27 January 2022
EMA/134759/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Breyanzi

International non-proprietary name: lisocabtagene maraleucel

Procedure No. EMEA/H/C/004731/0000

Note

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

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List of abbreviations

2L+	second-line or later
3L+	third-line or later
ACC	Analytic Comparator Cohort
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukaemia
allo-HSCT	allogeneic haematopoietic stem cell transplant
ANC	absolute neutrophil count
APS	Aseptic process simulation
ASTCT	American Society for Transplantation and Cellular Therapy
ATA	anti-therapeutic antibody
AUC0-28	area under the concentration-time curve through 28 days after infusion
auto-HSCT	autologous haematopoietic stem cell transplant
BCL2/BCL6	B-cell lymphoma gene 2 or 6
BLA	Biologics License Application
BLV	Bulk lentiviral vector
BOR	best overall response
BR	bendamustine and rituximab
BSA	Bovine serum albumin
BVH	Bulk vector harvest
CAPA	corrective and preventive actions
CAR	chimeric antigen receptor
CCIT	Container closure integrity testing
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CLOVER	Clinical Outcomes Across Manufacturing Process Versions (Report)
CMAT	cryopreserved material
Cmax	maximum observed concentration
CMO	contract manufacturing organisation
CNS	central nervous system
CoA	Certificate of analysis
COI	Chain of identity
CPP	Critical process parameter
CPV	Continuous process verification

CQA	Critical quality attribute
CR	complete response
CrCl	creatinine clearance
CRF	Controlled rate freezer
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	dose confirmation
DE	dose expansion
DF	dose finding
DF	diafiltration
DL	dose level
DL1D	Dose Level 1 (50 × 106 CAR+ T cells), 2-dose regimen
DL1S	Dose Level 1 (50 × 106 CAR+ T cells), single-dose regimen
DL2S	Dose Level 2 (100 × 106 CAR+ T cells), single-dose regimen
DL3S	Dose Level 3 (150 × 106 CAR+ T cells), single-dose regimen
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMSO	dimethylsulfoxide
DOR	duration of response
DOVER	Dosing Variance Explanatory Report
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGFRt	truncated epidermal growth factor receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EOPC	End of production cells
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-dimensions 5-levels
ESMO	European Society of Medical Oncology
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
FBS	Fetal bovine serum
FDA	Food and Drug Administration
FL	follicular lymphoma

FL3B	follicular lymphoma Grade 3B
FLV	Filled lentiviral vector
FS	Full scale
GCP	Good Clinical Practice
GI	Gamma irradiated
HBV	hepatitis B virus
HD	Healthy donor
Hgb	haemoglobin
HGL	high-grade lymphoma
HI	Heat inactivated
HLH	haemophagocytic lymphohistocytosis
HR	hazard ratio
HRQoL	health-related quality of life
HSCT	haematopoietic stem cell transplant
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IFNγ	interferon gamma
IgG	immunoglobulin G
iiNT	investigator-identified neurologic toxicity
IL	interleukin
INN	International Non-proprietary Name
IPC	In-process control
IQR	interquartile range
IRC	Independent Review Committee
ITT	intent-to-treat
IV	intravenous(ly)
JTAC	JCAR017-treated Analysis Cohort
KM	Kaplan-Meier
LDC	lymphodepleting chemotherapy
LDH	lactate dehydrogenase
NL2	Liquid nitrogen
LOC	Limit of detection
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
LVV	Lentiviral vector
MAA	Marketing Authorisation Application

MAS	macrophage activation syndrome
MCB	Master cell bank
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MOI	Multiplicity of infection
MYC	myelocytomatosis oncogene
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nCPP	Non-critical process parameter
ND	not done
ND/PD	Nervous System Disorders and Psychiatric Disorders
NE	not evaluable
NESI	neurotoxicity events of special interest
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
NR	not reached
NT	neurologic toxicity
ORR	overall response rate
OS	overall survival
PAR	Proven acceptable range
PAS	Primary Analysis Set
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMBCL	primary mediastinal B-cell lymphoma
pola-BR	polatuzumab vedotin plus bendamustine and rituximab
PPQ	Process performance qualification
PR	partial response
PRO	patient-reported outcomes
PT	Preferred Term
QoL	quality of life
QLQ-C30	Quality of Life Questionnaire C30
qPCR	quantitative polymerase chain reaction

