TITLE PAGE

Title	Non-interventional post-authorization safety study (PASS) of patients treated with idecabtagene vicleucel (ide-cel, bb2121) for multiple myeloma (MM) in the postmarketing setting
Protocol version identifier	BB2121-MM-006 (also known as CA089-P11)
Date of protocol version	24 Nov 2021
EU PAS register number	To Be Confirmed
Active substance	idecabtagene vicleucel (ide-cel, bb2121)
Medicinal product	Abecma®
Product reference	EU/1/21/1539/001
Procedure number	EMEA/H/C/004662
Marketing authorisation holder(s) (MAH)	Bristol-Myers Squibb Pharma EEIG
Joint PASS	No
Research question and objectives	Primary Objective • To characterize the incidence and severity of selected adverse drug reactions (ADRs), as outlined in the Summary of Product Characteristics (SmPC), in patients treated with ide-cel in the postmarketing setting and to monitor for potential clinically important adverse events (AEs) that have not yet been identified as part of the ide-cel safety profile. Secondary objective • To assess survival in patients treated with ide-cel in the postmarketing setting.

Country(-ies) of study	United States (US); European countries; other countries may be included
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MAH contact person	[redacted]

SIGNATURE PAGE

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Signature of Celgene [redacted]

[redacted]

Printed Name of Celgene [redacted]

Date Signed _____

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Signature of Celgene [redacted]

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Printed Name of [redacted]

Date Signed _____

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADAM	Analysis Data Model
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
AMT	Antimyeloma therapy
ASCT	Autologous stem cell transplantation
auto	Autologous
BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CIC	Center Identification Code
CLL	Chronic lymphocytic leukemia
Clopp Pears	Clopper Pearson
CR	Complete response
CRF	Case Report Form
CRID	CIBMTR Research Identification
CRS	Cytokine release syndrome
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FN3	FormsNet3
GPP	Good Pharmacoepidemiology Practice

Abbreviation	Definition
GVHD	Graft-versus-host disease
HCP	Health care professional
HCT	Hematopoietic cell transplantation
IARC	International Agency for Research on Cancer
ICF	Informed consent form
IS	Infused Set
IV	Intravenously
KM	Kaplan-Meier
LDC	Lymphodepleting chemotherapy
LVV	Lentiviral vector
MAA	Marketing Authorization Application
mAbs	Monoclonal antibodies
MAH	Marketing authorisation holder
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHA	Master Healthcare Data Agreement
MM	Multiple myeloma
MoA	Mechanism of action
M-protein	Monoclonal protein
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin lymphoma
NMSC	Non-melanoma skin cancer
OOS	Out of specification
ORR	Overall response rate
OS	Overall survival
PASS	Post-authorization safety study
PBMCs	Peripheral blood mononuclear cells
Pd	Pomalidomide and dexamethasone
PFS	Progression-free survival
PIs	Proteasome inhibitors

Abbreviation	Definition
PSUR	Periodic safety update report
PT	Preferred term
PVP	Pharmacovigilance Plan
Q	Quarter
RMP	Risk Management Plan
RNA	Ribonucleic acid
R/R	Relapsed and/or refractory
SAP	Statistical analysis plan
scFv	Single chain variable fragment
SCT	Stem cell transplantation
SDTM	Study Data Tabulation Model
SEER	Surveillance, Epidemiology, and End Results
SES	Safety and Effectiveness Set
SmPC	Summary of Product Characteristics
SOC	System organ class
SPM	Second primary malignancy
TLS	Tumor Lysis Syndrome
UPN	Unique Patient Number
US	United States
USA	United States of America
WHO	World Health Organization

3. RESPONSIBLE PARTIES

This post-authorization safety study (PASS) is sponsored by Celgene, a Bristol Myers Squibb Company, hereinafter "Celgene", and represents a condition of the European Medicines Agency (EMA) marketing authorization application (MAA) for ide-cel in multiple myeloma (MM).

The study will include treatment centers across the United States (US), the European Union (EU) and other countries that have an agreement with existing independent registries, such as, but not limited to, the European Society for Blood and Marrow Transplantation (EBMT) and/or the Center for International Blood and Marrow Transplant Research (CIBMTR), allowing data to be transferred from the registry holder databases and to be shared with competent health authorities, marketing authorisation holder (MAH) and other parties in line with the signed informed consent forms.

The responsibilities of the different parties will be listed in study-specific documents.

Table 1: Information for Operational Inquiries

Sponsor:	Celgene International II Sàrl, Route de Perreux 1 2017 Boudry Switzerland [redacted]
Study Manager:	Celgene GMA Operations
Physician:	[redacted]

BMS= Bristol-Myers Squibb; GMA = Global Medical Affairs; NJ = New Jersey; USA = United States of America.

4. ABSTRACT

Title: Non-interventional post-authorization safety study (PASS) of patients treated with idecabtagene vicleucel (ide-cel, bb2121) for multiple myeloma (MM) in the postmarketing setting

Rationale and background:

The purpose of this study is to characterize the safety profile of ide-cel in the postmarketing setting.

This study will include patients from existing independent registries, such as, but not limited to, the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR).

Ide-cel, bb2121 is a genetically modified autologous T cell immunotherapy product consisting of T cells transduced with an anti-BCMA02 chimeric antigen receptor (CAR) lentiviral vector (LVV). Autologous T cells transduced ex vivo with the anti- BCMA02 CAR LVV express the anti-BCMA02 CAR on the T cell surface.

Potential adverse reactions, associated with ide-cel therapy, include cytokine release syndrome (CRS), neurotoxicity, cytopenias, infections, and secondary malignancies.

The BB2121-MM-006 study will be part of the overall ide-cel Risk Management Plan (RMP) including any required regional Pharmacovigilance Plan (PVP) outside the European Union (EU).

Objectives:

Primary Objective

- To characterize the incidence and severity of selected adverse drug reactions (ADRs), as outlined in the Summary of Product Characteristics (SmPC), in patients treated with ide-cel in the postmarketing setting and to monitor for potential clinically important adverse events that have not yet been identified as part of the ide-cel safety profile.

Secondary Objective

- To assess survival in patients treated with ide-cel in the postmarketing setting.

Study design:

This study is designed as a non-interventional cohort study that is part of multiple registries of patients with MM treated with ide-cel therapy in the postmarketing setting which includes patients treated with out of specification (OOS) product.

Data from a total of 1000 patients treated with ide-cel, including a minimum of 300 EU patients, will be collected until death, lost to follow-up, or withdrawal of consent, or up to 15 years, whichever occurs first. This study is expected to require up to 5 years to select the planned 1000 patients.

No comparison groups will be defined, and no inferential testing will be performed.

Study Endpoints

Incidence and severity of selected adverse drug reactions (ADRs) reported post ide-cel infusion:

Primary Safety Endpoint(s)

Incidence and severity of the following adverse events (AEs) reported post ide-cel infusion:

- All secondary malignancies
- Cytokine release syndrome (CRS) Grade ≥ 3
- Neurotoxicity Grade ≥ 3
- Prolonged cytopenias
- Pregnancy outcome
- Other AEs considered related to ide-cel treatment

Secondary Effectiveness Endpoint

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

Eligibility Criteria

All patients who meet the following eligibility criterion will be selected from the registries:

- Patient must have been treated with at least one infusion of ide-cel in the postmarketing setting. Patients treated with OOS product will also be eligible.

Analysis Populations:

Due to the observational nature of the study, no formal analysis populations such as intent to treat or a per protocol population can be defined. Instead, the term "analysis sets" will be used.

- **Infused Set (IS):** Is defined as all patients selected from the registry and meeting the above-mentioned eligibility criterion, where baseline and disease classification information is available.
- **Safety and Effectiveness Set (SES):** Is defined as all patients from the IS with information collected at least after 100 days.

Data to be collected:

The information recorded will include, but not be limited to, the following variables:

- Demographics (eg, age, sex, height, weight)
- Center where ide-cel treatment was received

- Information on the underlying disease
- Functional status / prognostic characterization (performance status)
- Prior therapy for the underlying disease
- Ide-cel administration
- Survival status
- Ide-cel-related AEs including neurotoxicity, CRS, prolonged cytopenias, and related treatments
- Information on any secondary malignancy
- Pregnancy outcome
- Next treatment(s) for the underlying disease

Study size justification:

Since this is a single-arm non-interventional cohort study with no comparisons and no statistical hypothesis testing, no formal powered sample size calculation is possible. Instead, based on pragmatic nonstatistical reasons, the approach taken is to use a fixed number of 1000 patients from registries, which is considered feasible within the estimated 5-year selection period. The sample size is justified by reporting the precision of assumed incidences corresponding to certain safety endpoints chosen as examples.

For the chosen sample size of 1000 patients, there would be a 95% chance to observe at least one event if the true incidence rate is equal to or above 0.3 event per year (using normal approximation according to Wald).

To justify the sample size, precision estimates for example incidences, taken from the literature, are provided by calculating exact 95% (Clopper Pearson) confidence intervals (based on a binomial distribution).

