17 October 2024
EMA/500721/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Breyanzi

Lisocabtagene maraleucel / Lisocabtagene maraleucel

Procedure no: EMEA/H/C/004731/P46/023

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Steps taken for the assessment		
Description	**Planned date**	**Actual Date**
Start of procedure	19/08/2024	19/08/2024
CAT Rapporteur Assessment Report	23/09/2024	23/09/2024
CAT/CHMP members comments	03/10/2024	N/A
Updated CHMP Rapporteur Assessment Report	07/10/2024	N/A
CAT conclusions/RSI:	11/10/2024	11/10/2024
CHMP adoption of conclusions:	17/10/2024	17/10/2024

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1. Introduction

On August 19, 2024, the MAH submitted a completed paediatric study (study JCAR017-BCM-004) for Breyanzi (liso-cel), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that clinical study JCAR017-BCM-004 was part of a clinical development program. JCAR017-BCM-004 (hereafter, BCM-004) was a Marketing Authorisation Holder (MAH)'s sponsored Phase 1/2, single arm trial, evaluating the safety and efficacy of Breyanzi (lisocabtagene maraleucel; liso-cel) in paediatric subjects (<18 years old and weight ≥ 6 kg) with relapsed/refractory (r/r) B-cell acute lymphoblastic leukaemia (B-ALL) and B-cell non-Hodgkin Lymphoma (B-NHL).

Following the latest application for a modification to the agreed liso-cel paediatric investigation plan (PIP, decision EMEA-001995-PIP01-16-M04 dated 27 October 2023), a product specific waiver in accordance with Article 11(1)(c) of said Regulation was granted, on the grounds that the specific medicinal product did not represent a significant therapeutic benefit over existing treatments for paediatric patients. The waiver covered all subsets of the paediatric population in the following two conditions:

• Treatment of B-lymphoblastic leukaemia/lymphoma

• Treatment of mature B-cell neoplasms

Consequently, Study BCM-004 was early terminated on 26 January 2024.

2.2. Information on the pharmaceutical formulation used in the study

Liso-cel is a T-cell immunotherapy comprising autologous CD4+ and CD8+ T cells that have been transduced using a replication-incompetent, self-inactivating lentiviral vector encoding a CD19-specific CAR.

Each liso-cel dose consisted of a single infusion of two individually formulated CD4+CAR+ and CD8+CAR+ T cell suspensions administered separately in a 1:1 ratio in a formulation containing DMSO.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study JCAR017-BCM-004

2.3.2. Clinical study

Study JCAR017-BCM-004 - A Phase 1/2, Open-Label, Single Arm, Multicohort, Multicenter Trial to Evaluate the Safety and Efficacy of JCAR017 in Pediatric Subjects with Relapsed/Refractory B-ALL And B-NHL (Transcend Pedall)

Description

Study JCAR017-BCM-004 (hereafter referred to as BCM-004) was a Phase 1/2, open-label, single arm, multicohort, multicentre trial evaluating the safety and efficacy of liso-cel in paediatric subjects with r/r B-ALL and r/r B-NHL.

BCM-004 was originally included in the agreed liso-cel PIP (EMEA-001995-PIP01-16; original EMA decision P/0278/2017, dated 04-Oct-2017).

The study design is summarised in Figures below:

Figure 1. study design BCM-004

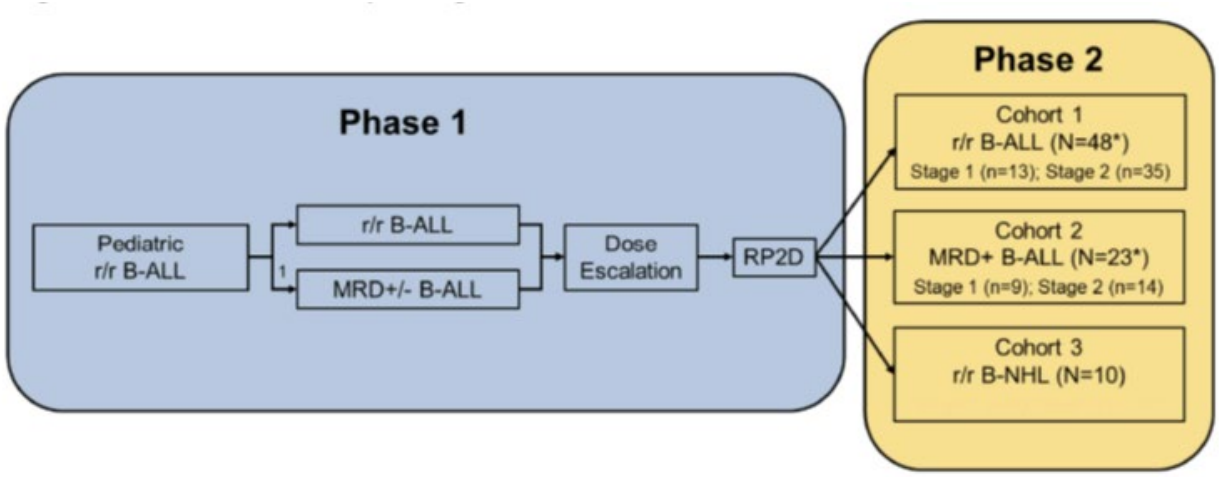
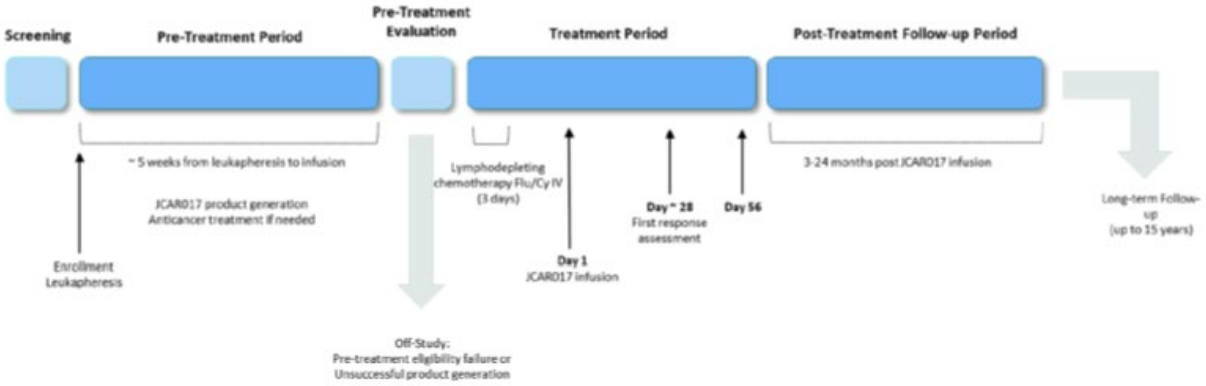


Figure 2. Study schematic



The study was composed of the following 3 treatment periods:

Pre-Treatment Period:

- Screening: study-specified screening assessments were performed within 14 days prior to enrolment.
- Leukapheresis and liso-cel product generation (approximately 5 weeks prior to liso-cel infusion): an unstimulated leukapheresis collection was performed on each subject to obtain a sufficient quantity of PBMCs for the production of the liso-cel investigational product.

Treatment Period (LD chemotherapy to Day 56):

- LD chemotherapy: LD chemotherapy was initiated and completed 2 to 7 days before liso-cel infusion.
- Liso-cel administration: infused on Day 1. The first response evaluation was performed at approximately 28 days after liso-cel infusion.

Post-treatment Follow-up Period (after Day 56 to EOS):

Subjects were followed at approximately 3, 6, 9, 12, 18, and 24 months (EOS) for PD/relapse, safety, CAR+ T cell persistence, second primary malignancies, and survival after administration of liso-cel unless the subject was lost to follow-up. All subjects who either completed the post-treatment follow-up period specified in this protocol or who prematurely withdrew after liso-cel infusion were asked to enrol in the separate LTFU protocol (GC-LTFU-001) for up to 15 years at the EOS visit or at the time of withdrawal, respectively.

Methods

Study participants

Main inclusion/exclusion criteria

Eligible subjects in the Phase 1 part of study BCM-004 were male and female patients who were ≤18 years of age (weight ≥ 6 kg) with evidence of CD19 expression via flow cytometry (peripheral blood or bone marrow) or immunohistochemistry (bone marrow biopsy) and diagnosis of B-ALL (defined as morphological evidence of disease in BM [5% or greater lymphoblast by morphology]) and one of the following:

- first or greater marrow relapse, or
- any marrow relapse after allogeneic HSCT, or
- primary refractory (defined as not achieving a CR or a CRi after 2 or more separate induction regimens), or chemo-refractory (defined as not achieving CR/CRi after 1 cycle of standard chemotherapy for relapsed leukemia), or
- ineligible for allogeneic HSCT

B-ALL subjects meeting the above definition were included regardless of MRD status.

Subjects must have exhibited a Karnofsky score of ≥50 (for ≥16 years of age) or a Lansky score of ≥50 (for <16 years of age).

Subjects with CNS-2 or CNS-3 involvement were eligible if they were asymptomatic and did not have significant neurological disorder per investigator assessment.