R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RCL	replication-competent lentivirus
RCT	randomised controlled trial
RFI	Release for infusion
R/R	relapsed or refractory
RR	relative risk ratio
RW	real world
RWE	real-world evidence
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
scFv	single-chain variable fragment
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	stable disease
SDM	Scale down model
SE	standard error
SIN	Self-inactivating
SLL	small lymphocytic lymphoma
SLR	systematic literature review
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA query
SOC	System Organ Class
SPD	sum of the product of perpendicular diameters
SPM	second primary malignancy
tCLL/SLL	DLBCL transformed from chronic lymphocytic leukaemia/small lymphocytic lymphoma
TEAE	treatment-emergent adverse event
tFL	DLBCL transformed from follicular lymphoma
tiNHL	DLBCL transformed from indolent non-Hodgkin lymphoma other than follicular lymphoma
tMZL	DLBCL transformed from marginal zone lymphoma
tOther	DLBCL transformed from other indolent lymphomas, including Waldenström's macroglobulinaemia
TLS	tumour lysis syndrome
tmax	time to maximum observed concentration
UF	ultrafiltration
US	United States
v	Manufacturing process version (v1, v2, v3, v4)

VAS	visual analog scale
WCB	Working cell bank
VCN	Vector copy number
VVDT	Vector volume determination test
WHO	World Health Organization
WM	Waldenström’s macroglobulinaemia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celgene Europe BV (*) submitted on 29 June 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Breyanzi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2016.

Breyanzi, was designated as an orphan medicinal product:

- EU/3/17/1890 on 17 Jul 2017 in the following condition: Treatment of diffuse large B-cell lymphoma
- EU/3/18/2018 on 25 May 2018 in the following condition: Treatment of follicular lymphoma
- EU/3/18/2099 on 19 Nov 2018 in the following condition: Treatment of primary mediastinal large-B-cell lymphoma.

Following the CHMP positive opinion on this marketing authorisation and at the time of review of the orphan designations by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 20 February 2022 on request of the sponsor. The relevant orphan designations withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi

The applicant applied for the following indication: Breyanzi is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after at least two prior therapies.

(*) during the procedure the applicant has changed from Celgene Europe BV to Bristol-Myers Squibb Pharma EEIG. Relevant documents for the change of applicant have been provided, validated and agreed.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that the following two active substances, which are covered by the single INN lisocabtagene maraleucel, were to be considered new active substances:

- CD19-directed genetically modified autologous cell-based product consisting of purified CD8+ T cells ("CD8+ cells")
- CD19-directed genetically modified autologous cell-based product consisting of purified CD4+ T cells ("CD4+ cells")

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

Breyanzi is presented as a combination pack of two separate pharmaceutical forms, each with a different active substance (CD8+ cells, CD4+ cells). The two individual active substances act as the different components of the medicinal product (henceforth referred as CD4+ cell component and CD8+ cell component). Further details on the qualitative and quantitative composition of the product can be found

in the quality section of this report.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) PIP (P/0198/2019) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0198/2019) was not yet completed as some measures were deferred

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

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

1.5.2. New active substance status

The applicant requested the two active substances described above, which are covered by the single INN lisocabtagene maraleucel and contained in the above medicinal product, to be considered as new active substances, as the applicant claims that they are not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Breyanzi was granted eligibility to PRIME on 15 Dec 2016 in the following indication: treatment of relapsed / refractory aggressive large B-cell Non-Hodgkin's Lymphoma (NHL).

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

- Based on the discussion and data presented by the applicant, the request for PRIME was considered for the population for which data has been presented, ie relapsed / refractory diffuse large B-cell lymphoma (DLBCL).
- Despite overall improvement in DLBCL outcomes after frontline therapy with R-CHOP, approximately 30-40% of patients will not respond to initial therapy or will eventually relapse and the unmet medical need in DLBCL is therefore agreed.
- The proposed mechanism of action of CAR T cells and presented in vitro and in vivo data are relevant and supportive.
- Clinical results available to date showed high ORR of 85% (17/20), a CR rate of 55% (11/20), and a PR rate of 30% (6/20). These results are further supported by follow-up data (3 months in 8

patients and >6 months in 3 patients). The most significant toxicities observed in adult subjects who have received CAR T cells have been cytokine release syndrome and neurotoxicity.

A kick-off meeting was held on 18 Apr 2017. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

Points for future CHMP Scientific Advice: Include discussion on the development options and differentiation (e.g. non-similarity) aspects in using EGFRt for in vivo ablation of CAR-T cells.

Points for future CHMP Scientific Advice: Include the ERA in MAA including free viral particles.

Points for future CHMP Scientific Advice: Include data driven evidence to demonstrate benefit/differentiation of unique defined product composition. Discuss data collection on feasibility of HSCT after CAR-T therapy with CAR-T as bridging treatment prior to allo-transplantation.

- Planning of post-authorisation aspects: long-term follow-up: considerations on type of registry and possible challenges

The Rapporteur reminded of the importance of long-term safety data in this hopefully curative setting and acknowledged the Company's plans.

The Rapporteur raised concerns on the planned registry, which is on a voluntary basis and therefore cannot ensure that all patients would be enrolled.

The Rapporteur recommended a common platform to be used by all CAR-T products that will be marketed to collect as much safety as possible and avoid loss of patient follow-up.

