with the majority of subgroups achieving a lower limit of the 95% CI above the pre-specified historical control ORR of 50% (infused population).

3.3. Uncertainties and limitations about favourable effects

The inclusion criteria defined a rather selected patient population with RRMM, including only patients with a PS of 0-1 and no major co-morbidities or organ dysfunction. While the exclusion of such patients is understood from a safety perspective, it affects the external validity of the trial and complicates the contextualisation with external data.

The lack of a comparator arm in MM-001 makes it difficult to determine the true effect size with respect to ORR, and the interpretation of time-to-event endpoints is intrinsically limited. The representativeness of the historical control rate for the ORR cutoff defining study success is uncertain, considering the strict inclusion criteria imposed in the pivotal trial. Furthermore, although adjusted comparisons were conducted against an external control arm, several uncertainties remain as to the representativeness of the historical cohort for the study population in MM-001.

The limited sample size (N=140), to some extent precludes interpretation of subgroup analyses. Furthermore, the somewhat short duration of follow up (median of 17 months for OS at the latest DCO), lends uncertainty to the long-term OS data. To what extent the observed responses will be reflected in long term OS benefit is not known. Data on less refractory patients are limited i.e only 16.4% (n=23) were mono or double refractory. The greater availability and benefit of SOC options in these less refractory patients, introduces uncertainty as to the true magnitude of the effect size, as robust comparative data on the benefit of ide-cel vs SOC in this population are lacking. These remaining uncertainties will be addressed by the confirmatory controlled MM-003 study included as a SOB to the CMA.

The B/R of retreatment with ide-cel is uncertain, as the responses reported in the re-treated population were infrequent (5 PR and one VGPR reported in 29 retreated patients in study MM-001), and a limited PFS was observed. Particularly, in ADA positive retreated patients, the B/R appears negative, considering the safety profile, and lack of responses. A warning has been included in the SmPC.

3.4. Unfavourable effects

The main safety concerns are related to CRS, neurological toxicity, cytopenias and infections.

CRS occurs in the first days following treatment, median time to onset was 1.0 day (range: 1 to 17) and the median duration was 5.0 days (range: 1 to 63), with median time to onset shorter for the highest dose level. There was a higher frequency in Grade $\geq$3 with the higher dose levels of 300 and 450 x 10^6 CAR+T cells compared to 150 x 10^6 CAR+T cells (0%, 5.7%, and 5.6%), but the frequencies at the highest dose levels are indeed low. The one subject with Grade 5 CRS (fatal) received a dose of 300 x 10^6 CAR+T cells. Other cases were all reversible with use of the management guide, including treatment with tocilizumab and/or corticosteroids or other interleukin receptor antagonists like anakinra or silituximab.

Neurotoxicity identified by the investigators, which was the primary method of assessing CAR T cell-associated neurotoxicity in the KarMMa study only, occurred in 18.0% of the 128 patients receiving Abecma, including Grade 3 in 3.1% of patients (with no Grade 4 or 5 events). The median time to onset of the first event was 2 days (range: 1 to 10). The median duration was 3 days (range: 1 to 26). There was an increase in frequency of Grade 3 or higher events with increased dose levels; 0%, 2.9%, and 9.3% across the target dose levels of 150, 300, and 450 x 10^6 CAR+ T cells, respectively. The neurological AEs seem to be reversible with use of the management guide including treatment with tocilizumab, corticosteroids or anakinra.

Almost all patients in the pivotal study (96.9%), had cytopenia first 8 weeks and most of them were of Grade 3 or 4, none of Grade 5. After first 8 weeks, 50% still had cytopenias, of which 35.2% were of Grade 3 or 4. No cases of Grade 5 cytopenia were reported, but several subjects had persistent neutropenia and/or thrombocytopenia at death or lost to follow up. There was no clear dose dependent increase in frequency of cytopenia with increasing dose across the targeted dose levels of 300 and 450 x 10^6. Cytopenias were managed primarily with the use of CSFs, RBC transfusions, and platelet transfusions. Infections are usually a complication to cytopenias and was observed in 70.7% for any grade, 21.2% for Grade 3 or 4, and 2.7% for Grade 5.

In addition, Hypogammaglobulinaemia was reported in 19.6% of patients treated with Abecma in the pooled studies with a median time to onset of 100 days (range 15 to 326). 4 cases of Macrophage Activation Syndrome and one case of Tumour Lysis Syndrome were seen.