Assumed incidences for secondary malignancies were based on second primary malignancies (SPMs) data from Mahindra et al (Mahindra, 2015) and Costa et al (Costa, 2018). The incidences for CRS and neurotoxicity correspond to incidences reported as AEs of special interest (AESIs) by Raje et al (Raje, 2019) based on the CRB-401 trial (ClinicalTrials.Gov#: NCT02658929). The populations from these three sources are characterized as follows:

- **Mahindra et al population**: MM patients with an age range from 22 to 80 years and a first autologous stem cell transplantation (ASCT) within 18 months of MM diagnosis, reported to the CIBMTR between 1990 and 2010.
- **Costa et al population**: Three cohorts of patients with an age range from 19 to 64 years, with MM as first malignant neoplasm, reported to the Surveillance, Epidemiology, and End Results (SEER) between 1995 and 2009.
- **Raje et al population**: MM patients in the United States (US) with an age range from 37 to 75 years and an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.

Data Source	Description	# Patients	Observed Incidence	Incidence Proportion	Clopp Pears 95% CI Lower	Clopp Pears 95% CI Upper
(Mahindra, 2015)	overall SPMs *(1990-2010)* *excluding NMSC, including MDS*	4161	145	0.035	0.025	0.048
(Costa, 2018)	overall SPMs *(1995-2009)* *excluding NMSC, excluding MDS*	9833	420	0.043	0.031	0.058
(Raje, 2019)	CRS ≥ Grade 3	33	2	0.061	0.047	0.078
(Raje, 2019)	Neurotoxicity ≥ Grade 3	33	1	0.030	0.020	0.043

CI = confidence interval; Clopp Pears = Clopper Pearson; CRS = cytokine release syndrome; MDS = myelodysplastic syndrome; NMSC = nonmelanoma skin cancer; SPM = second primary malignancy.

Thus, in conclusion, if similar incidences are observed in this study, this would provide sufficient precision for a meaningful interpretation of the observed incidences.

Data analysis: In this cohort study, results will be analyzed and reported descriptively; no formal hypothesis testing is planned.

Confidence intervals will be presented as 2-sided 95% intervals unless specified differently for specific analyses.

Summary statistics will consist of the number and percentage of patients in each category for discrete variables, whereas for continuous variables the sample size, mean, median, standard deviation, minimum, and maximum will be given.

Milestones:

- Date of Initial Registry Protocol Submission to EMA as part of Marketing Authorisation Application: 30 Apr 2020
- Date of Final Registry Protocol Approval from EMA: Quarter (Q)4 2021
- Start of data collection[a]: Q1 2022
- Registration in the EU PAS register: TBC
- Study Progress Updates: Per the periodic safety update report (PSUR) cycle, according to the EU reference dates (EURD) list
- Safety reports: Every 6 months (aligned with the reporting period of the PSUR)[b]. Additional reports every 3 months if a new safety concern is identified
- Interim reports[c]: At year 5, 10 and 15 or when last patient is out of the registry-based study
- Date of Study Completion[d]: Q1 2042
- Date of Final Study Report Submission to EMA: Q1 2043

[a] As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection corresponds to the date from which data extraction starts. First data extraction for study BB2121-MM-006 will take place three months after protocol approval from EMA.

[b] 6-month safety reports will be provided with the PSUR submission (PSUR single assessment [PSUSA]) as determined by the EURD list.
[c] Interim reports will be prepared at year 5, 10 and 15 after EC decision date or when last patient is out of the registry-based study.
[d] 15 years after reaching the defined patient number no further data will be included in the study analyses.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestones for this study are summarized in Table 2.

Table 2: Milestones

Milestone	Planned Date
Date of Initial Registry Protocol Submission to EMA as part of Marketing Authorisation Application	30 Apr 2020
Date of Final Registry Protocol Approval from EMA	Q4 2021
Start of data collection[a]	Q1 2022
Registration in the EU PAS register	TBC
Study Progress Updates	Per the periodic safety update report (PSUR) cycle, according to the EU reference dates (EURD) list
Safety reports	Every 6 months (aligned with the reporting period of the PSUR)[b]. Additional reports every 3 months if a new safety concern is identified
Interim reports[c]	At year 5, 10, and 15 or when last patient is out of the registry-based study
Date of Study Completion[d]	Q1 2042
Date of Final Study Report Submission to EMA	Q1 2043

EBMT = European Society for Blood and Marrow Transplantation; EMA = European Medicines Agency; EU = European Union; PAS = Post-authorization safety; Q = quarter; TBC= To Be Confirmed.

[a] As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection corresponds to the date from which data extraction starts. First data extraction for study BB2121-MM-006 will take place three months after protocol approval from EMA.

[b] 6-month safety reports will be provided with the PSUR submission (PSUR single assessment [PSUSA]) as determined by the EURD list.

[c] Interim reports will be prepared at year 5, 10 and 15 after EC decision date or when last patient is out of the registry-based study.

[d] 15 years after reaching the defined patient number no further data will be included in the study analyses.

7. RATIONALE AND BACKGROUND

7.1. Rationale

The purpose of this post-authorization safety study (PASS) is to characterize the safety profile of ide-cel in the postmarketing setting.

This study will include patients from existing independent registries, such as, but not limited to, the European Society for Blood and Marrow Transplantation (EBMT) and the CIBMTR.

The BB2121-MM-006 study will be part of the overall ide-cel Risk Management Plan (RMP) including any required regional Pharmacovigilance Plan (PVP) outside the European Union (EU).

7.2. Background

Multiple myeloma (MM) accounts for approximately 10% to 18% of hematologic malignancies (Moreau, 2017; Siegel, 2020) and primarily affects older individuals. 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). The number of MM patients is increasing in the general population due to aging populations and more patients living longer due to modern antimyeloma therapies (AMTs) (Turesson, 2018). The prevalence of MM varies from country to country in the EU. Overall, the estimated prevalence of MM in the EU in 2018 ranged from 1.79 to 3.61 in 10,000 persons (data on file). In Europe, 48,297 new cases of MM were estimated in 2018 (International Agency for Research on Cancer [IARC], 2019).

Multiple myeloma is a largely incurable blood cancer characterized by the clonal proliferation of malignant plasma cells both within the bone marrow and at localized extramedullary sites termed plasmacytomas (Rajkumar, 2016). 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 bone marrow failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures (Munshi, 2012).

The course of MM is characterized 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 (Larocca, 2017; Moreau, 2017). With each relapse and each subsequent line of AMT, tumors typically recur more aggressively, leading to shorter response duration and ultimately, refractory MM, which is associated with shortened survival times (Gandhi, 2019; Kumar, 2017; Yong, 2016). Furthermore, each line of therapy is associated with an increased risk of comorbidities, including treatment- and disease-related complications (Leleu, 2019; Song, 2016).

Progress has been made in improving overall survival (OS) in patients with MM. The increase in survival has been driven by more effective combination induction regimens composed primarily of immunomodulatory agents, proteasome inhibitors (PIs), and dexamethasone coupled with consolidation using autologous stem cell transplantation (ASCT) (Moreau, 2017; National Comprehensive Cancer Network [NCCN], 2019). Even with optimal upfront therapy, most MM patients progress or relapse, and further treatment is needed.

7.2.1. Current Treatment Options for Relapsed and/or Refractory MM

Many factors influence the choice of therapy in the relapsed or refractory MM setting, including age; performance status; 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; Sonneveld, 2017). The choice of an appropriate treatment regimen for a given patient should offer a balance of efficacy while limiting toxicity (Larocca, 2017; San-Miguel, 2017).

The goal of treatment at first relapse is to achieve a maximum response and a progression-free interval; the goal of treatment at second and later relapse is to rapidly achieve disease control and tumor burden/symptom control (Sonneveld, 2017). Given the chronic nature of MM, patients continue to require multiple lines of continuously dosed therapy to maintain adequate disease control over long periods. There is no consensus among guidelines regarding the optimum treatment for patients with relapsed or refractory MM (Cavo, 2018). Current recommended treatment options for previously treated (ie, relapsed or refractory) MM by the European Society for Medical Oncology (ESMO) (Moreau, 2017) and the NCCN (NCCN, 2019) are summarized in Table 3.

Both the ESMO and the current NCCN clinical practice guidelines (Version 2.2020) generally recommend the use of triplet regimens as standard therapy for patients with relapsed or refractory MM. These recommended treatment options typically include combinations of ≥ 2 drugs with diverse mechanism of action (MoA), usually combined with dexamethasone: immunomodulatory agents (lenalidomide and pomalidomide), PIs (bortezomib, carfilzomib, and ixazomib), monoclonal antibodies (mAbs; daratumumab and elotuzumab), a histone deacetylase inhibitor (panobinostat [NCCN guidelines only]), and older-generation treatments (eg, alkylating agent). For 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 (Table 1). For relapsed or 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, 2019).

Treatment is generally administered until disease progression. Importantly, the ESMO and NCCN MM guidelines do not specify clear sequencing recommendations for subsequent treatment combinations or the optimal approach for patients with multiple relapses. As most patients receive front-line 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. Even more challenging in the relapsed or refractory MM setting is the progressive incorporation of daratumumab-based therapy. Notably, there is no standard of care for patients with MM who have received at least 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody. There are no NCCN or ESMO-recommended therapies nor therapies approved or shown to be effective specifically for this patient population. Consequently, there is a significant unmet need for novel, effective therapies for patients with relapsed or refractory MM following treatment with these classes of drugs.