EMA would like CAR-T sponsors to work together, and may host a joint meeting with sponsors in the future.

Points for future Rapporteur's discussion: Include the pros and cons for LTFU platform across CAR-T products and attendance at discussion forum for LTFU common platform.

- Historical control: need for inclusion of patients representative of EU setting and statistical considerations

Overall proposal for systematic review is acceptable, however NICE guideline should be used and the following details would need to be discussed in Scientific Advice:

- Clarification on endpoints (ORR vs time to event)
- For time to event endpoints, different starting time points from different studies need to be taken into account in statistical analysis to ensure unbiased comparison
- Need to pre-specify selection of covariates for the propensity score model to minimise bias (selection bias and information bias)
- Need to pre-specify analysis to avoid cherry picking.

Recommendation was made to follow the NICE guidelines for indirect comparison.

Points for future CHMP Scientific Advice: Include the systematic literature review process, methodology and pre-specify analyses as per the points mentioned above.

Points for CHMP Protocol Assistance: Include data-driven evidence to demonstrate non similarity and significant benefit.

1.7. Scientific advice

The applicant received scientific advice on the development relevant for the indication subject to the present application.

The scientific advice pertained to the following quality, non-clinical and clinical aspects:

- The lentiviral vector microbial control strategy as well as the lentiviral vector comparability plan to demonstrate comparability between different vector suppliers; the change in analytical method for the enumeration of CAR expressing cells resulting in a change in the dose calculation; the proposed Process Performance Qualification strategy to demonstrate process control and consistency of the finished product;

- the proposed data-driven evidence to demonstrate benefit/differentiation of unique defined product composition and non-similarity demonstration strategy;

- the strategy for demonstrating comparability between the different versions of finished product; the proposed post-approval mycoplasma surveillance programme;

- the process characterisation strategy based on the risk-based approach; the approach to perform cellular composition characterisation of the leukapheresis material, and cellular composition and memory T-cell characterisation of the cryopreserved selected T-cells; the strategy to establish the commercial finished product specification based on the current potential critical quality attributes; the product and process-related impurities strategy; the manufacturing process performance qualification strategy; the viral safety testing strategies;

- the adequacy of the nonclinical development package to support MAA; the non-similarity strategy and specifically the suitability of the non-clinical proof-of-concept study for the EGFRt structural component of JCAR017 to demonstrate non-similarity *versus* authorised products in the same indication;

- the clinical pharmacology development plan; the justification for the target therapeutic dose, the clinical data package to provide robust evidence for the demonstration of a favourable benefit-risk for a full MA; the proposal to submit long-term findings regarding both safety and efficacy (at least 12 months) during the MAA procedure, and how to present the clinical data in the MAA dossier;

- the data sources (Real World Evidence and Systematic Literature Review) for external control and the associated statistical analysis methods to support comparative evidence for MA; the long-term post-marketing data collection strategy, i.e. through a post-approval study as part of the Risk Management Plan (RMP) and in line with EMA report on CAR T-cell therapy registries;

- the clinical development plan in DLBCL, PMBCL and FL to support the discussion of significant benefit over existing therapies at the time of marketing authorisation, to maintain orphan status;

- the designs of the pivotal studies TRANSCEND NHL-001 and TRANSCEND World to support a MAA, in particular, the inclusion/exclusion criteria, the clinical data and pooling strategy; the duration of follow up at time of MAA submission and during MAA review; the statistical approach for the historical control analyses; the post-authorisation data collection plan; the patient-reported outcomes (PROs) for benefit/risk assessment;

- the adequacy of the design of the randomised Phase 3 study to support a future indication extension in subjects with TE DLBCL.

1.8. Steps taken for the assessment of the product

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

CAT Rapporteur: Concetta Quintarelli CAT Co-Rapporteur: Claire Beuneu

The application was received by the EMA on	29 June 2020
Accelerated Assessment procedure was agreed-upon by CAT and CHMP on	30 April 2020
The procedure started on	16 July 2020
The CAT Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	20 October 2020
The CAT Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	15 October 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	19 October 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CAT during the meeting on	29 October 2020
The CAT agreed on the consolidated List of Questions to be sent to the applicant during the meeting on The procedure was reverted from accelerated to standard timetable on	4 November 2020
The applicant submitted the responses to the CAT consolidated List of Questions on	11 February 2021
In cases when a pre-authorisation inspection has been conducted, please reflect the following steps (include/delete information as applicable): The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at the manufacturing site has been conducted on 24th November 2021. The outcome of the inspection carried out was issued on	15 December 2021
The CAT Rapporteur circulated the Joint Assessment Report on the responses to the List of Questions to all CAT and CHMP members on	7 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 April 2021
The CAT agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 April 2021
The applicant submitted the responses to the CAT List of Outstanding Issues on	7 September 2021
The CAT Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	27 September 2021
The CAT agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	8 October 2021
The applicant submitted the responses to the 2nd CAT List of Outstanding	21 December 2021