Subjects with prior CAR T cell (or other genetically-modified T cell therapy), previous history of or active HBV, HCV or HIV infection, uncontrolled systemic fungal, bacterial, viral infection, acute or chronic graft-versus-host disease (GVHD), active autoimmune disease requiring immunosuppressive therapy, deep venous thrombosis (DVT) or pulmonary embolism (PE) within 3 months prior to leukapheresis, cardiac disorders (CTCAE version 4.03 Grade 3 or 4) within the past 6 months or history/presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, cerebral oedema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis, were excluded from study BCM-004.

Treatments

At the Investigator's discretion, subjects might have received a single cycle of anticancer treatment (ie, bridging chemotherapy) and/or supportive care for disease control while the liso-cel cell product was being manufactured. Chemotherapy or chemoimmunotherapy given after leukapheresis was stopped ≥7 days prior to lymphodepletion (LD) chemotherapy.

Subjects were treated for 3 days with fludarabine IV (30 mg/m^2/day) and cyclophosphamide IV (300 mg/m^2/day) prior to liso-cel infusion: LD chemotherapy was initiated and completed 2 to 7 days before liso-cel infusion (if any AEs occurred due to LD chemotherapy, liso-cel infusion was delayed for up to 14 days after LD chemotherapy upon discussion with the Investigator).

Per protocol, subjects should have been premedicated with paracetamol/acetaminophen 12.5 mg/kg (maximum dose of 650 mg) by PO or IV at an equivalent dose and diphenhydramine hydrochloride 1 mg/kg (maximum dose 50 mg) PO or IV 30 to 60 minutes prior to liso-cel infusion.

Liso-cel was given on Day 1: each liso-cel dose consisted of a single infusion of two individually formulated CD4+CAR+ and CD8+CAR+ T cell suspensions administered separately in a 1:1 ratio in a formulation containing DMSO.

The initial starting dose of 0.50 x 10^6 CAR+ T cells/kg (maximum dose of 50 x 10^6 liso-cel CAR+ T cells [non-weight adjusted]) in BCM-004 was established following the experience of the PLAT-02 study using SCRI-CAR19v1 (Gardner, 2017). However, an AE/DLT (Grade 4 neurotoxicity) was observed in the first r/r B-ALL paediatric subject treated under the original Protocol (dated 29-Mar-2018) and prompted the MAH to re-evaluate the dosing strategy. A lower starting dose was then identified and the protocol was amended (Protocol Amendment 2, dated 10-Sep-2019) to modify the dosing strategy and reduce the starting dose 10-fold to 0.05 x 10^6 CAR+ T cells/kg (maximum dose of 5 x 10^6 liso-cel CAR+ T cells [non-weight adjusted]).

Up to 5 dose levels of liso-cel were planned to be evaluated (see Table below).

Table 1. Dose escalation scheme for BCM-004, according to protocol amendment 2

Dose Level	liso-cel Dose	liso-cel Maximum Dose	
1	0.05x10^6 CAR+ T cells/kg	5x10^6 CAR+ T cells	← 10x fold dose reduction compared to original DL1 (Amendment 2)
2	0.15x10^6 CAR+ T cells/kg	15x10^6 CAR+ T cells	
3	0.30x10^6 CAR+ T cells/kg	30x10^6 CAR+ T cells	
4	0.50x10^6 CAR+ T cells/kg	50x10^6 CAR+ T cells	← Original DL1 (Amendment 1)
5	0.75x10^6 CAR+ T cells/kg	75x10^6 CAR+ T cells	

At DL1 (0.05x10^6 CAR+T cells/kg), a one-time retreatment with intra-patient dose escalation to 0.10 x 10^6 CAR+T cells/kg (maximum dose of 10 x 10^6 liso-cel CAR+ T cells) was allowed for subjects treated at DL1 who had not experienced severe toxicity and did not have a response on Day 28 after liso-cel infusion. Subjects that were re-treated received a cumulative liso-cel dose of 0.15 x 10^6 CAR+ T cells equivalent to DL2. However, data from subjects retreated as part of intra-patient dose escalation were not included in the mTPI-2 algorithm to estimate DLT rates at DL2.

During the study, not all planned dose levels were explored. Subjects were only treated under dose levels 1, 2 and 4. A RP2D could not be established based on the tolerability and preliminary efficacy in the DLT evaluable subjects treated in Phase 1.

Objective(s)

The protocol-specified objectives for safety/efficacy include the following:

Primary objective (Phase 1):

- To identify the recommended Phase 2 dose (RP2D) in paediatric subjects with r/r B-ALL

Secondary objectives (Phase 1 and 2):

- To evaluate the feasibility of manufacturing liso-cel
- To evaluate ORR in the non-selected dose levels from Phase 1
- To evaluate safety and tolerability assessments during 24 months after liso-cel infusion
- To further evaluate efficacy by assessing the DOR, RFS, EFS, BOR, and OS during 24 months after liso-cel infusion
- To evaluate the percentage of r/r B-ALL subjects who achieve CR or CRi with no MRD detected in BM (below the level of detection [<0.01%] by a validated assay) assessed during 24 months after liso-cel infusion
- To assess the percentage of subjects who achieve a response after liso-cel infusion and then proceed to HSCT

Outcomes/endpoints

Recommended Phase 2 Dose (Primary Endpoint): The Phase 1 portion of the study utilized the mTPI-2 algorithm to identify a safe and tolerable dose in paediatric subjects.

Efficacy (Secondary Endpoints): efficacy data were assessed by the Investigator using the 2019 NCCN response criteria guidelines for paediatric ALL. Efficacy endpoints included:

- Best overall response (BOR)
- Objective response rate (ORR, i.e. the proportion of subjects who achieved either CR/CRi on Day 28 that is confirmed on Day 56, divided by the number of subjects included in the analysis)
- DOR (the duration from initial CR/CRi to documented PD, relapsed disease or death due to any cause, whichever occurs first)
- RFS (time from conforming liso-cel infusion to the first PD, relapsed disease or death from any cause, whichever occurs first)
- EFS (time from liso-cel infusion to PD, relapsed disease, start of a new anticancer therapy including HSCT or death from any cause, whichever occurs first)
- OS (interval from the date of first liso-cel infusion to the date of from any cause)

Pharmacodynamics: B-cell aplasia, resulting from anti-CD19 CAR+ T cell therapy, was used as a PD biomarker for on-target functional assessment of liso-cel treatment in subjects. B-cell aplasia assessment in peripheral blood samples was made by a flow cytometry assay, which used an antibody against CD19 for B-cell identification. B-cell aplasia was defined as <1 CD19+ cell per microliter of whole blood.

Persistence of Vector Sequence (PVS) Monitoring: subjects treated with liso-cel were tested at 6-month intervals, at 12 months or any time after 12 months post-infusion for persistence of vector sequence in peripheral blood. Test results generated by ddPCR were reported as percentage (%) of total nucleated

blood cells containing vector sequence in whole blood. If vector sequence was detected in ≥1% of total nucleated blood cells at anytime ≥12 months post-treatment, ISA would be performed to assess clonality for any potential risk of clonal outgrowth or insertion oncogenesis.

Replication-competent Lentivirus (RCL) Testing: RCL was assessed using qPCR on genomic DNA obtained from peripheral blood samples.

Sample size

This study planned to enrol and treat approximately 101 total paediatric subjects (up to 30 in Phase 1 (r/r B-ALL only) and up to 71 additional subjects in Phase 2 (r/r B-ALL and B-NHL)) assuming all dose levels and cohorts enrolled the maximum number of subjects and no subjects would be replaced.

Randomisation and blinding (masking)

N/A. BCM-004 was an open-label, uncontrolled study.

Statistical Methods

The protocol was amended twice throughout the study. The study was initiated under the Original Protocol, dated 29-Mar-2018. Protocol Amendment 1 (dated 07-Jan-2019) was implemented to amend inclusion and exclusion criteria following an Urgent Safety Measure on another liso-cel clinical trial. Protocol Amendment 2 (dated 10-Sep-2019) was implemented to amend the initial starting dose of liso-cel and Phase 1 study design.

A Safety Review Committee (SRC), composed of the medical monitor, drug safety physician, statistician and up to 5 active Investigators, reviewed DLTs in Phase 1, and provided recommendations for dose escalation and de-escalation based on assessment of the safety, PK data and preliminary efficacy information. An independent Data Safety Monitoring Board (DSMB), composed of a statistician and selected physicians with experience in haematology/oncology and/or T cell therapy, reviewed cumulative study data over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial.

Liso-cel dose escalation/de-escalation followed an mTPI-2 algorithm. The decision to open a dose level for enrolment was made by the sponsor and informed by the SRC following review of safety, PK data and preliminary efficacy for subjects treated at each dose.

A dose level was considered unsafe if it had an estimated 95% or more probability of exceeding the target DLT rate of 30% (i.e., P (DLT > 30%|data) >95%) with at least 3 paediatric subjects treated at that dose level. A dose level was considered safe, if at least 3 DLT evaluable paediatric subjects completed the DLT period, and the DLT rate of 30% was not exceeded.