According to CancerMPact®, approximately 27% of patients in Western Europe[1] who have received 3 prior lines of AMT will receive a fourth line of systemic AMT (Kantar, 2019). In 2019, the most commonly used (≥ 5%) fourth-line AMTs in Europe were daratumumab monotherapy (14.1%); Pd (8.7%); and pomalidomide monotherapy (5.1%).

[1] Survey respondents included physicians from France, Germany, Italy, Spain, and the United Kingdom.

Table 3: Currently Recommended Treatment Options for Patients with Relapsed or Refractory Multiple Myeloma – ESMO and NCCN Guidelines

ESMO (Moreau, 2017)	NCCN (Version 2.2020) (NCCN-MM, 2019)
First Relapse	***Preferred Regimens[a-i]***
After Immunomodulatory Compound-based Induction	Category1[j]: DRd[k]; DVd[k]; ERd[l,m]; IRd[m]; Kd (K twice weekly)[n]; KRd[m] Category2A[o]: Kd (K weekly)[n]; RVd
• Doublets: – Kd – Vd • Triplets (bortezomib backbone): – DVd – EVd – PanoVd – VCd	
After Bortezomib-based Induction	***Other Regimens[a-i]***
• Doublet: – Rd • Triplets (Rd backbone) – DRd – ERd – IRd – KRd	Category1[j]: PanoVd[p]; Pd[n,q,r]; PVd[q]; Rd[n,r]; Vd[n]; Vd-liposomal dox Category2A[o]: BenRd; BenVd; Dara[k,s]; DKd[k]; DPd[k,t]; EPd[t]; EVd; ICd; Id[n]; IPd; KCd; PanoK[n,p]; PanoRd[p]; PCd[q]; PKd[q]; RCd; VCd
At Second or Subsequent Relapse	***Useful in Certain Circumstances[a-i]***
• Pd (as backbone) + Bort, Cyclo, Dara, Elo, or Ixa • Dara (single agent or combination) • Clinical trial	Category1: None Category2A[o]: Ben; DCEP[u]; DT-PACE [u] ± VTD-PACE[u]; High-dose cyclophosphamide; KCTd; Selinexor/dex[v]

Ben = bendamustine; BenRd = bendamustine, lenalidomide, and dexamethasone; BenVd = bendamustine, bortezomib, and dexamethasone; Bort = bortezomib; Cyclo = cyclophosphamide; Dara = daratumumab; DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; dex = dexamethasone; dox = doxorubicin; DPd = daratumumab, pomalidomide, and dexamethasone; DRd = daratumumab, lenalidomide, and dexamethasone; DT-PACE = dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; DVd = daratumumab, bortezomib, and dexamethasone; Elo = elotuzumab; EPd = elotuzumab, pomalidomide, and dexamethasone; ERd = elotuzumab, lenalidomide, and dexamethasone; ESMO = European Society for Medical Oncology; EVd = elotuzumab, bortezomib, and dexamethasone; ICd = ixazomib, cyclophosphamide, and dexamethasone; Id = ixazomib and dexamethasone; IPd = ixazomib, pomalidomide, and dexamethasone; DKd=daratumumab carfizomib, and dexamethasone
IRd = ixazomib, lenalidomide, and dexamethasone; Ixa = ixazomib; K = carfilzomib; KCd = carfilzomib, cyclophosphamide, and dexamethasone; KCTd = carfilzomib, cyclophosphamide, thalidomide, and dexamethasone; Kd = carfilzomib and dexamethasone; KRd = carfilzomib, lenalidomide, and dexamethasone; MM = multiple myeloma; NCCN = National Comprehensive Cancer Network;
PanoK = panobinostat and carfilzomib; PanoRd = panobinostat, lenalidomide, and dexamethasone; PanoVd = panobinostat, bortezomib, and dexamethasone; PCd = pomalidomide, cyclophosphamide, and dexamethasone; Pd = pomalidomide and dexamethasone; PI = proteasome inhibitor; PKd = pomalidomide, carfilzomib, and dexamethasone; PVd = pomalidomide, bortezomib, and dexamethasone; PI = proteasome inhibitor; RCd = lenalidomide, cyclophosphamide, and dexamethasone; Rd = lenalidomide and dexamethasone; Vd = lenalidomide, bortezomib, and dexamethasone;
VCd = bortezomib, cyclophosphamide, and dexamethasone; Vd = bortezomib and dexamethasone; VTD-PACE = bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide.

[a] Selected regimens are included, but are not inclusive of all regimens.
[b] See Supportive Care Therapy (MYEL-G) in NCCN MM Guidelines, Version 2.2020 (NCCN, 2019).
[c] Subcutaneous bortezomib is the preferred method of administration.
[d] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology (NCCN, 2019a).
[e] Both weekly and twice-weekly dosing schemas for bortezomib may be appropriate and acceptable.
[f] Carfilzomib can be used once or twice weekly and at different doses.
[g] Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[h] Consideration for appropriate regimen is based on the context of clinical relapse.
[i] If a regimen was used as a primary induction therapy and relapse is > 6 months, the same regimen may be repeated.
[j] Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

[k] Daratumumab may interfere with serological testing and cause false-positive indirect Coombs test. Type and screen should be performed before using daratumumab.
[l] Elotuzumab is indicated in combination with Rd for the treatment of patients who have received 1 to 3 prior therapies.
[m] Clinical trials with these regimens primarily included patients who were lenalidomide-naïve or with lenalidomide-sensitive MM.
[n] Triplet regimens should be used as the standard therapy for patients with MM; however, patients who cannot be considered for initiation of treatment with a 3-drug regimen can be started with a 2-drug regimen, with a third drug added once performance improves.
[o] Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
[p] Indicated for the treatment of patients who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.
[q] Indicated for the treatment of patients who have received at least 2 prior therapies including an immunomodulatory agent and a PI and who have demonstrated disease progression on or within 60 days of completion of the last therapy.
[r] Consider single-agent lenalidomide or pomalidomide for steroid-intolerant individuals.
[s] Indicated for the treatment of patients who have received at least 3 prior therapies, including a PI and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.
[t] Indicated for the treatment of patients who have received at least 2 prior therapies including an immunomodulatory agent and a PI.
[u] Generally reserved for the treatment of aggressive MM.
[v] Indicated for patients who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

Source: NCCN MM Guidelines, Version 2.2020 (NCCN, 2019)

7.2.2. Chimeric Antigen Receptor T Cell Therapies

T cell immunotherapy offers a promising approach for cancer treatment through harnessing the patient's own immune system to destroy malignant cells (June, 2015). Studies with tumor vaccines (Avigan, 2008; Nahas, 2016; Rosenblatt, 2011; Kantoff, 2010), immune checkpoint inhibitors (Hamid, 2013; Page, 2013), and tumor-infiltrating lymphocytes (Rosenberg, 2011) have demonstrated the potential of T cells to treat cancer.

The development of chimeric antigen receptor (CAR) T cell therapies represents a new targeted approach for treating malignancies. CAR T cells are recombinant receptors that target native surface antigens. The CAR is a fusion protein composed of several elements, including an extracellular binding domain (eg, single chain variable fragment [scFv], natural ligands, or fragment antigen binding [FAB]) that binds the antigen on the cell surface, a transmembrane domain, and intracellular endodomains that provide activation signaling to the T cell after target cell engagement by the binding domain (Sadelain, 2013).

Production of CAR T cells requires T cells to be genetically modified by ex vivo transduction using a recombinant viral (eg, lentiviral) vector containing the CAR ribonucleic acid (RNA) sequence. Transduced T cells express the CAR on the cell surface and are effectively redirected toward recognition and lysis of the cells expressing the target antigen. Autologous CAR T cells may be generated and expanded from a patient's leukapheresis-derived peripheral blood mononuclear cells (PBMCs) and subsequently cryopreserved. The CAR T cells can later be thawed and administered intravenously (IV) to the same patient.

CAR T cells directed against B-cell antigens have demonstrated promising antitumor activity across B-cell malignancies including B-cell non-Hodgkin's lymphoma (NHL) (Schuster, 2019; Neelapu, 2017; Abramson 2018), B-precursor acute lymphoblastic leukemia (ALL) (Maude, 2018; Lee, 2015), chronic lymphocytic leukemia (CLL) (Porter, 2011; Siddiqi, 2018) and multiple myeloma (Cohen, 2019; Raje, 2018).

Treatment with CAR T cell therapies showed significant clinical response. Initial studies demonstrated complete remissions of 63% of children with relapsed and/or refractory (R/R) ALL (Maude, 2018) and 40% to 45% of initial complete response in adults with R/R NHL (Schuster, 2019; Neelapu, 2017).

Administration of cellular products such as CAR-expressing T cells can be associated with cytokine release syndrome (CRS), a systemic inflammatory response caused by the release of various cytokines (Lee, 2019; Gardner, 2017).