Issues on	
The CAT Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	11 January 2022
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Breyanzi on	21 January 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Breyanzi on	27 January 2022
The CAT and CHMP adopted a report on similarity of Breyanzi with Kymriah, Yescarta, Gazyvaro, Polivy and Minjuvi on	21/27 January 2022
Furthermore, the CAT and CHMP adopted a report on New Active Substance (NAS) status of the two active substances contained in the medicinal product	21/27 January 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

2.1.2. Epidemiology

Non-Hodgkin lymphomas comprise a heterogeneous group of malignancies with several histological and molecular subtypes. Approximately 80% to 85% of all NHL cases are categorised as B-cell lymphomas, which include both aggressive (ie, rapidly growing) and indolent (ie, slow growing) forms. Diffuse large B-cell lymphomas represent the most common NHL subtype worldwide, accounting for at least 30% of all adult NHL cases (Chao, 2013) and 37% of B-cell lymphomas worldwide (Hunt, 2008; Martelli, 2013). Between 2011 and 2012, the annual age-adjusted incidence rates of DLBCL were between 3 to 4 per 100,000 persons in Europe and 6.9 per 100,000 persons in the US (Teras, 2016; Tilly, 2015; Sant, 2010). Incidence varies by ethnicity, with Caucasian Americans having higher rates than Blacks, Asians, and American Indian or Alaska Natives, in order of decreasing incidence (Morton, 2006; Shirley MH, 2013). The incidence of DLBCL is known to increase with age, with approximately half of all cases occurring in adults aged ≥ 65 years (median age 67 years) (Howlader, 2019). DLBCL not otherwise specified (NOS) can occur as *de novo* disease and can also arise as a transformation from other indolent forms of B-cell lymphoma including follicular lymphoma (FL), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL), Waldenström's macroglobulinaemia (WM), and marginal zone lymphoma (MZL).

Relative to DLBCL, other large B-cell lymphoma subtypes are less common. Primary large B cell lymphoma of the mediastinum (PMBCL) and FL3B comprise 3% and 1% of all NHL cases, respectively

(Mottok, 2019; Dreyling, 2016; NCCN, 2019; Salaverria, 2011; Swerdlow, 2016; Vitolo, 2016). These subtypes represent an important subgroup of the R/R large B-cell lymphoma population and are typically grouped with and treated in the same way as DLBCL. Estimated incidence in the EU is 3.8/100,000/year and is increasing with age (Sant, 2010; Tilly, 2015).

Secondary CNS lymphoma refers to cases where there is secondary CNS involvement from DLBCL, which have an especially poor prognosis (Tilly, 2015). Secondary CNS lymphoma is an infrequent but almost always fatal complication of lymphomas.

2.1.3. Biologic features and pathogenesis

The molecular pathogenesis of DLBCL is a complex, multistep process leading to the replication of a malignant clone of germinal or post-germinal B cell origin. While some steps in this pathway have been elucidated, many remain unknown.

- DLBCL is a heterogeneous clinicopathologic entity that includes tumours derived from germinal centre B cells or post-germinal centre B cells (also called activated B cells);
- Tumour cells in DLBCL generally express pan B cell antigens (CD19, CD20, CD22, CD79a). The majority has genetic abnormalities, but there is no single cytogenetic change that is typical or diagnostic.
- The majority of DLBCL tumours demonstrates translocations or mutations that result in the increased expression of the B cell lymphoma 6 (BCL6) gene. Overexpression of BCL6 leads to downregulation of target genes, including the TP53 tumour suppressor gene, which prevents the cells from undergoing apoptosis in response to DNA damage;
- Up to 20% of DLBCL demonstrate mutations or deletions of the TP53 tumour suppressor gene. In addition, TP53 transcription is at least partially controlled by the BCL6 gene. Downregulation of TP53 expression or expression of mutant p53 products results in a loss of the normal growth-limiting activities of this gene. Newer data suggest negative prognostic impact of p53 mutations or deletions in DLBCL (Schiefer, 2015).
- Other mechanisms important in the pathogenesis of a minority of DLBCL include aberrant somatic hypermutation, BCL2 activation, and MYC overexpression, evasion of host immunity, and altered tumour cell motility/trafficking;
- Primary large B cell lymphoma of the mediastinum (PMBL) is a variant of DLBCL arising in the mediastinum from the thymic (medullary) B cell. The pathogenesis of PMBL is largely unknown, but may be more similar to that of classical Hodgkin lymphoma than that of DLBCL, and appears to involve activation of JAK-STAT and NF-KB signaling as well as acquisition of genetic lesions that allow the tumour cells to escape from immune surveillance.