DLTs were defined as: Death not related to disease progression; Grade 4 neurotoxicity; Grade 3 neurotoxicity of greater than 7 days' duration; Grade 3 neurotoxicity not reverting to baseline within 28 days of the start date of the Grade 3 Event; Seizures of any grade not resolving within 7 days; Grade 4 CRS not resolving to Grade ≤ 3 within 3 days; Grade 3 CRS not resolving to Grade ≤ 2 within 7 days; any increase in AST or ALT > 3 × ULN and concurrent increase in total bilirubin >2 × ULN unrelated to CRS that has no other probable reason; Any cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic Grade 3 or 4 event not pre-existing or not due to the underlying malignancy; Any other Grade 3 or 4 event deemed unexpected by the Investigator and considered a DLT upon evaluation by the SRC.

The DLT Analysis Population included all Phase 1 enrolled subjects who received a liso-cel infusion and completed 28 days post liso-cel infusion, the DLT assessment period, if having not been observed as

having a DLT before this point. Subjects who received a nonconforming product were not included in the DLT Analysis Population.

The Efficacy Analysis Population included all subjects who fulfilled all study eligibility criteria and received liso-cel infusion in accordance with drug product release specifications (i.e.., conforming liso-cel product). Subjects who received a nonconforming liso-cel product were not included in the Efficacy Analysis Population. B-ALL subjects who demonstrated morphological remission at screening and were MRD negative upon restaging prior to initiation of LD chemotherapy (i.e., no baseline disease) were treated and followed on study but were not considered evaluable for the EAP.

The Safety Analysis Population included all subjects who have received an infusion of liso-cel cell product. Subjects who received a nonconforming product were not included in the Safety Analysis Population.

Endpoints that were rate/proportion based were reported as the number of subjects eligible for a given analysis along with the rate (percentage) and corresponding Clopper-Pearson 95% CI, while time-to-event data were analysed by Kaplan-Meier curves and the proportion of subjects remaining event free at given time points was presented along with the median time. Greenwood 95% CIs were also derived.

Study BCM-004 was conducted in accordance with the principles of Good Clinical Practice (GCP) as defined by the International Council on Harmonisation (ICH) and was conducted to meet the ethical requirements of European Directive 2001/20/EC.

Results

Participant flow

Patient disposition is summarised in Table below:

Table 2. Study disposition – screening/informed consent/assent set – phase 1

No of subjects (n [%])	Not Assigned N=1	DL1# N=9	DL2# N=8	DL4# N=3	Total* N=24
Subjects screened (a)					24
Subjects who discontinued screening period (a)					3
Screen failure					1 (4.2)
Death					1 (4.2)
Withdrawal by parent/guardian					1 (4.2)
Eligible subjects entered pre-treatment period (b)					21
Subjects leukapheresed (c)	1 (100)	9 (100)	8 (100)	3 (100)	21 (87.5)
Subjects discontinued pre-treatment period (d)	1 (100)	1 (11.1)	1 (12.5)	2 (66.7)	5 (23.8)
Death	1 (100)	0	1 (12.5)	0	2 (9.5)
Study drug manufacturing failure	0	1 (11.1)	0	0	1 (4.8)
Failure to meet treatment criteria	0	0	0	2 (66.7)	2 (9.5)
Subjects continued to treatment period (d)	0	8 (88.9)	7 (87.5)	1 (33.3)	16 (76.2)
Subjects received lymphodepleting chemotherapy	0	8 (88.9)	7 (87.5)	1 (33.3)	16 (76.2)
Subjects not received product after LDC (e)	0	1 (12.5)	0	0	1 (6.3)
Subjects received product after LDC (e)	0	7 (87.5)	7 (100)	1 (100)	15 (93.8)
Received non-conforming product (e)	0	0	1 (14.3)	0	1 (6.3)
Received conforming liso-cel product (e)	0	7 (87.5)	6 (85.7)	1 (100)	14 (87.5)
Subjects completed treatment period (e)	0	3 (37.5)	6 (85.7)	1 (100)	10 (62.5)
Subjects discontinued treatment period (e)	0	5 (62.5)	1 (14.3)	0	6 (37.5)

No of subjects (n [%])	Not Assigned N=1	DL1# N=9	DL2# N=8	DL4# N=3	Total* N=24
Death	0	1 (12.5)	0	0	1 (6.3)
Progressive disease	0	2 (25.0)	0	0	2 (12.5)
Lost to follow-up	0	0	1 (14.3)		1 (6.3)
Study terminated by sponsor	0	1 (12.5)	0	0	1 (6.3)
Other	0	1 (12.5)	0	0	1 (6.3)
Subject received product retreatment (e)	0	1 (12.5)	0	0	1 (6.3)
Subjects continued to follow-up period (e)	0	6 (75.0)	6 (85.7)	1 (100)	13 (81.3)
Subjects discontinued follow-up period (e)	0	5 (62.5)	3 (42.9)	1 (100)	9 (56.3)
Death	0	3 (37.5)	1 (14.3)	1 (100)	5 (31.3)
Study terminated by sponsor	0	2 (25.0)	1 (14.3)	0	3 (18.8)
Other	0	0	1 (14.3)	0	1 (6.3)
Subjects continued to long-term follow-up period	0	3 (37.5)	3 (42.9)	0	6 (37.5)

(*) 3 Screen Failure subjects are presented only in Total column.

#DL1: (0.05 x10^6 CAR+ T cells/kg)

#DL2: (0.15x10^6 CAR+ T cells/kg)

#DL4: (0.50x10^6 CAR+ T cells/kg); originally DL1 in original Protocol and Protocol Amendment 1

(a) Subjects signed informed consent.

(b) Subjects signed consent who meet all inclusion, exclusion criteria at the screening assessment and completed the screening period.

(c) Percentages are based on the number of subjects screened.

(d) Percentages are based on the number of subjects leukapheresed

(e) Percentages are based on the number of subjects received LDC (Lymphodepleting chemotherapy)

Of the 14 subjects who received liso-cel, 1 (6.3%) subject received a retreatment with liso-cel according to the intra-patient dose-escalation schema for DL1 in accordance with Protocol Amendment 2, and 11 subjects met the criteria to be included in the Efficacy Analysis population.

Of the 24 r/r B-ALL subjects screened, 13 (54.2%) subjects died from the time of informed consent and end of study. Twelve (50%) subjects died due to progression of their r/r B-ALL, 1 (4.2%) subject died due to an adverse event (respiratory insufficiency due to pulmonary haemorrhage) on Study Day 271 following complications post-HSCT. Of the 13 subjects who died, 5 (20.8%) subjects died due to progression of their r/r B-ALL prior to receiving liso-cel.

Recruitment

A total of 18 sites across 6 countries were activated on study BCM-005, of which 6 sites across 4 countries enrolled subjects.

Baseline data

Demographic and disease characteristics at baseline are summarised in Table below:

Table 3. Demographic and baseline characteristics

No of subjects (n [%])	Not Assigned N=1	DL1# N=9	DL2# N=8	DL4# N=3	Total N=21
Age (years)					
Mean (SD)	14 (NA)	7.6 (4.64)	6.3 (4.80)	5 (1.73)	7 (4.52)
Median (min, max)	14 (14, 14)	7 (1, 17)	5.5 (1, 14)	4 (4, 7)	7 (1, 17)
Age categorization (%)					
<6	0	3 (33.3)	4 (50.0)	2 (66.7)	9 (42.9)
≥6 to <12	0	5 (55.6)	3 (37.5)	1 (33.3)	9 (42.9)
≥12 to <18	1 (100)	1 (11.1)	1 (12.5)	0	3 (14.3)
Sex (%)					
Male	1 (100)	4 (44.4)	4 (50.0)	1 (33.3)	10 (47.6)
Female	0	5 (55.6)	4 (50.0)	2 (66.7)	11 (52.4)
Race (%)					
American Indian or Alaska Native	1 (100)	1 (11.1)	1 (12.5)	0	3 (14.3)
White	0	6 (66.7)	5 (62.5)	3 (100)	14 (66.7)
Not collected or unknown	0	2 (22.2)	2 (25.0)	0	4 (19.0)
Ethnicity (%)					
Hispanic or Latino	1 (100)	4 (44.4)	3 (37.5)	1 (33.3)	9 (42.9)
Not Hispanic or Latino	0	4 (44.4)	4 (50.0)	2 (66.7)	10 (47.6)
Not reported	0	1 (11.1)	1 (12.5)	0	2 (9.5)
Baseline characteristics					
Central nervous system disease pre-LDC*,^					
CNS-1	0	2 (22.2)	1 (12.5)	0	3 (14.3)
CNS -3	0	1 (11.1	0	0	1 (4.8)
CNS involvement not reported	1 (100)	6 (66.7)	7 (87.5)	3 (100)	17 (81.0)
Prior stem cell transplant received					
Yes	0	5 (55.6)	3 (37.5)	1 (33.3)	9 (42.9)
No	1 (100)	4 (44.4)	5 (62.5)	2 (66.7)	12 (57.1)
Presence of extramedullary disease pre-LDC					
Yes	0	2 (22.2)	2 (25.0)	0	4 (19.0)
No	0	6 (66.7)	5 (62.5)	0	11 (52.4)
Not reported	1 (100.0)	1 (11.1)	1 (12.5)	3 (100)	6 (28.6)

No of subjects (n [%])	Not Assigned N=1	DL1# N=9	DL2# N=8	DL4# N=3	Total N=21
Philadelphia-related abnormalities					
Non-Philadelphia positive or - like	1 (100)	9 (100)	8 (100)	3 (100)	21 (100)
MLL rearrangement-related abnormalities					
MLL rearrangement	0	0	2 (25.0)	1 (33.3)	3 (14.3)
Without MLL rearrangement	0	0	1 (12.5)	0	1 (4.8)
MLL rearrangement not reported	1 (100)	9 (100.0)	5 (62.5)	2 (66.7)	17 (81.0)

Baseline clinical characteristics are defined as the latest data collected before the (first) liso-cel infusion unless the timepoint is explicitly stated.