Cytokine release syndrome manifests typically with characteristic clinical symptoms such as fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia. Symptoms and severity of CRS are highly variable, and management can be complicated by concurrent conditions.

Cytokine release syndrome occurs in a variable fraction of patients after CAR T cell therapy, with incidences ranging from 35% to 93%. The variable incidence and severity of CRS between studies is likely due to differences in CAR construct, CAR T cell manufacturing, diagnosis, disease burden, eligibility criteria, and the systems used to grade CRS (Hirayama, 2019).

CAR T cell therapy is associated with unique neurotoxicities. Neurologic symptoms may appear within 4 weeks after CAR T cell infusion and include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity.

Focal neurologic deficits, seizures, encephalopathy, and acute cerebral edema have been reported, but are infrequent (Santomasso, 2018). Rates and severity of neurotoxicities vary, with severe (Grade ≥ 3) manifestations observed in 12% to 28% of patients receiving CAR T cell therapy (Schuster, 2019; Abramson 2018; Neelapu, 2017).

Recently, a panel of experts developed the American Society for Transplantation and Cellular Therapy Consensus Grading, a list of recommendations, proposed new definitions and grading for CRS and neurotoxicity to better categorize the severity of these toxicities (Lee, 2019).

Other toxicities that are important to assess in recipients of CAR T cells include prolonged time to recover blood counts and the development of infections (Hirayama, 2019).

Therapeutic advancements following the introduction of autologous stem cell transplantation and ‘novel’ agents have significantly improved clinical outcomes for patients with MM. Increased life expectancy, however, has led to renewed concerns about the long-term risk of second primary malignancies (SPMs). Overall, the risk of SPMs in MM is low, multifactorial (including treatment type), and partially related to the length of patients’ survival and MM intrinsic susceptibility (Musto, 2017). According to the Surveillance, Epidemiology, and End Results (SEER) registries, in a population of patients diagnosed at age < 65 years between 2005 and 2009, the cumulative incidence of SPM at 90 months was 6.3% [95% confidence interval {CI}: 5.5-7.1], with a standardized incidence ratio of secondary primary cancer for hematological malignancies of 2.17 [95% CI: 1.27-3.48] (Costa, 2018).

The potential impact of CAR T cell therapies on the risk of secondary malignancies following their use in MM patients is not known. Because CAR T cells are a genetically modified product, there is a hypothetical possibility of insertional mutagenesis resulting in secondary malignancies. The modified T cells could become capable of autonomous proliferation, independent of binding tumor-associated antigen but this event has not been observed in the clinic (Maus, 2016). In addition, the use of other therapies, such as lymphodepleting chemotherapy (LDC) concomitant with CAR T cell therapy, can also lead to a risk of secondary malignancies. This risk requires patients to be monitored long term.

Moreover, it is also possible that modified T cells could lead to or exacerbate graft-versus-host disease (GVHD) (Maus, 2016).

7.2.3. Compound Background

Ide-cel is a genetically modified autologous T cell immunotherapy product consisting of T cells transduced with an anti-BCMA02 chimeric antigen receptor (CAR) lentiviral vector (LVV).

The CAR is comprised of a murine extracellular single-chain variable fragment (scFv) specific for recognizing B-cell maturation antigen (BCMA) followed by a human CD8α hinge and transmembrane domain fused to the T cell cytoplasmic signaling domains of CD137 (4-1BB) and CD3ζ chain, in tandem.

B-cell maturation antigen is a member of the tumor necrosis factor superfamily consistently expressed on plasma cells and myeloma cells from MM patients and is thought to provide protection for myeloma cells in the bone marrow niche (Carpenter, 2013; Novak, 2004). B-cell maturation antigen expression increases with disease progression and soluble BCMA in serum acts as a prognostic factor for survival and indicator of response to therapy (Sanchez, 2012).

B-cell maturation antigen has limited distribution in normal non-hematopoietic tissue. Reports have demonstrated BCMA expression on differentiated plasma cells and a subset of mature B cells in normal lymphoid tissue (eg, bone marrow, spleen, lymph nodes and tonsil) but lack of expression on naïve B cells, other hematopoietic cells including neutrophils, macrophages, and T cells or other non hemato-lymphoid tissues (Carpenter, 2013).

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

Data from Study CRB-401 (ClinicalTrials.gov identifier: NCT02658929) as of the 22 Jul 2019 cutoff date in 33 patients with relapsed and refractory MM, with a median of 7 prior lines of therapy, demonstrate that treatment with ide-cel results in encouraging efficacy results and an acceptable safety profile. All patients received a single infusion at a dose range of 50 to 800×10^6 cells and the overall response rate (ORR) was 85%, with 45% achieving complete response (CR). In the 30 patients who received a dose of 150 x 10^6 CAR+ T cells or higher, the ORR was 90% and the median progression-free survival (PFS) was 11.8 months. Most common Grade ≥ 3 hematologic adverse events (AEs) included neutropenia (85%), leukopenia (58%), anemia (45%), and thrombocytopenia (45%). A total of 25 patients (76%) experienced CRS, mainly Grade ≤ 2; 2 patients (6%) had Grade 3 CRS and no Grade 4 CRS events were reported. Neurologic toxic events were observed in 14 patients (42%), mainly Grade ≤ 2; 1 patient (3%) had a reversible Grade 4 neurotoxicity (Raje, 2019).

Study BB2121-MM-001 (NCT03361748) is an ongoing, global, Phase 2, open-label, single-arm, multicenter study to confirm the efficacy and safety of ide-cel in subjects with relapsed and refractory MM. The patient population in this study had received at least 3 prior AMT regimens including an immunomodulatory agent, a PI, and an anti-CD38 antibody. All ide-cel-treated subjects received an actual dose within the allowed range of 150 to 540 x 10^6 CAR+ T cells/infusion. The maximum dose (540 x 10^6 CAR+ T cells) was defined by the upper limit of 450 x 10^6 CAR+ T cells (ie, the highest target dose) plus 20%, as detailed in the study protocol.

At the data cutoff date of 16 Oct 2019 for the planned primary analysis, Study MM-001 was able to demonstrate the efficacy and safety of ide-cel. The primary efficacy analyses were based on the Independent Response Committee-adjudicated assessment of response. The primary endpoint of ORR in the ide-cel-treated population (N = 128) was 73.4% (95% CI: 65.8, 81.1) ($p < 0.0001$). The key secondary endpoint of CR rate was 31.3% (95% CI: 23.2, 39.3), and the Kaplan-Meier (KM) estimate for median PFS was 8.6 months.

The most frequently reported AEs in the ide-cel-treated population on or after ide-cel infusion (preferred terms [PTs] reported in ≥ 40% of subjects) were neutropenia (91.4%), CRS (83.6%), anemia (69.5%), thrombocytopenia (63.3%), and leukopenia (42.2%). The most frequently reported Grade 3 or 4 AEs (≥ 20%) were neutropenia (89.1%), anemia (60.2%), thrombocytopenia (52.3%), leukopenia (39.1%), and lymphopenia (26.6%). The most frequently reported serious adverse events (≥ 5% of subjects) were CRS (17.2%), general physical health deterioration (10.2%), pneumonia (8.6%), and febrile neutropenia (7.0%). The overall frequency of subjects with CRS was 83.6%, with 5.5% of subjects having ≥ Grade 3 CRS and 1 subject having Grade 5 CRS. Neurotoxicity (investigator-identified AE related to ide-cel) was a common AE after ide-cel but was mainly Grade 1 or 2 in severity, with only 3.1% of subjects reporting Grade 3 events and no Grade 4 or 5 events reported. Infection, which is a leading cause of death in patients with myeloma (Nucci, 2009), was reported in 68.8% of subjects after ide-cel infusion, with 21.1% of subjects having Grade 3 or 4 infections and 5 subjects (3.9%) having infections leading to death. There were 8 (6.3%) subjects with reported secondary malignancies after initial ide-cel infusion and an additional 1 subject with reported secondary malignancy after ide-cel retreatment; none of these events were consistent with clonal T cell malignancies.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

This post-authorization safety study (PASS) is an observational study of MM patients treated with ide-cel in the postmarketing setting to further investigate the research objective described in Section 8.2.

8.2. Research Objectives

8.2.1. Primary Objective

- To characterize the incidence and severity of selected adverse drug reactions (ADRs), as outlined in the Summary of Product Characteristics (SmPC), in patients treated with ide-cel in the postmarketing setting and to monitor for potential clinically important adverse events that have not yet been identified as part of the ide-cel safety profile.

8.2.2. Secondary Objective

- To assess survival in patients treated with ide-cel in the postmarketing setting.

9. RESEARCH METHODS

9.1. Study Design

This study is designed as a non-interventional cohort study that is part of multiple registries of patients with MM treated with ide-cel in the postmarketing setting which includes patients treated with out of specification (OOS) product.

Data from a total of 1000 patients treated with ide-cel, including a minimum of 300 EU patients, will be collected until death, lost to follow-up, or withdrawal of consent, or up to 15 years, whichever occurs first. This registry study is expected to require up to 5 years to select the planned 1000 patients.