A specific high-risk group is High-Grade Lymphoma (HGL) with concurrent chromosomal rearrangements of MYC and the anti-apoptotic oncogene BCL2 and/or BCL6, referred to as double-hit lymphoma (DHL) or triple-hit lymphoma (THL). The 2016 revision of the WHO classification for lymphoma has included these lymphomas, which occur in <10% of cases of DLBCL, into a new category of lymphoma, termed HGL with MYC and BCL2 and/or BCL6 rearrangements (Swerdlow, 2016). Double-hit lymphomas represent approximately 5% of de novo cases of DLBCL with very poor OS of ≤ 12 months when treated with R-CHOP (Camicia, 2015).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Patients with DLBCL typically present with a rapidly enlarging symptomatic mass, most usually nodal enlargement in the neck or abdomen, or, in the case of primary mediastinal large B cell lymphoma, the mediastinum, but may present as a mass lesion anywhere in the body. Extranodal involvement is common among those presenting with stage I/II disease [Hui D, 2010]. Systemic "B" symptoms (i.e., fever, weight loss, drenching night sweats) are observed in approximately 30 percent of patients, and the serum lactate dehydrogenase (LDH) is elevated in over one-half (Armitage JO, 1998). Approximately 60 percent of patients will present with advanced stage DLBCL (usually stage III or IV disease) while 40 percent have more localised disease, usually defined as that which can be contained within one irradiation field (Armitage JO, 1998). The bone marrow is involved in up to 30 percent of cases, but may be of a discordant histologic type, such as follicular lymphoma (Sehn LH, 2011), in as many as half of those cases. In up to 40 percent of cases, the disease arises in extranodal extramedullary tissues [Moller MB, 2004]. The most common site of primary extranodal disease is the stomach/gastrointestinal tract, but the disease can arise in virtually any tissue (Alives A, 2002; Munch-Petersen HD, 2015). Conversely, primary nodal disease may secondarily involve the liver, kidneys, lung, bone marrow, and central nervous system. DLBCL also can be locally highly invasive, leading to compression of vessels (eg, superior vena cava syndrome) or airways (eg, tracheo-bronchial compression), involvement of peripheral nerves, and destruction of bone (eg, cord compression), requiring urgent attention. DLBCL is an AIDS-defining malignancy. When compared with lymphoma in the HIV-negative population, systemic lymphoma in the HIV-positive population has been associated with more frequent B symptoms (ie, fever, weight loss, night sweats), extranodal disease, involvement of unusual locations (eg, body cavity, rectum, soft tissue), and advanced stage at diagnosis.

Pre-treatment evaluation determines the extent of the disease and provides information about the individual's comorbidities that are likely to affect treatment options. In addition to a history and physical examination, it is practice performing laboratory studies, unilateral bone marrow biopsy, and imaging (PET) in all patients. A molecular risk assessment should be performed in all cases to help determine prognosis and direct therapy. This includes both an evaluation of MYC, BCL2, and BCL6 status (by immunohistochemistry or fluorescence *in situ* hybridisation [FISH]) and an evaluation of cell of origin. Using this information, an individual case may be subclassified as one of the following:

- *Germinal centre B cell (GCB) DLBCL* – Cases with GCB DLBCL without MYC and BCL2 gene rearrangements. These patients have a relatively good prognosis following standard therapy with R-CHOP;
- *Activated B cell (ABC) DLBCL or non-GCB DLBCL* – Cases with non-GCB DLBCL, without double hit DLBCL, have high relapse rates and a poor prognosis following treatment with R-CHOP;
- *Double hit DLBCL* – Cases with MYC translocation plus gene rearrangement of BCL2, BCL6 (or both) have a poor prognosis with standard therapy;
- *Double expressor DLBCL* – There are limited data regarding the treatment of the larger population of patients with double expressor DLBCL (immunohistochemistry identifies co-expression of MYC and BCL2, but gene rearrangements are not present or were not evaluated).

2.1.5. Management

Following current standard of care first-line therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) immune-chemotherapy, approximately 50% to 60% of patients achieve a long-term response and will be cured of the disease (Tilly, 2015). The remainder of patients are either refractory to first-line treatment or relapse after a period of treatment response (Raut, 2014;

Tilly, 2015). Early relapses (≤1 year) and late relapses (>5 years) may also occur, with incidence rates of 10–15 and 3%, respectively. The prognosis of patients with R/R DLBCL is poor, with a life expectancy of 12 months with currently available therapies; approximately 37% of DLBCL patients die within 5 years of diagnosis (Friedberg, 2011; Howlader, 2019; Raut, 2014). High–dose immunotherapy followed by autologous stem cell transplantation (ASCT) is the standard treatment for patients with relapsed/refractory (RR) DLBCL that are <65 years and without major comorbidities; however, >60% of patients are ineligible for transplant, presenting a therapeutic challenge (Zhang J, 2018). The prognosis of patients who fail salvage chemotherapy and/or ASCT or are not eligible to ASCT due to age or comorbidity, is unsatisfactory and durable responses with additional chemotherapy are anecdotical (Van Den Neste et al, 2017).