#DL1: (0.05 x10^6 CAR+ T cells/kg)

#DL2: (0.15x10^6 CAR+ T cells/kg)

#DL4: (0.50x10^6 CAR+ T cells/kg); originally DL1 in original Protocol and Protocol Amendment 1

*No CNS-2 reported

^National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Pediatric Acute Lymphoblastic Leukemia; V.1.2020 - May 2019. Available from: https://www.nccn.org.

Number analysed

A total of 16 (76.2%) subjects received at least one dose of LDC. Out of the 16 subjects who received at least one dose of LDC, 14 (87.5%) subjects received liso-cel, 1 (6.3%) subject received non-conforming product and 1 (6.3%) subject was not infused due to AEs (leukopenia and neutropenic fever) and disease progression during the administration of LDC.

Of the 14 subjects who received liso-cel, 1 (6.3%) subject received a retreatment with liso-cel according to the intra-patient dose-escalation schema for DL1 in accordance with Protocol Amendment 2, and 11 subjects met the criteria to be included in the Efficacy Analysis population.

Efficacy results

Objective remission rate (ORR), duration of response (DoR) and minimal residual disease (MRD) negativity rate

In the Efficacy Analysis population (EAP N=11), ORR was observed in 5 (45.5%) subjects (95%CI: 16.7, 76.6) and consisted of CRi only, with no CRs observed. Median DOR was 13.7 months (95% CI: NA, NA) and 3 (27.3%) subjects who achieved a CRi in the EAP also achieved MRD-negative response with 95% CI (6.0, 61.0) (see Tables below).

Table 4. Analysis of ORR – Investigator assessment

Parameter	DL1# N=6	DL2# N=4	DL4# N=1	Total N=11
Best Overall response				
Complete response (CR), n (%)	0	0	0	0
Complete response with incomplete blood count recovery (CRi), N (%)	3 (50.0)	1 (25.0)	1 (100)	5 (45.5)
Refractory disease, n (%)	0	0	0	0
Progressive disease (PD), n (%)	0	0	0	0
Relapsed disease, n (%)	1 (16.7)	0	0	1 (9.1)
Not applicable (NA), n (%)	2 (33.3)	3 (75.0)	0	5 (45.5)
Overall response rate (ORR)				
N (%)	3 (50.0)	1 (25.0)	1 (100)	5 (45.5)
95% CI (a)	(11.8, 88.2)	(0.6, 80.6)	(2.5, 100.0)	(16.7, 76.6)
Complete response rate (CRR)				
N (%)	0	0	0	0
95% CI (a)	(0.0, 45.9)	(0.0, 60.2)	(0.0, 97.5)	(0.0, 28.5)

Response is assessed per the NCCN Response Criteria Guidelines for pediatric ALL (NCCN, 2019).

ORR is defined as the proportion of subjects who achieved either a CR or CRi on Day 28 that is confirmed on Day 56, divided by the number of subjects included in the analysis.

CRR is the proportion of subjects who achieved a BOR of CR. CR is defined as CR on Day 28 that is confirmed on Day 56.

Disease assessments recorded on or after start of a new anti-cancer therapy including HSCT, will not be considered, nor will disease assessments reported after a PD or relapse has been observed.

The 95% confidence interval could not be estimated due to lack of data variability.

(a) Two-sided 95% confidence interval based on exact Clopper-Pearson method.

NA = Not Applicable; includes subjects who did not have disease assessments performed per protocol.

#DL1: (0.05 x10^6 CAR+ T cells/kg)

#DL2: (0.15x10^6 CAR+ T cells/kg)

#DL4: (0.50x10^6 CAR+ T cells/kg); originally DL1 in original Protocol and Protocol Amendment 1

Table 5. Analysis of DOR – Investigator assessment – All responders in efficacy analysis set – Phase 1

Parameter	DL1# N=3	DL2# N=1	DL4# N=1	Total N=5
Number of patients with event, n (%)	1 (33.3)	0	0	1 (20.0)
Death, n (%)	0	0	0	0
Progressive disease, n (%)	0	0	0	0
Relapsed disease, n (%)	1 (33.3)	0	0	1 (20.0)
Censored, n (%)	2 (66.7)	1 (100)	1 (100)	4 (80.0)
Duration of response (months)				
Median (95% CI) (a)	13.70 (NA, NA)*	NA	NA	13.70 (NA, NA)*
Min, max (b)	2.46+, 13.70	4.93+, 4.93+	2.23+, 2.23+	2.23+, 13.70

DOR is defined as the duration from initial response (either a CR or CRi) to documented PD, relapsed disease or death due to any cause, whichever occurs first.

(a) Median, 25th, and 75th percentile estimates of time to event are from Kaplan-Meier product-limit estimates.

(b) Symbol + indicates a censored value.

N.A. = Not Available. * The 95% confidence interval could not be estimated due to lack of data variability.

#DL1: (0.05 x10^6 CAR+ T cells/kg)

#DL2: (0.15x10^6 CAR+ T cells/kg)

#DL4: (0.50x10^6 CAR+ T cells/kg); originally DL1 in original Protocol and Protocol Amendment 1

Table 6. Analysis of MRD negative response rate

Parameter	DL1# N=6	DL2# N=4	DL4# N=1	Total N=11
MRD NEGATIVE RESPONSE RATE	1/6 (16.7%)	1/4 (25.0%)	1/1 (100.0%)	3/11 (27.3%)
95% CI	0.4, 64.1	0.6, 80.6	2.5, 100.0	6.0, 61.0

Minimal Residual Disease (MRD) Negative Response Rate is defined as the proportion of subjects achieving either a CR or CRi with a MRD negative bone marrow on Day 28, confirmed on Day 56, divided by the number of subjects included in the analysis.

Disease assessments recorded on or after start of a new anticancer therapy, including HSCT, will not be considered, nor will disease assessments reported after a PD or relapse has been observed.

CR and CRi are considered as assessed by the investigator.

The 95% confidence interval is estimated based on Clopper-Pearson exact method.

#DL1: (0.05 x10^6 CAR+ T cells/kg)

#DL2: (0.15x10^6 CAR+ T cells/kg)

#DL4: (0.50x10^6 CAR+ T cells/kg); originally DL1 in original Protocol and Protocol Amendment 1

One (9.1%) subject did not achieve a response at Day 28 and had a best response of relapsed disease and was re-treated with liso-cel per the intra-patient dose-escalation schema. No subjects had documented best response of refractory disease or PD. Five (45.5%) subjects were considered to have a BOR of 'Not Applicable' because they did not have efficacy assessments performed per protocol (3 subjects discontinued from the study prior Day 28 and 2 subjects did not have disease assessments confirmed at Day 56).

Non-responders generally exhibited low expansion of both CD8+ EGFRt+ and CD4+ EGFRt+ cells. Responders exhibited expansion of CD8+ EGFRt+ cells. Limited expansion of CD4+ EGFRt+ cells was observed in both responders and non-responders.

Relapse-free survival (RFS), Event-free survival (EFS) and Overall survival (OS)

The Kaplan-Meier (KM) estimates for the median for RFS was 8.97 months (95% CI: 0.79, NA), EFS was 4.99 months (95% CI: 0.79, 8.97), and for OS was 8.90 months (95% CI: 0.92, NA) (see Table below).