Secondary malignancies were reported for 17 (9.2%) of patients in the pooled analysis. Particularly the incidence of basal cell carcinomas (n=7) was high. No secondary malignancies from insertional oncogenesis have been reported after ide-cel infusion, including initial infusion and retreatment, as of the data cutoff date of 07 Apr 2020.

In the pivotal study, 34 (26.6%) deaths were reported. Of the 34 deaths, 25 deaths occurred after initial ide-cel infusion and 9 deaths occurred after ide-cel retreatment. Most of the 34 deaths were related to malignant disease under study or complication due to malignant disease under study (24 [18.8%]) and 6 deaths (4.7%) due to AE. Frequencies and severity of AEs were in general higher among subjects >65 years of age compared to younger.

Overall, the safety profile is similar to other CAR-T products as to main AEs observed, severity and seriousness. The frequency may be a bit different, but that can also be related to different indications.

3.5. Uncertainties and limitations about unfavourable effects

Safety assessment is based on a single arm study. The patient population enrolled is highly selected: relatively young and fit, yet heavily pre-treated and largely refractory to other treatments. This raises concerns about generalizability of the safety results to real world RRMM patient population.

Main limitations for the safety assessment are that few subjects are included (184 subjects) and the majority of subjects included are <65 years of age (median age 61 years), meaning that the safety assessment of the target population is based on very few subjects. This means that only common AEs have been detected. A registry study (BB2121-MM-006) is proposed to further characterise the incidence and severity of selected ADRs.

The follow-up time is short 15.5 months, meaning that long-term safety cannot be assessed. This is particularly important for the observed long-term toxicities. These include:

- The persistent cytopenias, particularly neutropenia
- The long-lasting neurotoxicity
- Secondary malignancies

A 15 years follow-up of patients that have been included in the clinical trials (Long-term follow-up study GC-LTFU-001) are proposed together with the registry study (BB2121-MM-006) to monitor long-term safety..

The bridging therapies, and more importantly LDC, will lead to AEs that cannot be separated from those resulting from ide-cel infusion.

3.6. Effects Table

Table 38: Effects Table for Abcma/Becmya, for the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody (data cut-off 7 April 2020)

Effect	Short Description	Treatment	Result	Uncertainties/ Strength of evidence
Favourable effects				
ORR (%)	Percentage of subjects who achieved PR or better as assessed by an IRC according to IMWG uniform response criteria for multiple myeloma.	150 x 10^6 CAR+T cells n=4	2 (50.0%)	No control arm. Patients were not randomised to the different dose cohorts.
		300 x 10^6 CAR+T cells n=70	48 (68.6%)	
		450 x 10^6 CAR+T cells n=54	44 (81.5%)	
		150-450 x 10^6 CAR+T cells n=128 Ide-cel treated pop.	94 (73.4%) (95% CI: 65.8, 81.1) *	
		Enrolled pop. n= 140	94 (67.1%) (95% CI: 59.4, 74.9)	*p < 0.0001, 1-sample binomial test rejecting the null hypothesis of ⩽ 50% for ORR [and ⩽ 10% for CR rate]
CR (%)	Percentage of subjects who achieved CR or sCR as assessed by an IRC according to IMWG uniform response criteria for multiple myeloma.	150-450 x 106 CAR+T cells n=128 Ide-cel treated pop.	42 (32.8%)* (95% CI 24.7, 40.9)	
		Enrolled pop. n= 140	42 (30.0%) (95%CI 22.4,37.6)	
DOR, (median, months) -EMA censoring	Time from first documentation of response of PR or better to first documentation of disease progression or death from any cause, whichever occurred first.	150-450 x 10^6 CAR+T cells n=128 Idecel treated pop.	10.6 (95% CI 8.0, 11.4)	
		Enrolled pop. n= 140	10.6 (95% CI 8.0, 11.4)	
Unfavourable effects pooled analysis MM-001 and CRB-401				