Patients with large B-cell lymphoma whose disease progresses after 2 or more lines of systemic therapy are unlikely to benefit from additional chemoimmunotherapy (Zelenetz, 2019). A variety of chemotherapy-based and monoclonal antibody-based regimens have been explored as salvage regimens for patients with 3L+ large B-cell lymphoma, but none is considered standard of care. Regimens currently in use in this setting include rituximab alone or in combination with other agents, cytotoxic chemotherapy agents, and lenalidomide (Chao, 2013). In a study of the most commonly used salvage regimens, bendamustine and rituximab (BR), in patients with R/R DLBCL after at least one prior therapy, an overall response rate (ORR) of 45% and complete response (CR) rate of 15.5% were reported. The median duration of response (DOR) was 17.3 months and the median progression-free survival (PFS) was 3.6 months (Vacirca, 2014). A retrospective analysis of pooled DLBCL patients whose disease was refractory to the last chemotherapy-containing regimen received, or relapsed within 12 months after auto-ASCT (SCHOLAR-1 study) demonstrated an ORR of 26%, a CR rate of 7%, and a median overall survival (OS) of 6.3 months (Crump, 2017).

For patients who have chemoresistant disease (i.e., inadequate response to salvage chemoimmunotherapy) or relapse after autologous transplant, allogeneic HCT and chimeric antigen receptor T (CAR-T) cell therapy are appropriate options. Allogeneic HCT can achieve durable responses but is associated with substantial treatment-related mortality and graft-versus-host disease.

The treatment landscape for R/R large B-cell lymphoma recently changed with the marketing authorisation of 2 CAR T-cell products, axicabtagene ciloleucel (Yescarta®) (Yescarta Summary of Product Characteristics [SmPC], 2020) and tisagenlecleucel (Kymriah®) (Kymriah SmPC, 2020), and conditional marketing authorisation of the CD79b-directed antibody-drug conjugate polatuzumab vedotin (Polivy™) (Polivy SmPC, 2020). In addition, pixantrone (Pixurvi®) (Pixurvi SmPC, 2020), an anthraquinone-based inhibitor of topoisomerase II, was conditionally authorised initially in 2012 then received full approval in 2020 for the broad indication of R/R aggressive B-cell NHL. CAR T-cell treatments, in particular, have shown to induce long-lasting remissions in up to 30% - 50% of subjects, at the cost of a non-negligible toxicity (Locke, 2019; Schuster, 2019). However, the registrational studies for axicabtagene ciloleucel and tisagenlecleucel did not allow enrolment of patients with specific comorbidities such as prior allo-HSCT, secondary CNS involvement by lymphoma, and reduced renal function. The axicabtagene ciloleucel study excluded patients with an immediate need for anticancer therapy for disease control. Overall, these studies excluded patients who are part of a greater population with unmet medical need. Despite these new products, current evidence suggests there remains a substantial unmet need for therapies that demonstrate a combination of compelling and durable efficacy with favourable safety in 3L+ large B-cell lymphoma, particularly in less common NHL subtypes (eg, PMBCL, DLBCL transformed from indolent lymphoma other than FL, and FL3B) and in other populations excluded or under-represented in the clinical studies of recently approved products.

Primary mediastinal large B-cell lymphoma (PMBCL) is an aggressive B-cell lymphoma that represents 2% to 3% of B-cell NHLs and 10% of LBCLs (Mottok, 2019; NCCN, 2019). It tends to occur in younger female patients, and has distinct clinical and biological presentations, characterised by diffuse

proliferation of medium to large B-cells associated with sclerosis (Liu, 2016; Martelli, 2017). Patients with PMBCL who do not respond to first-line therapy are treated similarly to those with R/R DLBCL (Vitolo, 2016) and tend to have a poorer prognosis (Lees, 2019).

Follicular lymphoma Grade 3B is considered an aggressive lymphoma with a clinical behavior similar to DLBCL and is generally treated according to the treatment recommendations for DLBCL (NCCN, 2019; Tilly, 2015; Dreyling, 2016; Dreyling, 2017). Currently, there are no products approved specifically for the treatment of patients with FL3B.

Overall, the therapeutic strategies for FL3B and HGL with rearrangements of MYC and BCL2 and/or BCL6 generally follow the treatment algorithm for DLBCL. Although recommendations have recently changed for first-line treatment of PMBCL (NCCN, 2019), salvage therapy for R/R PMBCL is treated similarly to R/R DLBCL. Patients who relapse or who do not respond to initial therapy are treated similarly to patients with R/R DLBCL (Vitolo, 2016).