Table 7. Efficacy Endpoints

Parameter	DL1# N=6	DL2# N=4	DL4# N=1	Total N=11
Relapse-free survival				
Number of patients with event, n(%)	4 (66.7)	3 (75.0)	0	7 (63.6)
Death, n (%)	1 (16.7)	2 (50.0)	0	3 (27.3)
Progressive disease, n (%)	1 (16.7)	0	0	1 (9.1)
Relapsed disease, n (%)	2 (33.3)	1 (25.0)	0	3 (27.3)
Censored, n (%)	2 (33.3)	1 (25.0)	1 (100)	4 (36.4)
Relapse-free survival (months)				
Median (95% CI) (a)	7.77 (0.46, NA)	6.98 (1.15, NA)	NA	8.97 (0.79, NA)
Min, max (b)	0.46, 14.62	1.15, 8.97	3.12+, 3.12+	0.46, 14.62
Event-Free Survival				
Number of patients with event, n (%)	5 (83.3)	4 (100)	1 (100)	10 (90.9)
Death, n (%)	1 (16.7)	2 (50.0)	0	3 (27.3)
Progressive disease, n (%)	1 (16.7)	0	0	1 (9.1)
Relapsed disease, n (%)	2 (33.3)	1 (25.0)	0	3 (27.3)
Start of a new therapy, n (%)	1 (16.7)	1 (25.0)	1 (100)	3 (27.3)
Censored, n (%)	1 (16.7)	0	0	1 (9.1)
Event-free survival (months)				
Median (95% CI) (a)	3.24 (0.46, NA)	5.42 (1.15, NA)	3.12 (NA, NA)*	4.99 (0.79, 8.97)
Min, max (b)	0.46, 14.62	1.15, 8.97	3.12, 3.12	0.46, 14.62
Overall Survival				
Number of deaths, n (%)	4 (66.7)	3 (75.0)	1 (100)	8 (72.7)
Number censored, n (%)	2 (33.3)	1 (25.0)	0	3 (27.3)
Time to event (months)				
Median (95% CI) (a)	7.13 (0.76, NA)	7.08 (4.99, NA)	8.90 (NA, NA)*	8.90 (0.92, NA)
Min, max (b)	0.76, 23.98+	4.99, 24.97+	8.90, 8.90	0.76, 24.97+

RFS is defined as time from conforming liso-cel infusion to the first progressive disease (PD), relapsed disease or death from any cause, whichever occurs first.

EFS is defined as time from conforming liso-cel infusion to progressive disease (PD), relapsed disease, start of a new anticancer therapy including HSCT or death from any cause, whichever occurs first.

OS is defined as the interval from the date of first confirming liso-cel infusion to the date of from any cause.

N.A. = Not Available. *The 95% confidence interval could not be estimated due to lack of data variability.

(a) Median, 25th, and 75th percentile estimates of time to event are from Kaplan-Meier product-limit estimates.

(b) Symbol + indicates a censored value.

NA = Not Available

#DL1: (0.05 x10^6 CAR+ T cells/kg)

#DL2: (0.15x10^6 CAR+ T cells/kg)

#DL4: (0.50x10^6 CAR+ T cells/kg); originally DL1 in original Protocol and Protocol Amendment 1

Allogenic haematopoietic stem cell transplant (HSCT) rate

Of the 14 subjects received liso-cel, 5 (35.7%) who achieved a CR/CRi post liso-cel proceeded to allogeneic HSCT:

- In DL1: 2 (14.3%) subjects proceeded to HSCT after liso-cel (174 and 598 days after liso-cel, respectively); 1 subject had a best response post-HSCT of relapsed disease and 1 subject had a best response post-HSCT of CRi.

- In DL2: 2 (14.3%) subjects proceeded to HSCT after liso-cel (98 and 183 days after liso-cel, respectively); 1 subject had a best response post-HSCT of MRD negative CR and 1 subject had a best response post-HSCT of CR.
- In DL4: 1 (7.1%) subject proceeded to HSCT 101 days after liso-cel and had a best response post-HSCT of CR.

Pharmacodynamic B-cell aplasia Results

Overall, rapid CD19+ B-cell recovery was observed in paediatric r/r B-ALL patients treated with liso-cel at all dose levels. CD19+ cells from 13 of 14 liso-cel treated patients had either recovered by month 6 (>1 cell/µL) and/or the subjects have clinically progressed.

Safety results

Extent of Exposure

All 14 subjects who received liso-cel were infused with the planned volume of CD8+ and CD4+ $\times 10^6$ CAR+ T cells i.e, no difference was noted between the planned volume and the actual volume of infused cells.

The median total number of CD8+ cells infused was 1.25×10^6 (range: 0.3, 25.3) and CD4+ cells were 1.24×10^6 (range: 0.3, 24.5) for the overall liso-cel treated population.

Adverse events (AEs), Serious AEs (SAEs) and Deaths

All (n=14) subjects who received liso-cel experienced at least 1 TEAE between (first) liso-cel infusion and 30 days after (last) liso-cel infusion, while 7 (50%) subjects had experienced at least 1 TEAE between 31 and 90 days after (last) liso-cel infusion. Twelve (85.7%) subjects experienced at least 1 NCI CTCAE Grade 3/4 TEAE and 8 (57.1%) subjects experienced at least 1 NCI CTCAE Grade 3/4 TEAE that was related to liso-cel (see Table below).

Table 8. Treatment-emergent adverse events summary – safety analysis set

Safety Parameter n(%)	DL1# N=7	DL2# N=6	DL4# N=1	Total N=14
Subjects with at least one TEAE	7 (100)	6 (100)	1 (100)	14 (100)
Subjects with at least one CTCAE Grade 3/4 TEAE	6 (85.7)	5 (83.3)	1 (100)	12 (85.7)
Subjects with at least one TEAE leading to death	0	0	0	0
Subjects with at least one TEAE related to liso-cel	5 (71.4)	5 (83.3)	1 (100)	11 (78.6)
Subjects with at least one CTCAE Grade 3/4 TEAE related to liso-cel	3 (42.9)	4 (66.7)	1 (100)	8 (57.1)
Subjects with at least one serious TEAE	5 (71.4)	3 (50.0)	1 (100)	9 (64.3)
Subjects with at least one serious TEAE related to liso-cel	1 (14.3)	3 (50.0)	1 (100)	5 (35.7)
Subjects with at least one TEAE related to LDC	4 (57.1)	3 (50.0)	1 (100)	8 (57.1)
Subjects with at least one TEAE leading to liso-cel discontinuation	0	0	0	0
Subjects with at least one TEAE recorded between (first) liso-cel infusion and 30 days after (last) liso-cel infusion, inclusive	7 (100)	6 (100)	1 (100)	14 (100)
Subjects with at least one TEAE recorded between 31 and 90 days after (last) liso-cel, inclusive	3 (42.9)	3 (50.0)	1 (100)	7 (50.0)
Subjects with at least one non- TEAE recorded after 90 days following the (last) infusion of liso-cel	3 (42.9)	1 (16.7)	1 (100)	5 (35.7)

N = number of subjects in analysis set; n (%) = number (percentage) of subjects.

LDC = Lymphodepleting chemotherapy

Treatment-emergent AEs (TEAEs) are defined as any AE occurring on or after the liso-cel infusion and within 90 days after the liso-cel infusion date. Any AE occurring after the initiation of another anticancer therapy or liso-cel retreatment will not be considered as a liso-cel TEAE.

AEs graded using CTCAE version 4.03.

Modified CTCAE is used for CRS (Lee, 2014).

#DL1: (0.05 x10^6 CAR+ T cells/kg)

#DL2: (0.15x10^6 CAR+ T cells/kg)

#DL4: (0.50x10^6 CAR+ T cells/kg); originally DL1 in original Protocol and Protocol Amendment 1

The most frequently (≥40%) reported TEAEs by PT overall were anaemia (78.6%), CRS (64.3%), thrombocytopenia (57.1%), leukopenia, and neutropenia (with 42.9% each) (see Table below).

Table 9. Treatment-emergent adverse events (TEAEs) by SOC and PT safety analysis set

System Organ Class n(%) Preferred Term n(%)	DL1[#] N=7	DL2[#] N=6	DL4[#] N=1	Total N=14
Total subjects with an event	7 (100)	6 (100)	1 (100)	14 (100.0)
Blood and lymphatic system disorders	6 (85.7)	5 (83.3)	1 (100)	12 (85.7)
Anaemia	5 (71.4)	5 (83.3)	1 (100)	11 (78.6)
Thrombocytopenia	4 (57.1)	3 (50.0)	1 (100)	8 (57.1)
Leukopenia	4 (57.1)	1 (16.7)	1 (100)	6 (42.9)
Neutropenia	3 (42.9)	2 (33.3)	1 (100)	6 (42.9)
Coagulopathy	0	0	1 (100)	1 (7.1)
Febrile Neutropenia	1 (14.3)	0	0	1 (7.1)
Immune system disorders	5 (71.4)	4 (66.7)	1 (100)	10 (71.4)
Cytokine release syndrome	4 (57.1)	4 (66.7)	1 (100)	9 (64.3)
Hypogammaglobulinaemia	1 (14.3)	1 (16.7)	1 (100)	3 (21.4)
Haemophagocytic lymphohistiocytosis	0	1 (16.7)	0	1 (7.1)
Investigations	4 (57.1)	3 (50.0)	1 (100)	8 (57.1)
Alanine aminotransferase increased	4 (57.1)	0	1 (100)	5 (35.7)
Aspartate aminotransferase increased	4 (57.1)	0	0	4 (28.6)
Gamma-glutamyltransferase increased	4 (57.1)	0	0	4 (28.6)
Oxygen saturation decreased	0	2 (33.3)	0	2 (14.3)
Bilirubin conjugated increased	1 (14.3)	0	0	1 (7.1)
Blood bilirubin increased	1 (14.3)	0	0	1 (7.1)
Blood creatinine increased	1 (14.3)	0	0	1 (7.1)
Blood fibrinogen decreased	1 (14.3)	0	0	1 (7.1)
Blood triglycerides increased	1 (14.3)	0	0	1 (7.1)
Blood uric acid increased	1 (14.3)	0	0	1 (7.1)
Interleukin level increased	0	1 (16.7)	0	1 (7.1)
International normalised ratio increased	1 (14.3)	0	0	1 (7.1)
Serum ferritin increased	0	1 (16.7)	0	1 (7.1)
Gastrointestinal disorders	3 (42.9)	3 (50.0)	1 (100)	7 (50.0)
Vomiting	1 (14.3)	3 (50.0)	0	4 (28.6)
Nausea	2 (28.6)	1 (16.7)	0	3 (21.4)
Abdominal pain	1 (14.3)	1 (16.7)	0	2 (14.3)
Anal fissure	1 (14.3)	1 (16.7)	0	2 (14.3)
Diarrhoea	0	1 (16.7)	1 (100)	2 (14.3)
Anaesthesia oral	0	1 (16.7)	0	1 (7.1)
Colitis	1 (14.3)	0	0	1 (7.1)
Constipation	0	1 (16.7)	0	1 (7.1)
Intestinal haemorrhage	1 (14.3)	0	0	1 (7.1)
Lip dry	0	1 (16.7)	0	1 (7.1)
Oral mucosal erythema	0	1 (16.7)	0	1 (7.1)
Metabolism and nutrition disorders	4 (57.1)	2 (33.3)	1 (100)	7 (50.0)
Hypertriglyceridaemia	3 (42.9)	0	0	3 (21.4)
Decreased appetite	1 (14.3)	1 (16.7)	0	2 (14.3)
Hyperphosphataemia	1 (14.3)	0	1 (100)	2 (14.3)
Hypoalbuminaemia	2 (28.6)	0	0	2 (14.3)
Hypophosphataemia	1 (14.3)	0	1 (100)	2 (14.3)
Fluid retention	1 (14.3)	0	0	1 (7.1)
Hyperamylasaemia	1 (14.3)	0	0	1 (7.1)
Hyperlipidaemia	1 (14.3)	0	0	1 (7.1)
Hypermagnesaemia	1 (14.3)	0	0	1 (7.1)
Hypernatraemia	1 (14.3)	0	0	1 (7.1)