Effect	Short Description	Treatment	Result	Uncertainties/ Strength of evidence
Favourable effects				
CRS		150 - 450 x 10^6 CAR+T cells N=184	81.0% Grade ≥ 5.4%	Few subjects with dose 150 x 10^6 CAR+T cells
Neurologic toxicity - "focused" Neurologic toxicity – "broad"		150 x 450 10^6 CAR+T cells N=184 150-450 x 10^6 CAR+T cells N=184	41.8% 73.4%	Few subjects with dose 150 x 10^6 CAR+T cells Two other ways of recording neurotoxicity have been used
Cytopenias		150 – 450 x 10^6 CAR+T cells n=184	95.7% Grade ⩾3: 95.1%	Few subjects with dose 150 x 10^6 CAR+T cells
Infections		150 – 450 x 10^6 CAR+T cells n=184	71.2% Grade ⩾3: 23.4%	Few subjects with dose 150 x 10^6 CAR+T cells
Secondary malignancy		150 - 450 x 10^6 CAR+T cells n=184	8.7%	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

MM remains incurable, with significant therapeutic challenges in subjects with multiple relapsed/refractory disease. As such this patient population has a clear unmet medical need for novel therapies. Across the target dose-levels, ide-cel demonstrated a significant anti-tumour activity, with an ORR of 67.1% (95% CI: 59.4, 74.9) and CR 30.0 % (95% CI 22.4, 37.6). This is well above, the pre-specified ORR cutoff for study success, as well as the response rates reported with current standard of care in the RWS and in the literature (32% ORR with recently approved belantamab mafodotin). Responses were durable (median DoR of 10.6 months), with ongoing responses observed in 29 of the 94 responders at the last data cutoff. Again, this compares favourably to that observed with current standard of care and is considered clinically meaningful in this heavily pre-treated patient population.

The main uncertainties regarding the benefit/risk assessment relate to the non-comparative nature of the data, and the limited sample size, in addition to a somewhat short duration of follow-up, especially for OS.

Contextualisation of the effect is challenging. The robustness of the adjusted indirect treatment comparison based on the RWS is difficult to verify, considering the rather selected study population, and the missing data of several important prognostic factors. Thus, although the ORR/DoR benefit is

considered sufficiently compelling in the context of a single arm trial, the true magnitude of the treatment effect, including to what extent the observed responses will be reflected in long term benefit in OS, cannot be reliably ascertained. Data on less refractory patients are limited i.e only 16.4% (n=23) were mono or double refractory. The greater availability and benefit of SOC options in these less refractory patients introduces uncertainty as to the true magnitude of the effect size, as robust comparative data on the benefit of ide-cel vs SOC in this population are lacking. Due to these deficiencies, the clinical data package is not considered comprehensive and a formal request for a CMA was submitted.

The B/R of retreatment is uncertain since the responses reported in the retreated patients were infrequent with limited PFS. Particularly, in ADA positive patients, the B/R appears negative, considering the safety profile, and lack of responses. A warning has been included in the SmPC.

Overall, the AEs observed are anticipated toxicities consistent with the mechanism of action of CAR T cell therapies with main safety concerns related to CRS, neurological toxicity, cytopenias and infection. There was a higher frequency in Grade ≥3 of CRS and neurological toxicity with the higher dose levels of 300 and 450 x 10^6 CAR+T cells compared to 150 x 10^6 CAR+T cells (CRS: 0%, 5.7%, and 5.6%, neurological toxicity: 0%, 2.9%, and 9.3%). There are few subjects treated with the lowest dose of 150 x 10^6 CAR+T cells, in particular in the pivotal study, bringing some uncertainties in the interpretation of safety profile at this dose level. With proper use of management guidance and use of proposed additional risk minimisation measures (controlled distribution programme including HCP educational programme and a patient educational programme), these safety concerns are considered adequately manageable across all dose levels.

Main limitations for the safety assessment is that few subjects are included (184 subjects) and the majority of subjects included are <65 years of age, meaning that the safety assessment of the target population of MM is based on very few subjects. Based on the number of subjects exposed, only common AEs have been detected. A non-interventional, post authorisation, registry-based study (BB2121-MM-006) is proposed to further characterise the incidence and severity of selected ADRs.

The short follow-up time means that long-term safety cannot be assessed. A 15 years follow-up of patients that have been included in the clinical trials (Long-term follow-up study GC-LTFU-001) are proposed together with the registry study (BB2121-MM-006) to monitor long-term safety.