In summary, DLBCL patients who progress or who do not respond after 2 lines of treatment have a poor prognosis (Van Den Neste, 2016; van Imhoff, 2017). While the treatment landscape has changed with the approval of two CAR T-cell products, Yescarta and Kymriah, there remains an unmet need for therapies that have favorable benefit/risk profile in 3L+ LBCL, particularly in less common NHL subtypes and in other populations excluded from the registrational trials of the recently approved products.

2.2. About the product

JCAR017 (lisocabtagene maraleucel/lisocabtagene maraleucel) is a CD19-directed genetically modified autologous cellular immunotherapy consisting of purified CD8-positive and CD4-positive T cells in a defined composition, that have been separately activated and transduced with a replication incompetent lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). The CAR comprises an FMC63 monoclonal antibody-derived single-chain variable fragment (scFv), immunoglobulin G (IgG)4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. In addition, JCAR017 includes a non-functional truncated Epidermal Growth Factor Receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR. Although the EGFRt was mainly included as a cell surface protein for analytical detection of transfected T cells, it is also claimed to represent a potential target for the selective ablation of JCAR017 cells, which might prove useful in the case of severe late adverse drug reactions (e.g. secondary neoplasms and/or symptomatic, prolonged hypogammaglobulinaemia).

JCAR017 is a T-cell product prepared from a patient's T cells, which are purified from the product of a standard leukapheresis procedure. The purified CD8+ and CD4+ T cells are separately activated and transduced with the replication-incompetent lentiviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved as separate CD8+ and CD4+ component vials that together constitute a single dose of JCAR017. The product is thawed prior to administration.

The JCAR017 formulation contains 75% (v/v) Cryostor® CS10 (containing 7.5% dimethylsulfoxide ([v/v]); 24% (v/v) Multiple Electrolytes for Injection, Type 1; and 1% (v/v) of 25% albumin (human).

A single dose of JCAR017 contains a target of 100 x 10^6 (range 44-120 × 10^6) CAR-positive viable T cells consisting of a defined composition of CD8+ and CD4+ cell components:

- **CD8+ cell component:** Each vial contains 5.1-322 × 10^6 CAR-positive viable T cells in 4.6 mL (1.1-70 × 10^6 CAR-positive viable T cells/mL).

- **CD4+ cell component:** Each vial contains 5.1-322 × 10^6 CAR-positive viable T cells in 4.6 mL (1.1-70 × 10^6 CAR-positive viable T cells/mL).

More than one vial of each of the CD8+ cell component and CD4+ cell component may be needed to achieve the dose of JCAR017.

2.3. Type of application and aspects on development

The CHMP and CAT agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the fact that JCAR017 (Breyanzi) for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL, and FL3B after at least 2 prior therapies has the potential to address the unmet medical need in the advanced setting of relapsed/refractory large B-cell lymphomas and therefore can be considered of major interest from the point of view of public health, since based on the presented high-level data the availability of an anti-CD19 CAR T-cell treatment characterised by a similar efficacy compared to the currently available products (the current efficacy standard in this clinical setting) and less stringent manufacturing prerequisites (patients with very low ALC counts could also be eligible) might improve patient access to a such a survival, potentially curative, extending option. Therefore, the request for accelerated assessment has been duly substantiated and is agreed.

However, during the assessment the CAT and CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as following the initial assessment of the dossier submitted by the applicant the Rapporteurs identified several critical issues resulting in 5 Quality and 2 Clinical major objections. The additional data requested to overcome the identified uncertainties and concerns entailed significant amendments and integrations of the initial dossier and required a deeper and more extensive data assessment than usually expected in later phases of review. Furthermore, during the assessment a GMP inspection and provision of a GMP certificate were considered necessary which did not allow maintenance of the accelerated assessment timetable.

2.4. Quality aspects

2.4.1. Introduction

Breyanzi (product code JCAR017) is an autologous cell therapy product consisting of a defined composition of purified CD8+ and CD4+ T cells, which have been separately activated and transduced with a replication incompetent lentiviral vector (LVV) encoding an anti-CD19 chimeric antigen receptor (CAR) and a non-functional truncated epidermal growth factor receptor (EGFRt). The latter is co-expressed on the cell surface with the anti-CD19 CAR and can serve for a potential CAR T cell ablation system.
The two finished product cell components (CD4+ and CD8+) are presented as dispersions for infusion. The calculated dose volume is reported on the Release for Infusion (RFI) certificate provided to the clinical sites together with the finished product, and may account for up to 18.4 mL/component. The target dose is 100x10^6 CAR-positive viable T cells (ranging from 44x10^6 to 120×10^6 cells), accounting for a target CD4+:CD8+ cell components' ratio of 1:1 (ranging from 0.8 to 1.2).

Other ingredients are Cryostor CS10, sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, human albumin, N-acetyl-DL-tryptophan, caprylic acid and water for injections.

Breyanzi is supplied in cryopreservation vials made of cyclic olefin copolymer. Each 5 mL vial contains 4.6 mL cell dispersion.