No comparison groups will be defined and no inferential testing will be performed.

Secondary malignancies must be reported to the Sponsor by the treating physicians in order to expedite AE reporting. In the event that a secondary malignancy of T cell origin is suspected, the Sponsor should be contacted to obtain instructions on the collection and transfer of a tumor tissue sample for testing in a separate process, outside of this PASS. In the postmarketing setting, the Sponsor will offer transgene assay service testing for all secondary malignancies of suspected T cell origin where a sample is available, as a routine pharmacovigilance measure to ensure gathering the most information possible for clinical assessment of the reported spontaneous case.

9.1.1. Primary Safety Endpoint(s)

Incidence and severity of selected AEs reported post ide-cel infusion:

- All secondary malignancies
- CRS Grade ≥ 3
- Neurotoxicity Grade ≥ 3
- Prolonged cytopenias
- Pregnancy outcome
- Other AEs considered related to ide-cel

9.1.2. Secondary Effectiveness Endpoint(s)

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

9.2. Setting

This noninterventional cohort study will be based on secondary data that are collected from existing independent registries, such as the EBMT and the CIBMTR. Both registries use electronic Registry Case Report Forms (CRFs) forms onto which data may be entered directly by the treating centers.

All patients included in the EBMT and the CIBMTR registries are treated by their physicians according to real-world clinical practice. Physicians are trained to identify and approach patients treated with at least one dose of ide-cel to obtain their written informed consent according to the registries' standard procedures, to transfer the data to the EBMT or the CIBMTR and to be shared with competent health authorities, MAH and other parties in line with the signed informed consent forms.

9.2.1. Eligibility Criteria

All patients who meet the following eligibility criterion will be selected from the registries:

- Patient must have been treated with at least one infusion of ide-cel in the postmarketing setting. Patients treated with OOS product will also be eligible.

9.3. Variables

The following variables will be recorded and used within this study:

Table 4: Variables

Classification	Category	Variable	Description
Baseline (at infusion date)	General Identifiers	Patient Code / ID	Unique de-identified ID for patient
		Reporting Center (RC) Name / ID	Center name or ID reporting to the registry
		Manufacturing Site (MFS) Name /ID	Site name or ID producing the CAR T product
		Apheresis Center (AC) Name / ID	Center name or ID conducting leukapheresis
		Site of Care (SC) Name / ID	Center name or ID treating patient and infusing the CAR T product
Baseline	Product Information	Product Name	Name of CAR T product
		Product Code / ID (Join ID)	Product ID for the first product
		Product Quality: OOS	Product: out of specification, yes/no
Baseline	Key Treatment Processes and Timing	Patient Registering Date	Date patient was registered into the registry DB by the RC
		Leukapheresis Date	Date blood was collected at the AC
		Blood Shipment Date	Date blood was shipped from the AC to the MFS
		Blood Arrival Date	Date blood arrived at the MFS
		Manufacturing Start Date	Date MFS started production of CAR T
		Manufacturing End Date	Date MFS completed production of CAR T
		Product Shipment Date	Date CAR T was shipped to the SC
		Product Receipt Date	Date CAR T arrived at the SC
		Lymphodepleting Therapy Date	Date when lymphodepleting therapy started at SC
		Infusion Date	Date when CAR T was infused to the patient at the SC
		Product Infusion Count	Infusion counting number and total number of infusions
		Diagnosis Date	Date when primary disease was diagnosed
		Last Contact Date	Date when patient was last time in contact with the SC
		Safety Assessment Date	Date of any safety assessments findings (as listed in the safety section below)
		Effectiveness Assessment Date	Date of any effectiveness assessments findings (as listed in the effectiveness section below)

Table 4: Variables (Continued)

Classification	Category	Variable	Description
Baseline	Demographics	Age	Age at infusion (years)
		Weight	Body weight at infusion (kg)
		Height	Body height at infusion (cm)
		Gender	Gender of patient
		Country	Country of the infusion center
		Region	Region of treatment: North America/Europe/Japan/Rest of the World
Baseline	Clinical Variables (Disease History/ Prior Therapy/ Infusion Related)	Karnofsky Performance Score	Karnofsky performance score at infusion
		ECOG Performance Score	ECOG performance score at infusion
		Disease History/Co-Morbidity	Comorbidity prior to infusion and organ involvement (eg, cardiac, hepatic, obesity, pulmonary renal, diabetes, solid tumor, and others)
		Prior Therapy 1: Lines	Number of prior therapy lines
		Prior Therapy 2: List	Names of prior therapies (systemic therapies, standard regimens)
		Prior Therapy 3: HCT	Number of prior hematopoietic cell transplantations (HCTs)
		Prior Therapy 4: HCT Type	Types of prior HCTs
		Disease Status 1: Primary Disease	Primary disease and disease status prior to LD chemotherapy
		Disease Status 2: International Staging System	Classification according to albumin and beta 2 microglobulin levels into stages I, II or III
		Disease Status 3: Cytogen. FISH	Chromosome changes identified via FISH at diagnosis
		Disease Status 4: Cytogen. Karyotyping	Chromosome changes identified via karyotyping at diagnosis
		Lymphodepleting Treatment	Types and names of lymphodepleting chemotherapy agents

Table 4: Variables (Continued)

Classification	Category	Variable	Description
Outcome (reported at 100 d, 6 months, yearly)	Safety	Secondary Malignancies (SM)	Subsequent neoplasms assessment and types of SM reported during FU
		Cytokine Release Syndrome 1: Presence	Assessment and presence of CRS reported during FU
		Cytokine Release Syndrome 2: Grade	CRS grade
		Cytokine Release Syndrome 3: Symptoms	CRS symptoms: fever, hypotension, hypoxia
		Cytokine Release Syndrome 4: Therapy	CRS therapy: intraven. fluids, vasopressors, positive pressure vent support, other therapy, CRS resolution date
		Neurotoxicity 1: Presence	Assessment and presence of NT reported during FU
		Neurotoxicity 2: Grade	NT grade
		Neurotoxicity 3: Symptoms	NT symptoms: consciousness, dysphasia, seizure, paraparesis, cerebral edema, hallucination, tremors, other neurologic symptoms
		Neurotoxicity 4: Therapy	NT therapy: antiepileptic and other therapy given, NT resolution date
		Prolonged Cytopenia 1: Presence	Neutrophil count < 500/mm^3, platelet count < 20 x 10^9/L
		Prolonged Cytopenia 2: Recovery	Neutrophil and platelet recovery
		Hypogammaglobulinemia 1: Presence	Assessment and presence of hypogammaglobulinemia during FU
		Hypogammaglobulinemia 2: Therapy	Hypogammaglobulinemia therapy (immunoglobulin replacement) and resolution
		Tumor Lysis Syndrome 1: Presence	Assessment and presence of TLS reported during FU
		Tumor Lysis Syndrome 2: Grade	TLS grade
		Organ Toxicity Grade ≥ 3	AE/symptoms/type at heart, gastrointestinal, kidney, liver, lungs, musculoskeletal, neurologic and "other" reported during FU
		Aggravated graft-versus-host disease (GVHD)	Information regarding chronic and acute GVHD
		Infections	Types and sites of serious (ie, requiring treatment) infection reported during follow-up (1st-5th reported infection)
		Pregnancy Outcome	Pregnancy reported during FU for female and for male partner
		Concomitant Medication	Other systemic therapy (other than for CT/HCT) given for maintenance or consolidation reported during FU

Classification	Category	Variable	Description
Outcome	Effectiveness	Best Overall Response 1: Biochemical Assessment	Assessment of response based on biochemical assessment
		Best Overall Response 2: Bone Marrow Assessment	Assessment of response based on bone marrow assessment
		Relapse and Progression 1	Outcome of relapse or progression detected by bone marrow and/or biochemical/radiologic assessment
		Relapse and Progression 2: Therapy	Therapy given for treatment of relapse or progression
		Progression Status	Status of progression
		Relapse Status	Status of relapse
		Cause of Death	Primary cause of death and contributing causes of death #1 to #4
		Survival Status	Survival status at last contact

AC = apheresis center, AE = adverse event, ASTCT = American Society for Transplantation and Cellular Therapy, B2M = beta 2 microglobulin, CAR T = chimeric antigen receptor T cell, CRS = cytokine release syndrome, CT = cell therapy, Cytogen. = cytogenetic, d = day, DB = database, ECOG = Eastern Cooperative Oncology Group, FISH = fluorescence in situ hybridization, FU = follow-up, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplantations, ID = Identifier, Intraven. = intravenous, LD = lymphodepleting, MFS = manufacturing site, NT = neurotoxicity, OOS = out of specification, RC = reporting center, SC = site of care, SM = secondary malignancies, TLS = tumor lysis syndrome.

9.4. Data Sources and Data Management

Data will be extracted from the EBMT and the CIBMTR electronic cellular therapy forms, which are captured with web-based software used by the 2 registry holders.