Table 10. Treatment-emergent adverse Events (TEAEs) by SOC and PT - safety analysis set

System Organ Class n(%) Preferred Term n(%)	DL1[#] N=7	DL2[#] N=6	DL4[#] N=1	Total N=14
Hypoglycaemia	0	1 (16.7)	0	1 (7.1)
Hypokalaemia	1 (14.3)	0	0	1 (7.1)
Hypomagnesaemia	1 (14.3)	0	0	1 (7.1)
Tumour lysis syndrome	0	1 (16.7)	0	1 (7.1)
Infections and infestations	4 (57.1)	1 (16.7)	1 (100)	6 (42.9)
Bacteraemia	1 (14.3)	1 (16.7)	0	2 (14.3)
Clostridium difficile infection	0	0	1 (100)	1 (7.1)
Cytomegalovirus infection	1 (14.3)	0	0	1 (7.1)
Paronychia	1 (14.3)	0	0	1 (7.1)
Pneumonia	1 (14.3)	0	0	1 (7.1)
Pneumonia fungal	1 (14.3)	0	0	1 (7.1)
Sepsis	1 (14.3)	0	0	1 (7.1)
Staphylococcal bacteraemia	0	0	1 (100)	1 (7.1)
Upper respiratory tract infection	1 (14.3)	0	0	1 (7.1)
Viraemia	1 (14.3)	0	0	1 (7.1)
Nervous system disorders	2 (28.6)	2 (33.3)	1 (100)	5 (35.7)
Neurotoxicity	1 (14.3)	2 (33.3)	1 (100)	4 (28.6)
Brain oedema	0	0	1 (100)	1 (7.1)
Dizziness	0	1 (16.7)	0	1 (7.1)
Hemiplegia	1 (14.3)	0	0	1 (7.1)
Skin and subcutaneous tissue disorders	1 (14.3)	3 (50)	1 (100)	5 (35.7)
Dermatitis atopic	0	1 (16.7)	0	1 (7.1)
Erythema	0	1 (16.7)	0	1 (7.1)
Night sweats	0	0	1 (100)	1 (7.1)
Rash	1 (14.3)	0	0	1 (7.1)
Rash maculo-papular	0	1 (16.7)	0	1 (7.1)
Skin erosion	0	1 (16.7)	0	1 (7.1)
Skin exfoliation	0	1 (16.7)	0	1 (7.1)
Injury, poisoning and procedural complications	1 (14.3)	2 (33.3)	0	3 (21.4)
Extradural haematoma	1 (14.3)	0	0	1 (7.1)
Infusion related reaction	0	1 (16.7)	0	1 (7.1)
Refractoriness to platelet transfusion	0	1 (16.7)	0	1 (7.1)
Vascular disorders	1 (14.3)	1 (16.7)	1 (100)	3 (21.4)
Hypertension	1 (14.3)	0	1 (100)	2 (14.3)
Cyanosis	0	1 (16.7)	0	1 (7.1)
Cardiac disorders	0	1 (16.7)	1 (100)	2 (14.3)
Bradycardia	0	1 (16.7)	1 (100)	2 (14.3)
Tachycardia	0	0	1 (100)	1 (7.1)
Respiratory, thoracic and mediastinal disorders	2 (28.6)	0	0	2 (14.3)
Cough	1 (14.3)	0	0	1 (7.1)

System Organ Class n(%) Preferred Term n(%)	DL1[#] N=7	DL2[#] N=6	DL4[#] N=1	Total N=14
Pleural effusion	1 (14.3)	0	0	1 (7.1)
Ear and labyrinth disorders	1 (14.3)	0	0	1 (7.1)
Ear pain	1 (14.3)	0	0	1 (7.1)
General disorders and administration site conditions	1 (14.3)	0	0	1 (7.1)
Pyrexia	1 (14.3)	0	0	1 (7.1)
Hepatobiliary disorders	1 (14.3)	0	0	1 (7.1)
Cholecystitis	1 (14.3)	0	0	1 (7.1)
Hyperbilirubinaemia	1 (14.3)	0	0	1 (7.1)
Musculoskeletal and connective tissue disorders	0	0	1 (100)	1 (7.1)
Myalgia	0	0	1 (100)	1 (7.1)
Psychiatric disorders	1 (14.3)	0	0	1 (7.1)
Insomnia	1 (14.3)	0	0	1 (7.1)
Renal and urinary disorders	0	1 (16.7)	0	1 (7.1)
Haematuria	0	1 (16.7)	0	1 (7.1)

N = number of subjects in analysis set; n (%) = number (percentage) of subjects.

Treatment-emergent AEs (TEAEs) are defined as any AE occurring on or after the liso-cel infusion and within 90 days after the liso-cel infusion date. Any AE occurring after the initiation of another anticancer therapy or liso-cel retreatment will not be considered as a liso-cel TEAE.

AEs coded using MedDRA version 26.0. A subject is counted only once for multiple events within preferred term/system organ class.

#DL1: (0.05 x10^6 CAR+ T cells/kg)

#DL2: (0.15x10^6 CAR+ T cells/kg)

#DL4: (0.50x10^6 CAR+ T cells/kg); originally DL1 in original Protocol and Protocol Amendment 1

Four (26.6%) subjects experienced a TEAE of iiNT: 1 subject experienced a Grade 4 iiNT event with cerebral oedema that was considered serious and a DLT at DL4; 1 subject experienced a Grade 4 iiNT event with cerebral oedema and seizures that was considered serious and a DLT at DL2; 1 subject experienced a Grade 3 iiNT event with seizures that was considered serious but not a DLT at DL1; 1 subject experienced a Grade 1 iiNT event at DL2 that was not considered serious.

Nine (64.3%) subjects experienced at least one serious TEAE during the treatment period. The most frequently (≥20%) reported serious TEAEs by PT overall were CRS and iiNT, in 3 (21.4%) subjects each (see Table below).

Table 11. Serious treatment-emergent adverse events (TEAEs) by SOC and PT- safety Analysis set

System Organ Class n(%) Preferred Term n(%)	DL1# N=7	DL2# N=6	DL4# N=1	Total N=14
Total subjects with an event	5 (71.4)	3 (50.0)	1 (100)	9 (64.3)
Immune system disorders	0	3 (50.0)	0	3 (21.4)
Cytokine release syndrome	0	3 (50.0)	0	3 (21.4)
Infections and infestations	3 (42.9)	0	0	3 (21.4)
Pneumonia	1 (14.3)	0	0	1 (7.1)
Sepsis	1 (14.3)	0	0	1 (7.1)
Viraemia	1 (14.3)	0	0	1 (7.1)
Nervous system disorders	1 (14.3)	1 (16.7)	1 (100)	3 (21.4)
Neurotoxicity	1 (14.3)	1 (16.7)	1 (100)	3 (21.4)
Brain oedema	0	0	1 (100)	1 (7.1)
Injury, poisoning and procedural complications	1 (14.3)	1 (16.7)	0	2 (14.3)
Extradural haematoma	1 (14.3)	0	0	1 (7.1)
Infusion related reaction	0	1 (16.7)	0	1 (7.1)

N = number of subjects in analysis set; n (%) = number (percentage) of subjects.