3.7.2. Balance of benefits and risks

Ide-cel treatment lead to a compelling ORR, substantially higher than the pre-specified ORR cutoff as well as the response rates reported with current standard of care in the RWS and in the literature. Responses are considered durable.

Uncertainty remains with reference to the true magnitude and duration of the treatment effect, which cannot be reliably ascertained based on the uncontrolled data. Furthermore, the limited follow-up especially for OS in the highest target dose cohort, preclude the characterisation of the long-term effects. Data on less refractory patients (i.e mono or double refractory only) are limited and the greater availability and benefit of SOC options in these less refractory patients introduces uncertainty as to the true magnitude of the effect size.

Due to these deficiencies, the clinical data package is not considered comprehensive and a CMA is proposed.

Limited data indicating efficacy may be substantially reduced at the lowest dose level (150 x 10^6 CAR+ T-cells), and a positive B/R for this dose cannot be concluded. Therefore, the 150 x 10^6 CAR+ T cell dose level was excluded from the label.

The safety profile seems to be similar to what is known for other products in the same class. Management guidelines used in the clinical trials have shown to manage the serious AEs adequately at the dose levels proposed. Management guidelines for CRS and neurological toxicity and close monitoring of patients in the SmPC and additional risk minimisation measures (controlled distribution programme including HCP educational programme and a patient educational programme) have been proposed to manage serious AEs in clinical practice. Studies are proposed to further characterise the incidence and severity of selected ADRs and long-term safety.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product is not available, a conditional marketing authorisation was proposed, and the applicant submitted a formal request for a CMA in accordance with Article 14-a of the above-mentioned Regulation. The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Furthermore, it is considered that the product fulfils the requirements for a conditional marketing authorisation, as follows:

- The benefit/risk is considered positive in a patient population consistent with the MM-001 study population. Ide-cel has a mechanism of action that is different from that of authorised treatments and has been shown to be associated with a 67.1% objective response rate and a median duration of response of 10.6 months in this group of highly pre-treated patients. The toxicity profile of Abecma is largely in line with the known adverse effect profile of products in the same class. The main safety concerns are cytokine release syndrome, cytopenias and neurotoxicity, and the treatment is tolerated when adverse effects are closely monitored and actively managed.

- It is likely that the applicant will be able to provide comprehensive data by post-approval specific obligations as follow:

- In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH should submit 24 months post-Abecma infusion follow-up data (in the enrolled and treated population) of the pivotal study KarMMa (MM-001). Expected date for submission is 31 December 2021.
- In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH should submit the results of the Phase 3 study KarMMa-3 (MM-003) comparing the efficacy and safety of Abecma vs. standard triplet regimens in subjects with relapsed and refractory multiple myeloma. Expected date for submission is 30 June 2023.

In the ongoing randomised study (MM-003), ide-cel is compared to SOC triplet regimens in an overlapping patient population i.e. relapsed and refractory MM with 2-4 prior therapies and this study is considered to be suitable as a specific obligation to the CMA. As of 06 Jan 2021, 261 subjects have

been randomised, and patient enrolment is currently targeted to be completed by Q2 2021. Thus, a CMA granted 2021 would most probably not interfere with completion of this phase 3 study and data can be expected to be available within an appropriate timeframe. Updated efficacy and safety data (24 months after the last subject has received ide-cel) from the ongoing Study BB2121-MM-001 will also be provided as a SOB to the CMA.

- An unmet medical need exists in the target MM population, as available therapies in this setting offer limited clinical benefit. Current therapies in the RRMM setting aim to achieve durable disease control/remission but are not curative. Almost all patients eventually relapse and become resistant to available treatments, where the remission duration generally decreases with each subsequent treatment regimen, and where the toxicity of different regimens is significant and quite different between products. In this context, medicinal products with a positive benefit-risk balance and new mechanism of action can provide a major therapeutic advantage to patients if they offer possible alternative or additional treatment options based on a different safety profile, or based on therapeutic efficacy.

Recently approved products for RRMM include lenalidomide, pomalidomide, bortezomib, carfilzomib, ixazomib, panobinostat, daratumumab, isatuximab, and elotuzumab. All of these treatments are set from first line to second line or beyond also in different combinations. Belantamab mafodotin was recently granted a CMA for treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is triple refractory and who have demonstrated disease progression on the last therapy. Selinexor recently received a positive opinion (CMA) for use in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody.