The databases and software used by EBMT during the course of the study meet the internationally recognized ethical and scientific quality requirements for designing, conducting, recording and reporting studies involving human subjects. Sites need to be registered to the EBMT Registry system. This registration generates a unique EBMT Center Identification Code (CIC) and includes trainings on the data collection system. Sites initiate patient reporting through the generation of an EBMT Registry Unique Identification Code, which is unique to every patient. In addition, sites may enter an internal Unique Patient Number (UPN). The Therapy Indication Form will identify that the patient is a recipient of ide-cel and triggers a series of forms appropriate for the specific indication that will be under that UPN.

FormsNET3 (FN3), the CIBMTR's web-based data collection system, is compliant with the United States (US) database security requirements established by the Health Resources and Services Administration Office of Information Technology and with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11. Sites need to be registered as a CIBMTR member and sign a Master Healthcare Data Agreement (MHA) and a Sample Submission Agreement to allow the transfer of data between organizations (CIBMTR and Site). Upon MHA completion, site staff are provided access to FN3, and are provided trainings on the CIBMTR data collection processes including the use of the FN3 system. Sites initiate patient reporting through the FN3 generation of a CIBMTR Research Identification (CRID) number, which is unique to every patient. The Therapy Indication Form will identify that the patient is a recipient of ide-cel and triggers a series of forms appropriate for the indication. With the CRID, the patient's record can be tracked over time as well as multiple indications. In addition, data are managed through a role-based security model and the CIBMTR data collection, data storage and data sharing systems are externally audited every year.

Data from the two registries will be exported following internationally agreed data standards for clinical data sharing (eg, Study Data Tabulation Model [SDTM]-Clinical Data Interchange Standards Consortium [CDISC]) and then combined into Analysis Data Model (ADAM)-like data sets including derived variables to allow consistent and periodic analyses. These data sets will include the characteristics, outcome variables and other covariates. Data dictionaries will be prepared to describe all variables and values included. If in the future, analyses software specifications change, formats and file conventions will be modified and adapted to the required needs.

The data from all sources will be integrated into one internal data system built and managed by the Sponsor.

For details on data monitoring and source data verification refer to Section 9.7, further below.

9.5. Study Size

Since this is a single-arm noninterventional cohort study with no comparisons, no statistical hypothesis testing and no formal powered sample size calculation is possible. Instead, a fixed number of 1000 patients from registries is used based on pragmatic non statistical reasons, which is considered feasible within the estimated 5-year selection period. The study size is justified by providing precision estimates (see below).

For the chosen sample size of 1000 patients, in general there would be a 95% chance to observe at least one event if the true incidence is ≥ 0.3 events per year (using normal approximation according to Wald).

To justify the sample size, precision estimates for example incidences, taken from the literature, are provided by calculating exact 95% Clopper Pearson confidence intervals (based on a binomial distribution). (see table below).

Assumed incidences for secondary malignancies were based on SPMs data from Mahindra and co-workers (Mahindra, 2015) and Costa and co-workers (Costa, 2018). The incidences for CRS and neurotoxicity correspond to incidences reported as AEs of special interest (AESIs) by Raje and co-workers (Raje, 2019) based on the CRB-401 trial (ClinicalTrials.Gov#: NCT02658929). The populations from these three sources are characterized as follows:

- **Mahindra et al population**: MM patients with an age range from 22 to 80 years and a first autologous stem cell transplantation (auto SCT) within 18 months of MM diagnosis, reported to the CIBMTR between 1990 and 2010.
- **Costa et al population**: Three cohorts of patients with an age range from 19 to 64 years, with MM as first malignant neoplasm, reported to the SEER between 1995 and 2009.
- **Raje et al population**: MM patients in the US with an age range from 37 to 75 years and an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.

Table 5: Assumed Incidence for Safety Endpoints

Data Source	Description	Patients	Observed Incidence	Incidence Proportion	Clopp Pears 95% CI lower (for 1000 patients)	Clopp Pears 95% CI upper (for 1000 patients)
(Mahindra, 2015)	overall SPMs *(1990-2010) excluding NMSC, including MDS*	4161	145	0.035	0.025	0.048
(Costa, 2018)	overall SPMs *(1995-2009) excluding NMSC, excluding MDS*	9833	420	0.043	0.031	0.058
(Raje, 2019)	CRS ≥ Grade 3	33	2	0.061	0.047	0.078
(Raje, 2019)	Neurotoxicity ≥ Grade 3	33	1	0.030	0.020	0.043

CI = confidence interval; Clopp Pears = Clopper Pearson; CRS = cytokine release syndrome;
MDS = myelodysplastic syndrome; NMSC = nonmelanoma skin cancer; SPM = second primary malignancy.

Thus, in conclusion, if similar incidences are observed in this study, this would provide sufficient precision for a meaningful interpretation of the observed incidences.

9.6. Data Analysis

In this noninterventional cohort study, results will be analyzed and reported descriptively; no formal hypothesis testing is carried out.

Confidence intervals will be presented as 2-sided 95% intervals unless specified differently for specific analyses.

Summary statistics will consist of the number and percentage of patients in each category for discrete variables, whereas for continuous variables the sample size, mean, median, standard deviation, minimum, and maximum will be given.

A detailed statistical analysis plan (SAP) will be finalized before the first analysis.

9.6.1. Analysis Populations

Due to the observational nature of the study, no formal analysis populations such as intent to treat or a per protocol population can be defined. Instead, the term "analysis sets" will be used.

- Infused Set (IS): Is defined as all patients selected from the registry and meeting the eligibility criterion (see Section 9.2.1), where baseline and disease classification information is available.
- Safety and Effectiveness Set (SES): Is defined as all patients from the IS with information collected at least after 100 days.

9.6.2. Analysis of Study Conduct and Study Discontinuation

An adapted CONSORT diagram will be provided for documenting the number of patients at each reporting schedule. It will also present the patients' situation with regards to their participation in the registry and, if relevant, the reason why and when they stopped to participate.

The total number of patients selected from the registries as well as the number and percentage of patients will also be presented by country and center.

Patient disposition will be summarized and defined as patients who receive ide-cel and are reported to the corresponding registries with either ongoing follow-up, completed follow-up at 15 years or discontinued post-infusion follow-up due to death.

9.6.3. Baseline and Demographic Characteristics

Patients are included into the registry from 2 weeks prior to the ide-cel infusion to any time afterwards. Baseline data are retrospectively reported by data managers after the administration of ide-cel and are collected only once. All information, including any medical history and measurements done prior to the administration of ide-cel, becomes available in the registry as baseline data.

The baseline data will be summarized using descriptive statistics. Individual patient listings will also be provided to support the summary tables. The number and percentage of patients in each of the categories, as listed in Section 9.3, will also be given.

The following baseline data will be presented:

- **Demographics:** Demographic information collected at baseline will be presented using descriptive statistics.
- **Disease History/Comorbidities**: The frequency of patients with at least one comorbidity, as well as frequency counts of different comorbidities will be presented. The ECOG Performance Status score and disease status at infusion will be summarized by frequency counts.
- **Prior Therapy/Prior Medications**: Number of lines of prior therapies will be presented using descriptive statistics. Number of lines of prior therapies will be described as frequency counts. A frequency tabulation of the number of patients with the different types of prior therapies will be given. Also, a frequency tabulation of whether the patient had prior hematopoietic cell transplantations (HCTs) and the types of prior HCTs will be given.
- **Lymphodepleting Treatment**: A frequency tabulation of the list of lymphodepleting agents will be given.

9.6.4. Effectiveness Analysis

9.6.4.1. Analysis of the Secondary Effectiveness Endpoints

- **Overall Survival (OS)**: Overall survival is defined as the time from the date of first infusion to the date of death due to any cause. All patients will be followed for survival information, regardless of whether they receive additional treatment post-infusion. Patients who are alive at last contact date will be censored at that time, but no censoring will be done for additional treatment.
- **Progression-Free Survival (PFS)**: PFS is defined as the time from the date of first ide-cel infusion to the date of event defined as the first documented relapse or progression or death due to any cause, whatever happens first. Patients who are alive at last contact date will be censored at that time, but no censoring will be done for additional treatment.
- **Time To Event (TTE) Analysis:** Kaplan-Meier estimates and the associated 95% CIs of the median, 25th and 75th percentile will be presented. The two-sided 95% CIs will be computed using the log-log transformation. The survivor function will be displayed graphically using a KM curve.

9.6.5. Safety Analysis

9.6.5.1. Analysis of the Primary Safety Endpoints

The primary endpoint is the incidence and severity of the following selected AEs reported post ide-cel infusion. These AEs are equivalent to the AESIs:

- All secondary malignancies
- CRS Grade ≥ 3

- Neurotoxicity Grade ≥ 3
- Prolonged cytopenias
- Pregnancy outcome
- Other AEs considered related to ide-cel treatment, for example:
    - hypogammaglobulinemia
    - tumor lysis syndrome (TLS) Grade ≥ 3
    - serious infections (ie, requiring treatment)
    - organ toxicities Grade ≥ 3
    - others (eg, aggravated GVHD)

The primary endpoints will be analyzed and reported as described in Section 9.6.5.2 (below). Furthermore, suitable measures (incidence proportions and incidence rates) will be calculated with the appropriate time periods and methods. Analyses will be carried out without accounting for competing risks as well as accounting for competing risks using the cumulative incidence function method. Details are described in the SAP.