Treatment-emergent AEs (TEAEs) are defined as any AE occurring on or after the liso-cel infusion and within 90 daysafter the liso-cel infusion date. Any AE occurring after the initiation of another anticancer therapy or liso-cel retreatment will not be considered as a liso-cel TEAE.

AEs coded using MedDRA version 26.0. A subject is counted only once for multiple events within preferred term/system organ class.

#DL1: (0.05 x10^6 CAR+ T cells/kg)

#DL2: (0.15x10^6 CAR+ T cells/kg)

#DL4: (0.50x10^6 CAR+ T cells/kg); originally DL1 in original Protocol and Protocol Amendment 1

Eleven subjects were included in the DLT Analysis Set. Of the 11 subjects, 3 (27.3%) subjects experienced a DLT: no subjects in DL1 experienced DLTs, 1 out of 11 (9.1%) subjects (in DL4) experienced a DLT of Grade 4 neurotoxicity with cerebral oedema. This DLT was observed in the first subject treated on-study, and prompted Protocol Amendment 2 which reduced the initial starting dose 10-fold. Two out of 11 (18.2%) subjects (both in DL2) experienced DLTs, both of these DLTs prompted dose de-escalations per protocol (1 subject experienced a DLT of Grade 4 liso-cel infusion reaction and 1 subject experienced a DLT of Grade 4 neurotoxicity with cerebral oedema and seizures, accompanied by Grade 1 CRS).

No second primary malignancies were reported during the study.

Exploratory Safety Assessment of Transgene Involvement

Persistence of Vector Sequence (PVS) Monitoring

Of 10 samples from 4 subjects that were collected and tested at any time point after 12-months post-infusion, there were no samples that met the criteria (≥1% of the total nucleated blood cells containing transgene) for ISA.

Replication-competent Lentivirus (RCL) Testing

Of 37 samples tested from 15 subjects, no RCL was detected in any of the samples.

MAH's conclusions

Data from BCM-004 demonstrated that liso-cel treatment in the paediatric r/r BALL population exhibited sub-optimal duration of clinical response, unfavourable adverse events with early occurrence of cerebral oedema at low dose levels, rapid CD19+ B-cell recovery (which is a biomarker that associates with a lack of CAR+ T cell function), and low overall in vivo CAR+ T cell expansion for the explored dose levels.

The very narrow therapeutic window described prevented a safe and effective RP2D dose from being established for the patient population of BCM-004, and therefore prohibited expansion into the Phase 2 portion of the study.

Considering the evolution of the treatment landscape since the trial initiation, including an approved CAR+ T cell therapy for this patient population that enables long term remissions with curative potential for children suffering from highly aggressive disease, this trial was terminated early to avoid exposing more children to suboptimal dose levels, and depriving them of potentially available curative treatment options.

2.3.3. Discussion on clinical aspects

The MAH of Breyanzi has submitted this variation application in accordance with Article 46 of regulation 1901/2006 to provide clinical data from Phase 1/2 study JCAR017-BCM-004 (hereafter referred to as study BCM-004).

Study BCM-004 was originally included in the PIP for Breyanzi and was designed to investigate the efficacy and safety of lisocabtagene maraleucel (liso-cel) for the treatment of paediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) or non-Hodgkin lymphoma (R/R B-NHL). However, due to the early closure of the study, no patient with R/R B-NHL was eventually enrolled and only limited data from subjects with R/R B-ALL were submitted.

Disease context

ALL is the most common malignancy in children (~40 cases per million diagnosed each year in the EU, with a peak incidence occurring between 0 and 5 years of age; see Parkin DM et al, WHO Fact Sheet 2009); significant improvements in cure rates have been observed in the last 30 years, especially following the introduction of multi-drug chemotherapy and allogeneic haematopoietic stem cell transplant (alloHSCT). Recent data showed that, in industrialised countries, the cure rate of paediatric B-ALL approximated 90% (see e.g. Hunger SP et al, NEJM 2015). On the other hand, ALL treatments are highly complex, prolonged and demanding for the patients, being associated with significant short- and long-term toxicity.

Further, the outcomes of children with ALL who relapse following frontline treatment (especially in the case of early relapse) or have refractory disease are still unsatisfactory, and the long-term OS rate for these patients is ~50% (see e.g. Hunger SP et al, Blood 2020).

The therapy of R/R B-ALL in children is complex and include several different options. Conventional "re-induction" chemotherapy regimens are the standard choice in first relapse for subjects with "lower" risk disease (e.g. patients in late relapse). The main objective or re-induction is to achieve a second complete remission (CR2, possibly with no detectable minimal residual disease), and most re-induction regimens are based on "standard" four-drug chemotherapy backbones, which include corticosteroids, vincristine, an anthracycline or mitoxantrone, and asparaginase. Drugs, doses and schedules are known to vary across cooperative groups/centres.

With the possible exceptions of MRD negative subjects with late/isolated extramedullary relapse, most children with R/R B-ALL who achieve CR2 and have a suitable donor procced to receive alloHSCT as "consolidation". AlloHSCT can improve, in fact, the patient chances for long-term disease-control/cure, and the best results are achieved in patients who are MRD negative before transplant (see e.g. Merli P

et al, Front Pediatr. 2021). Unfortunately, alloHSCT is also associated with severe toxicity both in the short and long-term.

The outcomes of patients who are primary refractory, or who are in their second/later relapse, or who have failed alloHSCT are inferior and treatment options are limited.

Blinatumomab (Blincyto), a bispecific T cell engager (BiTE) targeting CD3 on T cells and CD19 on B-ALL blasts, is approved in the EU as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome-negative (Ph-) CD19 positive B-ALL which is refractory or in relapse after receiving at least two prior therapies, or in relapse after receiving prior alloHSCT. The safety and efficacy of blinatumomab in this indication were assessed in single-arm trial MT103-205: the CRR was 28.6%, the median relapse-free survival was 6.8 months and the most frequently reported serious adverse reactions were pyrexia (11.4%), febrile neutropenia, (11.4%), cytokine release syndrome (CRS 5.7%), sepsis (4.3%), device-related infection (4.3%), overdose (4.3%), convulsion (2.9%), respiratory failure (2.9%), hypoxia (2.9%), pneumonia (2.9%), and multi-organ failure (2.9%) (see Blincyto SmPC).

Tisagenlecleucel (tisa-cel, Kymriah) is an anti-CD19 CAR T-cell ATMP approved in the EU for the treatment of paediatric and young adult patients ≤25 years of age with B-ALL who are refractory, in relapse post-transplant or in second or later relapse. The approval of tisa-cel was based on the results from one single-arm phase II study (B2202, ELIANA) that showed high ORR and CRR (82% and 62%, respectively) in infused patients. The median DoR was 46.8 months and the 30-month DoR rate (56.2%) showed the potential for durable remissions. The most common non-haematological adverse reactions were CRS (75%), infections (70%), hypogammaglobulinaemia (49%) and pyrexia (43%). Grade 3 and 4 adverse reactions were reported in 86% of patients, with CRS (37%) being the most common (see Kymriah SmPC and Laetsch TW et al, JCO 2023).

Methods

Study BCM-004 comprised a Phase 1, dose-finding part, designed to identify the recommended Phase 2 dose (RP2D) in two distinct cohorts (R/R B-ALL and MRD+/- B-ALL), and a Phase 2 part in which the efficacy and safety of liso-cel were to be further characterised in specific disease cohorts (R/R B-ALL, MRD+ B-ALL and R/R B-NHL).

The study structure was standard for CARTs and included a screening phase, a pre-treatment period (lasting from leukapheresis to infusion) and a treatment period starting from the administration of lymphodepleting chemotherapy (LD) and lasting until Day 56, when confirmation of disease response was planned. All patients were further monitored for AEs/response in the follow-up phase until month 24, and up to 15 years in a separate long-term FU study.

Eligible subjects were paediatric patients with R/R B-cell ALL aged <18 year (weight ≥ 6 kg), with evidence of CD19+ blasts via flow-cytometry/immunohistochemistry and at least 5% blasts in the bone marrow (BM). To be included, subjects were required to be in first or greater BM relapse or in any BM relapse after alloHSCT, to have primary refractory disease and/or to be ineligible to alloHSCT. The high unmet medical need in the advanced setting of relapse/refractoriness identified by the study inclusion criteria can be recognised.

As expected with CAR T cell products, subjects were also required to have a Karnofsky/Lansky score of 50% or higher and no clinically relevant co-morbidities; subjects with CNS-2 and CNS-3 disease could be enrolled, provided that no neurologic symptoms/disorders were present.

During the manufacturing/turnaround time between lymphocyte apheresis and liso-cel infusion patients were allowed to receive a single cycle of bridging therapy to control rapid disease progression. A 3-day LD chemotherapy regimen including fludarabine (30 mg/m^2/day) and cyclophosphamide (300 mg/m^2/day) was administered 2 to 7 days before liso-cel infusion, in line with the approved

recommendations for Breyanzi in the adult LBCL indications. It should be noted, however, that the LD regimen in study BCM-004 differed from the one approved for tisa-cel in the paediatric R/R B-ALL indication: in the tisa-cel label it is recommended, in fact, that fludarabine is administered for 4 days and a different cyclophosphamide posology (500 mg/m^2/day for 2 days) is reported (see Kymriah SmPC). The possible consequences of such differences on CARTs efficacy and safety in the paediatric setting is not well characterised.