Refractoriness to prior therapies largely defines the available treatment options for RRMM patients in late line setting in which several different treatment combinations may be used. Although indirect comparisons of efficacy are challenging in this heterogeneous population, based on high response rate and durability of responses, ide-cel can be considered to address the unmet medical need to a similar or greater extent than other approved medicinal products.

Abecma has a mechanism of action that is different from that of authorised treatments and has shown to be associated with a 67% objective response rate and a median duration of response of 10.6 months in this group of highly pre-treated patients who received at least three classes of agents. Abecma has a distinct toxicity profile including significant toxicities like cytokine release syndrome (CRS), neurological toxicity, cytopenias and infections. Adverse effects of idecabtagene vicleucel are mostly clinically manageable and considered reversible. The pivotal study population was heavily pre-treated (median 6 prior therapies 6, 84% were triple refractory), nonetheless the response rates achieved with ide-cel in less refractory small population included in study MM-001 seem compelling leading to the proposed indication only requiring prior exposure to an immunomodulatory agent, a PI, and an anti-CD38 antibody and that patients have progressed on the last treatment. The MM-003 study is also expected to enrol patients who are less refractory (ie, mono- or double-refractory only), allowing for a more robust assessment of the efficacy and safety of ide-cel in these patients when compared to SOC.

Therefore, Abecma can be considered a major therapeutic advantage and will fulfil an unmet medical need in the approved indication as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least three prior therapies including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy.

-The benefit-risk assessment supports that the benefits to public health of the immediate availability of ide-cel in the proposed indication would outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall B/R of Abecma is positive.

The CHMP endorse the CAT conclusion on Benefit Risk balance as described above.

4. Recommendations

Similarity with authorised orphan medicinal products

The CAT/CHMP by consensus is of the opinion that Abecma (idecabtagene vicleucel) is not similar to Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro and Blenrep within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CAT review of data on quality, safety and efficacy, the CAT considers by consensus that the benefit- risk balance of Abecma is favourable in the following indication:

Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy.

The CAT therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Based on the draft CHMP opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit- risk balance of Abecma in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Availability of tocilizumab and site qualification via the controlled distribution programme

The MAH will ensure that hospitals and their associated centres that dispense Abecma are qualified in accordance with the agreed controlled distribution programme by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Abecma infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.
- healthcare professionals (HCP) involved in the treatment of a patient have completed the educational programme.

Educational programme

Prior to the launch of Abecma in each Member State, the MAH must agree on the content and format of the educational materials with the National Competent Authority.

HCP educational programme

All HCPs who are expected to prescribe, dispense and administer Abecma shall be provided with a healthcare professional guide, which will contain information about:

- identification of CRS and serious neurologic adverse reactions;
- management of the CRS and serious neurologic adverse reactions;
- adequate monitoring of CRS and serious neurologic reactions;
- provision of all relevant information to patients;

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Abecma infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose;
- contact details for tumour sample testing after development of a secondary malignancy of T cell origin;
- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study;
- ensure that adverse reactions are adequately and appropriately reported;
- ensure that detailed instructions about the thawing procedure are provided.

Patient educational programme

All patients who receive Abecma shall be provided with a patient card, which will contain the following key messages:
- the risks of CRS and serious neurologic adverse reactions associated with Abecma;
- the need to report the symptoms of suspected CRS and NT to their treating doctor immediately;
- the need to remain in the proximity of the location where Abecma was received for at least 4 weeks following Abecma infusion;
- the need to carry the patient card at all times;
- a reminder to patients to show the patient card to all HCPs, including in conditions of emergency and a message for HCPs that the patient is using Abecma;
- fields to record contact details of the prescriber and batch number.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Interim reports to be submitted in accordance with the RMP. Final report: Q3 2042

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH should submit 24 months post-Abecma infusion follow-up data (in the enrolled and treated population) of the pivotal study KarMMa (MM-001).	December 2021

Description	Due date
In order to confirm the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, the MAH should submit the results of the Phase 3 study KarMMa-3 (MM-003) comparing the efficacy and safety of Abecma vs. standard triplet regimens in subjects with relapsed and refractory multiple myeloma.	June 2023

New Active Substance Status

Based on the CAT review of the available data, the CAT considers that idecabtagene vicleucel is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

The CHMP endorse the CAT conclusion on the new active substance status claim.