9.6.5.2. General Handling and Analysis of Symptoms or Adverse Events

The registry collection of safety data is specific to certain symptoms of toxicity associated with CAR T cell therapy and recorded as safety outcomes. These safety data include CRS, neurotoxicity, hypogammaglobulinemia, TLS, infections, prolonged cytopenias, organ toxicities and secondary malignancies. All of the above, except for the secondary malignancies, are collected in a calendar format in an aggregate and summarized form based on the prior reporting period. Secondary malignancies, pregnancies and any deaths are reported on an event driven form upon knowledge at the site of care (center).

The incidence of organ toxicities will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Organ toxicities will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 or higher. Only organ toxicities of Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death) will be summarized in reports. A patient who reports multiple occurrences of an organ toxicity with the same SOC and PT is counted only once using the maximum severity grade for summaries. If a patient experiences the same organ toxicity more than once with different grades, then the event with the highest grade will be tabulated in "by grade" tables. If a patient experiences multiple organ toxicity under the same PT and SOC, then the patient will be counted only once for that PT (SOC).

The incidence of each AESI and of most frequent AEs (≥ 10%) will be summarized using the number and percentage of patients experiencing the event. Exact 95% Clopper Pearson CIs will be provided for the percentages.

Adverse Events will be reported according to the following structure:

1) **Overall Summary of Organ Toxicities/Symptoms:** Summaries of AEs will be produced overall as described above.

2) **Summaries by System Organ Class and Preferred Term:** Summary tables by SOC and PT of the number of events and the number, percentage and exact 95% Clopper Pearson CIs for patients having events will be presented separately for each of the event types.
3) **Summaries by System Organ Class, Preferred Term and Highest Grade:** Events will be presented by SOC, PT and highest grade. Number, percentage and exact 95% Clopper Pearson CIs of patients for each of the event types will be presented using the patient's maximum grade.

Other toxicological symptoms recorded using free text fields are coded using SOC and PT based on the most recent version of the MedDRA.

9.7. Quality Control

9.7.1. Quality Control Performed by the EBMT and the CIBMTR Registries

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2015) and according to the ENCePP code of conduct (EMA, 2018).

Data in the PASS will be managed according to the processes of the EBMT and/or the CIBMTR. The quality control details will be further described in the operational plans of the EBMT and/or the CIBMTR which will be written for this study specifically.

The EBMT and/or the CIBMTR will secure the data in line with local applicable regulatory law and procedures. Access will be limited to authorized individuals only. Controls, such as document encryption, will be used to ensure the authenticity, integrity and confidentiality of electronic records when transmitted over open systems (eg, the internet). The study data are adequately backed up at regular intervals.

All individuals at sites responsible for the integrity of the data will be trained by the EBMT and/or the CIBMTR staff on the requirements of the PASS.

For data stored at the corresponding registries, the standard processes of the EBMT and/or the CIBMTR will be followed. This procedure will ensure the quality of the data in the registry and will ensure that the data are reviewed and queried on an ongoing basis to support data accuracy and completeness. In addition, the system will contain automatic edit checks that validate data entry according to prespecified standards, as well as regular data review by data management and site monitors that will generate manual edit checks to ensure the quality of data.

Furthermore, the data from the EBMT and/or the CIBMTR registries will be checked against source documents for 10% of patients; this approach will be risk-based and can be done remotely and/or on site. Details will be documented in the specific operational plans of both organizations.

9.7.2. Quality Control Performed by the Sponsor

The Sponsor retains the right to audit the study data and processes of the EBMT and the CIBMTR at any time if required. Findings of such audits will be documented and filed. If necessary, appropriate measures will be taken if issues are detected at audits.

The Sponsor will develop and implement an internal platform to store all data obtained in the frame of this study from external sources. These data will be assumed clean and no quality control procedures will be applied to the raw data because the quality of these data, and the source verification is the responsibility of the registry holders as described in Section 9.7.1 and Section 9.7.3.

Any data manipulation (eg, merging, transformation, calculations) will be documented according to appropriate data management practices used by the Sponsor for clinical trial data (eg, programming data specifications, data management plan) using appropriate quality control measures.

9.7.3. Study Center Monitoring and Source Data Verification

Treating physicians, or appropriate site designees, will enter data online into the registry-owned databases. All data will be stored securely and confidentially. The data will be electronically verified using programmed edit checks.

Data quality control reports will be run by the EBMT and/or the CIBMTR to check for missing or incorrect data on a regular basis.

Remote and/or limited onsite monitoring, to ensure source data verification, will be performed by the EBMT and/or the CIBMTR according to their standard procedures and regulatory recommendations.

Regular on-site monitoring visits are not planned by the EBMT and/or the CIBMTR; however, a risk-based approach with remote and limited onsite monitoring will be performed by the EBMT and/or the CIBMTR to ensure the data integrity.

A representative or delegate from the EBMT and/or the CIBMTR may visit the centers that participate in the study at periodic intervals to review medical records and source documentation. During remote/onsite audit of data, patients' source documents and all other study documentation will be inspected/reviewed by the EBMT and/or the CIBMTR representative or delegate according to a prespecified data monitoring plan.

9.8. Limitations of the Research Methods

As this is an observational PASS based upon secondary use of data, sporadic missing data are inevitable, because certain variables may not have been routinely recorded in the patient medical charts. Furthermore, data will also be missing due to gaps in the follow-up (as routine scheduled visits cannot be mandated in an observational study), and loss to follow-up, especially in this study with a planned duration of 15 years. Details of how missing data are handled are also outlined in the SAP.

The above-mentioned potential issue can lead to significant biasing effects on time to event analyses as well as analyses quantifying a duration. In the EBMT and the CIBMTR registries, data are recorded at baseline, 100 days, 6 months and then yearly. Thus, owing to center specific different levels of compliance, a high variability in the recording of assessment dates is to be expected.

To minimize selection bias, sites are requested to ask every patient treated with ide-cel to share data with the registry. Nevertheless, not all patients will consent to have their data sent to the

EBMT or the CIBMTR registries, possibly resulting in a biased sample of patients. A high rate of attrition (particularly if mortality is not captured well) could bias the results. In addition, in order to monitor the reporting, the study team will reconcile shipped products to each center participating in the study with the subsequent compliance of the patient and center with the study.

Additionally, as with every observational study, there will be unmeasured factors that can confound safety and effectiveness analyses. This PASS will attempt to collect accurate and complete data on all known critical confounders; however, residual confounding is always a possibility in any observational study analysis.

9.9. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

Data will only be part of the PASS if the patients (and parental/legal representative, when applicable) have given their voluntarily informed consent according to the registries' standard procedures, to allow data to be provided to the EBMT or the CIBMTR and to be shared with competent health authorities, MAH and other parties in line with the signed informed consent forms.

The informed consent form (ICF) used to consent patients will be based upon the ICF templates of the EBMT and/or the CIBMTR, updated in line with the treatment center's standard practices/regulations to fulfil data protection and/or national requirements for informed consent.

In accordance with local regulations, this study will complete all required regulatory and ethical review requirements.

Given that this is an observational PASS, it does not give rise to additional risks for the safety of the patients.

In case a patient treated with ide-cel in the postmarketing setting develops a secondary malignancy of suspected T cell origin, a separate ICF will be used for tumor tissue sample collection and ide-cel transgene testing outside the scope of this PASS.

11. COLLECTION AND REPORTING OF SELECTED ADVERSE EVENTS

Selected AEs associated with ide-cel treatment will be reported by health care professionals (HCPs) at participating centers using standard Registry CRFs per protocol and collected by the EBMT and/or the CIBMTR per standard registry procedures. The EBMT and/or the CIBMTR will extract data from CRFs and provide the Sponsor with a summary aggregate report and line listing every 3 months. The registry outputs will be periodically reported by the Sponsor to health authorities in an aggregate manner, according to applicable legislations, to support postmarketing ide-cel pharmacovigilance performed by both Sponsor and the health authorities.

In addition to AEs collected in Registry CRFs, participating HCPs will be encouraged to spontaneously report adverse reactions directly to the Sponsor and/or to the applicable national health authorities in the EU (via spontaneous reporting tools).

In the event that a secondary malignancy of T cell origin is suspected, the Sponsor should be contacted to obtain instructions on the collection and transfer of a tumor tissue sample for testing in a separate process, outside of this PASS. In the postmarketing setting, the Sponsor will offer transgene assay service testing for all secondary malignancies of suspected T cell origin where a sample is available, as a routine pharmacovigilance measure to ensure gathering the most information possible for clinical assessment of the reported spontaneous case.

Training on the HCP's responsibilities regarding reporting of adverse reactions, including secondary malignancies, will be provided by the Sponsor during the site certification process and it will also be communicated by the EBMT and/or the CIBMTR. Health care professionals will be trained in AE severity grading by a Sponsor-retained third party and organ toxicities will be graded using the NCI CTCAE version 5.0 or higher.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The EBMT and the CIBMTR are the registry holders and responsible for the data held within the respective registry. As part of the regulatory commitments, the Sponsor will receive a pseudonymised data file to support postmarketing ide-cel pharmacovigilance requirements (eg, periodic safety update report [PSUR]), PASS study status updates and/or responses to health authority requests.