The initial starting dose for liso-cel was 0.5 x 10^6 CAR+ T cells/Kg (max dose 50 x 10^6 total CAR+ T cells) and was based on previous experience in the PLAT-02 study (see Gardner RA et al, Blood 2022). Due to severe neurotoxicity (see below), however, the original protocol was amended to identify a lower starting dose (0.05 x 10^6 CAR+ T cells/Kg, i.e. a 10-fold reduction compared to the initial starting dose). Although up to 5 dose levels were planned in study BCM-004, subjects were eventually treated only at DL1, DL2 and DL4 (i.e. the original starting dose).

A mTPI-2 algorithm was employed to guide dose-escalation decisions and to identify the RP2D; a DL was considered unsafe if it had an estimated 95% or more probability of exceeding the target DLT rate of 30% when at least 3 patients had received liso-cel at each DL. The use of the mTPI-2 design is endorsed in a paediatric setting to minimise the risk of ineffective/toxic exposures, especially considering the CARTs potential for fatal adverse reactions and an unclear dose/toxicity relationship. The definitions for DLTs in study BCM-004 were adequate; even though the "acceptable" levels of toxicity were not negligible, this can be justified since maximising anti-tumour efficacy is the primary aim in advanced disease settings characterised by limited life expectancy. Additional safety measures were anyway in place, e.g. the decision to open a new dose level for enrolment was informed by a dedicated safety review committee (SRC), and an independent data safety monitoring board (DSMB) oversaw the review of cumulative safety data over the curse of the study.

The main endpoint to explore efficacy in Phase 1 (i.e. BOR, ORR, DoR, CRR) are considered adequate to initially characterise liso-cel activity in advanced settings of R/R ALL, when response to therapy is expected to be limited and short-lasting.

Results

Efficacy

Overall, the study planned to treat approximately 30 patients in Phase 1 and 71 patients in Phase 2. However, only 24 subjects were eventually enrolled in Phase 1 (N=9 at DL1, N=8 at DL2, N=3 at DL4 and N=1 not assigned) and Phase 2 was never started because the RP2D could not be identified.

The efficacy analysis population (EAP) included only those subjects who fulfilled all study eligibility criteria, were at least MRD+ at baseline, and had received liso-cel manufactured in accordance with release specifications.

Of the 24 subjects enrolled, 13/24 died (12/13 because of PD and 1/13 because of post-transplant toxicity on Day 271), and 5/13 experienced fatal progression prior to receiving liso-cel, suggesting that the proportion of patients at higher risk of rapid progression was non-negligible in study BCM-004. The EAP eventually included 11 subjects: due to the limited sample size, efficacy data should be interpreted with caution.

Limited patient characteristic data were provided: the median age of the 21 subjects who were able to enter the pre-treatment period was 7 years (range 1, 17), with 18/21 subjects being aged <12 years. With respect to disease characteristics, 43% of patients had previously undergone HSCT, CNS involvement was not reported for the majority of subjects (yet 1 patient had CNS-3 at baseline), and no patient had Ph+ B-ALL. MLL rearrangements could be identified in 3 subjects, yet the majority of patients (81%) had no MLL status reported.

Five out of 11 subjects in the EAP set were able to achieve CRi with liso-cel (ORR 45.5%, 95%CI 16.7, 76.6). Although no CR was observed in study BCM-004, 3 subjects who achieved CRi were also MRD negative. Five subjects could not be evaluated for efficacy because of lack of disease response assessment at Day 28 (N=3) or lack of response confirmation at Day 56 (N=2). Five out of 11 subjects underwent alloHSCT after treatment with liso-cel, yet the available data are too limited to characterise liso-cel potential as bridging to alloHSCT. The median DoR in responders was 13.7 months (95%CI not estimable due to lack of data variability).

Overall, the limited efficacy data with liso-cel in this heavily pre-treated paediatric population were of some interest, since some potential for deep responses could be observed. However, the MAH's opinion that response duration was sub-optimal is agreed, especially when the results from study BCM-004 are looked in the context of the efficacy threshold set by tisa-cel in R/R B-ALL in the ELIANA study.

RFS, EFS and OS were of difficult interpretation in the absence of proper controls, yet the available data can be considered supportive of the reduced potential for long-lasting remission with liso-cel in paediatric R/R B-ALL.

Safety

All 14 subjects in the "infused" data-set received the planned liso-cel dose according to DL. The median total number of infused CD8+ and CD4+ CAR T cells was approximately 1.25 x 10^6 (range max 0.3, 25), which was significantly reduced compared to the median total dose received by adult subjects in the approved indications, and also to the dose approved in this setting for Kymriah for patients 50 kg and below (i.e. 0.2 to 5 × 10^6 CAR-positive viable T cells per kg body weight).

Despite the low starting dose, all subjects in study BCM-004 experienced at least one TEAE during the treatment phase, 12/14 had at least one Grade 3/4 TEAE, and 9/14 had at least one serious TEAE.

At least one TEAE of CRS was reported for the majority of patients (64%) and 4/14 subjects reported at least one TEAE of neurotoxicity (iiNT). One subject who received liso-cel experienced a Grade 4 iiNT event (cerebral oedema) that was considered a DLT at DL4, and another subject experienced a Grade 4 iiNT event (cerebral oedema and seizures) that was adjudicated as a DLT at DL2. One additional patient experienced a Grade 3 iiNT event (seizures) that was not considered a DLT at DL1.

Both DLT events prompted dose de-escalation according to the mTPI-2 algorithm and eventually prevented the identification of a safe and effective dose for Phase 2.

PK/PD

As already observed with liso-cel in the adult LBCL population, non-responders generally exhibited lower expansions of both CD4+ and CD8+ CAR T cell populations compared to responders. However, in this paediatric population, a limited expansion of the CD4+ component could also be observed in responders.

Further, rapid CD19+ B-cell recovery was observed at all the explored DLs, which has been associated with poor long-term disease control after anti-CD19 CAR T cell therapies (see e.g. Pulsipher MA et al, Blood Cancer Discov 2022). In particular, 13/14 subjects who received liso-cel in study BCM-004 experienced either CD19+ B cel recovery or PD by month 6.

The mechanisms behind these findings and their possible contribution to the limited efficacy and unacceptable toxicity observed in study BCM-004 have not been sufficiently characterised, at present.

Conclusions

Overall, the MAH's conclusions that further expansion of study BCM-004 in Phase 2 was prevented by the observed limited efficacy and the uncertain relationship between dose and severe iiNT is agreed. Based on the available data, the therapeutic window of liso-cel in paediatric R/R B-ALL is considered too

narrow to allow for further investigation, especially considering the presence of effective approved alternatives in this clinical setting (e.g. tisa-cel).

Based on the available data, a product specific waiver in accordance to Article 11(1)(c) of the current paediatric Regulation was granted by the PDCO on October 2023, on the ground that liso-cel did not represent a significant therapeutic benefit over existing treatments for paediatric patients with B-ALL and mature B cell neoplasms. Consequently, study BCM-004 was terminated on Jan 2024.

Considering the low risk for off-label use (liso-cel is commercialised under a controlled distribution program in the EU and more effective and safer alternatives are currently approved) and the limited information provided by data from study BCM-004, the MAH's opinion that no change is warranted in the current SmPC of Breyanzi is agreed.

3. Overall conclusion and recommendation

Fulfilled:

No regulatory action required.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Quality and Clinical studies originally included in the PIP v. 3.0 (see EMEA-001995-PIP01-16-M03)

Product Name: Breyanzi Active substance:liso-cel

Study title	Study number	Date of completion	Date of submission of final study report
Development of a new manufacturing process and formulation to generate JCAR017 product for paediatric patients (and young adults)	1	December 2024	N/A
Open-label, single dose, single-arm, multi-cohort trial to evaluate the activity and safety of JCAR017 in children less than 18 years of age (and adults) and weighing at least 6 kg with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (B-ALL) or with r/r B-cell non-Hodgkin's lymphoma (B-NHL)	2	December 2024	NA
Open-label, non-randomised, multi-cohort trial to assess the safety, feasibility, and efficacy of administering a T cell product containing CD4 and CD8 cells derived from patient peripheral blood mononuclear cells that has been genetically modified using a self-inactivating lentiviral vector to express a CD19-specific chimeric antigen receptor (CAR) and the EGFRt (truncated epidermal growth factor receptor) to children from 1 year to less than 18 years of age (and adults) weighing at least 10 kg with relapsed or refractory CD19+ leukaemia	3	December 2024	N/A

Following the latest application for a modification to the agreed liso-cel paediatric investigation plan (PIP, decision EMEA-001995-PIP01-16-M04 dated 27 October 2023), a product specific waiver in accordance with Article 11(1)(c) of said Regulation was granted, on the grounds that the specific medicinal product did not represent a significant therapeutic benefit over existing treatments for paediatric patients. The waiver covered all subsets of the paediatric population in the following two conditions:

- Treatment of B-lymphoblastic leukaemia/lymphoma
- Treatment of mature B-cell neoplasms

Consequently, ongoing study 2 was early terminated on 26 January 2024.