Results from the study may also be presented at congresses of hematology and/or oncology or submitted for publication to an appropriate scientific and medical journal.

13. REFERENCES

Abramson JS, Gordon LI, Palomba ML, Lunning MA, Arnason JE, Forero-Torres A, et al. Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisobtagene maraleucel (JCAR017) in R/R aggressive NHL [abstract]. J Clin Oncol. 2018 ASCO Annual Meeting Abstracts. 2018;36(15 Suppl May 20): Abstract 7505.

Avigan D. Vaccine therapy and adoptive immunotherapy in hematologic malignancies. Best Pract Res Clin Haematol. 2008 Sep;21(3):373-4.

Carpenter RO, Evbuomwan MO, Pittaluga S, Rose JJ, Raffeld M, Yang S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clin Cancer Res. 2013 Apr 15;19(8):2048-60.

Cavo M, Terpos E, Bargay J, Einsele H, Cavet J, Greil R, de Wit E. The multiple myeloma treatment landscape: international guideline recommendations and clinical practice in Europe. Expert Rev Hematol. 2018;11(3):219-37.

Cohen AD, Garfall AL, Stadtmauer EA, Melenhorst JJ, Lacey SF, Lancaster E, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. J Clin Invest. 2019 Mar 21;129(6):2210-2221.

Costa LJ, Godby KN, Chhabra S, Cornell RF, Hari P, Bhatia S. Second primary malignancy after multiple myeloma-population trends and cause-specific mortality. Br J Haematol. 2018 Aug;182(4):513-20.

European Medicines Agency. The ENCePP Code of Conduct. 2018. Available from: http://www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct.pdf.

Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33(9):2266-75.

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

Hamid O, Carvajal RD. Anti-programmed death-1 and anti-programmed death-ligand 1 antibodies in cancer therapy. Expert Opin Biol Ther. 2013 Jun;13(6):847-6.

Hirayama AV, Turtle CJ. Toxicities of CD19 CAR-T cell immunotherapy. Am J Hematol. 2019;94:S42-S49.

Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al, eds. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.

International Agency for Research on Cancer (IARC). GLOBOCAN 2018. Cancer Today population fact sheets: Europe region. May, 2019. Available from: https://gco.iarc.fr/today/data/factsheets/populations/908-europe-fact-sheets.pdf.

June CH, Riddell SR, Schumacher TN. Adoptive cellular therapy: a race to the finish line. Sci Transl Med. 2015 Mar 25;7(280):280ps7.

Kantar. CancerMPact® treatment architecture: multiple myeloma, EU5. November 2019.

Kantoff PW, Schuetz TJ, Blumenstein BA, Glode LM, Bilhartz DL, Wyand M, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol. 2010 Mar 1;28(7):1099-105.

Kumar SK, Dimopoulos MA, Kastritis E, Terpos E, Nahi H, Goldschmidt H, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. Leukemia. 2017;31(11):2443-8

Larocca A, Mina R, Gay F, Bringhen S, Boccadoro M. Emerging drugs and combinations to treat multiple myeloma. Oncotarget. 2017;8(36):60656-72.

Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015 Feb 7;385(9967):517-528.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.

Leleu X, Martin TG, Einsele H, Lyons RM, Durie BGM, Iskander KS, et al. Role of proteasome inhibitors in relapsed and/or refractory multiple myeloma. Clin Lymphoma Myeloma Leuk. 2019;19(1):9-22.

Mahindra A, Raval G, Mehta P, Brazauskas R, Zhang MJ, Zhong X, et al. New cancers after autotransplantations for multiple myeloma. Biol Blood Marrow Transplant. 2015 Apr;21(4):738-45.

Maude SL. Tisagenlecleucel in pediatric patients with acute lymphoblastic leukemia. Clin Adv Hematol Oncol. 2018 Oct;16(10):664-6.

Maus MV, Levine BL. Chimeric Antigen Receptor T-Cell Therapy for the Community Oncologist. Oncologist. 2016 May;21(5):608-17.

Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv52-iv61.

Munshi NC, Longo DL, Anderson KC. Plasma cell disorders. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 18th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012;1:936-44.

Musto P, Anderson KC, Attal M, Richardson PG, Badros A, Hou J, et al. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. Ann Oncol. 2017 Feb 1;28(2):228-45.

Nahas MR, Avigan D. Challenges in vaccine therapy in hematological malignancies and strategies to overcome them. Expert Opin Biol Ther. 2016 Sep;16(9):1093-104.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Multiple myeloma; Version 1.2020; 2019. Available from: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Older adult oncology; Version 2.2019; 2019a. Available from: https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf.

Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017 Dec 10;377(26):2531-44.

Novak AJ, Darce JR, Arendt BK, Harder B, Henderson K, Kindsvogel W, et al. Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. Blood. 2004 Jan 15;103(2):689-94.

Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis. 2009 Oct 15;49(8):1211-25.

Page DB, Postow MA, Callahan MK, Wolchok JD. Checkpoint modulation in melanoma: an update on ipilimumab and future directions. Curr Oncol Rep. 2013;15(5):500-8.

Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med. 2011 Aug 25;365(8):725-33.

Raje N, Berdeja J, Lin Y, Siegel D, Jagannath S, Madduri D, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med. 2019 May 2;380(18):1726-37.

Raje NS, Berdeja JG, Lin Y, Munshi NC, DiCapua Siegel DS, Liedtke M. et al. bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: Updated results from a multicenter phase I study. J Clin Oncol. 2018;36:15 suppl:8007-8007.

Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016 Jul;91(7):719-34.

Rosenberg SA, Kochenderfer JN. Personalized cell transfer immunotherapy for B-cell malignancies and solid cancers. Mol Ther. 2011 Nov;19(11):1928-30.

Rosenblatt J, Glotzbecker B, Mills H, Vasir B, Tzachanis D, Levine JD, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. J Immunother. 2011 Jun;34(5):409-18.

Sadelain M, Brentjens R, Riviere I. The basic principles of chimeric antigen receptor design. Cancer Discov. 2013 Apr;3(4)388-98.

Sanchez E, Li M, Kitto A, Li J, Wang CS, Kirk DT, et al. Serum B-cell maturation antigen is elevated in multiple myeloma and correlates with disease status and survival. Br J Haematol. 2012 Sep;158(6):727-38.

San-Miguel J, Mateos MV, Rodríguez-Otero P, Bladé J, Lahuerta JJ, Spanish Myeloma Group. New approaches to myeloma treatment in 2017. Hematology Education: the Education Program for the Annual Congress of the European Hematology Association. 2017;11(1):9-12.

Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov. 2018 Aug;8(8):958-71.

Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019 Jan 3; 380(1):45-56.

Siddiqi T, Soumerai JD, Wierda WG, Dubovsky JA, Gillenwater HH, Gong, et al. Rapid MRD-negative responses in patients with relapsed/refractory CLL treated with liso-cel, a CD19-directed CAR T-cell product: preliminary results from Transcend CLL 004, a Phase 1/2 study including patients with high-risk disease previously treated with ibrutinib [abstract]. Blood. 2018 ASH Annual Meeting Abstracts. 2018;132(1): Abstract 300.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. Epub 2020 Jan 8.

Song X, Cong Z, Wilson K. Real-world treatment patterns, comorbidities, and disease-related complications in patients with multiple myeloma in the United States. Curr Med Res Opin. 2016;32(1):95-103.

Sonneveld P, De Wit E, Moreau P. How have evolutions in strategies for the treatment of relapsed/refractory multiple myeloma translated into improved outcomes for patients? Crit Rev Oncol Hematol. 2017;112:153-70.

Turesson I, Bjorkholm M, Blimark CH, Kristinsson S, Velez R, Landgren O. Rapidly changing myeloma epidemiology in the general population: increased incidence, older patients, and longer survival. Eur J Haematol. 2018;101(2):237-44.

Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. 2016;175(2):252-64.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Non-interventional post-authorization safety study (PASS) of patients treated with idecabtagene vicleucel (ide-cel, bb2121) for multiple myeloma (MM) in the postmarketing setting

EU PAS Register® number: to be confirmed
Study reference number (if applicable): BB2121-MM-006

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☒	☐	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2/9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1
	4.2.2 Age and sex	☒	☐	☐	9.3
	4.2.3 Country of origin	☒	☐	☐	3/9.2
	4.2.4 Disease/indication	☒	☐	☐	9.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1.2/9.2.1

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☒	☐	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1/9.3

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1/9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.8
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.8

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.2/9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2/9.3/ 9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.2/9.3/9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2/9.3/9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4/9.6.5.2/9.6.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4/9.6.5.2/9.6.3
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.6
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.6
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.4
11.2 Are methods of quality assurance described?	☒	☐	☐	9.7
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.8
12.1.2 Information bias?	☒	☐	☐	9.8
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	3/9.2/10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol:
[redacted]

Date:

Signature: *{See appended electronic signature page}*

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