The CAR+ viable T cells (CD8+ cell component or CD4+ cell component) are presented in individual cartons containing up to 4 vials of each component, depending upon the cryopreserved finished product CAR+ viable T cell concentration. The cartons of CD8+ cell component and CD4+ cell component are contained in a single outer carton.

2.4.2. Active Substances

The section on the active substance is separated into two parts; part 1 for the lentiviral vector and part 2 for the transduced cells.

Unless otherwise specifically stated, the information on the transduced cells applies to both of the active substances, i.e., autologous CD8+ and CD4+ T cells transduced with a LVV to co-express an anti-CD19 CAR and EGFRt.

PART 1: LVV

General Information (LVV)

The LVV is the gene delivery vehicle for the CD19-specific chimeric antigen receptor (CAR) transgene. It is a third-generation replication-incompetent self-inactivating (SIN) vector produced using design features in which the necessary viral genes are expressed from four separate plasmids that minimise the risk of replication competent lentivirus generation. The vector system consists of the transfer plasmid, containing the CAR transgene, and three helper plasmids containing all the genes for viral packaging and delivery.

In addition to capsid proteins and VSV-G pseudotyped envelope, the viral particles contain two copies of the RNA viral genome, that carries key viral elements necessary for LVV function, as well as sequences encoding a truncated form of the EGFR (EGFRt), which is intended to be co-expressed with the CD19-specific CAR in the transduced T cells.

Manufacture, process controls and characterisation (LVV)

The facilities involved in manufacturing, testing and/or storage of the bulk lentiviral vector (BLV) and final filled lentiviral vector (FLV) are indicated in the dossier.

Description of manufacturing process and process controls

The manufacture of the LVV starts with the thaw of a single vial of the working cell bank (WCB) and the cells are expanded over several passages The cells are transiently transfected and the cell culture supernatant containing the LVV is harvested and pooled into a common collection bag. Concerning the downstream process, the LVV undergoes a series of purification steps, and the clarified LVV supernatant is recovered, diluted with formulation buffer, and the resulting BLV is frozen. Subsequently, the frozen BLV is shipped to the FLV manufacturing site where it is filled into sterile vials.

The LVV is manufactured under aseptic conditions using sterile connections, manifolds and closed systems. Any open manipulations are performed aseptically in an ISO 5 (Grade A) environment.

Control of materials

Generation of the Master Cell Bank (MCB) and WCBs has been adequately described. The overall testing strategy of for the cell banks is considered adequate

With respect to the plasmids, adequate information and acceptance criteria including Certificates of Compliance, TSE-BSE Statements and certificates of analysis (CoAs) for all four plasmid lots including release specifications for cell banks have been provided and are acceptable.

Information on the raw materials, formulated media and buffers, and materials of contact used during the LVV manufacturing process, has been provided and adequate information on testing before release has been given.

Control of critical steps and intermediates

The LVV manufacturing process has been described in sufficient detail, including flow charts and tables indicating the implemented in-process controls (IPCs), critical process parameters (CPPs) and non-critical process parameters (nCPPs) along with the relative operating ranges and/or acceptance criteria. The information provided is considered adequate.

Process validation

The BLV and FLV commercial manufacturing processes were validated. The process validation strategy for BLV and FLV consists in process design, process performance qualification (PPQ), continuous process verification (CPV), aseptic process validation, and shipping qualification in addition to BLV/FLV material qualification and validation of the holding conditions of buffers and media used in the manufacturing process. Adequate information on the WCB lot numbers and on the process parameters monitored during PPQ (CPPs, IPCs and nCPPs) has been provided. All quality attribute results met the specifications. All CPP results met the Proven Acceptable Ranges (PARs).

The release results and the relative certificates of analysis (CoAs) have been provided. Aseptic process simulation (APS) was executed for BLV batches and for FLV batches and the information submitted is deemed acceptable.

Validation studies on media and buffers formulated in advance for use in the BLV manufacturing process, were performed, to demonstrate that the solutions can be formulated adequately. Results from the buffer and media chemical hold studies and buffer and media microbial hold studies were combined to determine the expiry for the buffers and media used in the BLV manufacturing process. Mixing validation studies were performed using representative surrogate solutions to demonstrate that FLV processes can consistently produce homogeneous solutions. The approach described is overall acceptable.

As regards BLV and FLV shipping validation, both studies were carried out with simulated product and transportation conditions, and all obtained results demonstrated that the shipping of BLV and FLV is a well-controlled part of the whole process.

The list of parameters and attributes that will be monitored for the CPV programme have been provided.

Manufacturing process development

On the basis of quality risk management principles, vector quality attributes were evaluated and categorised as critical quality attributes (CQAs) and non-CQAs based on the predicted severity of impact on the finished product safety and efficacy.

The BLV and FLV were initially manufactured according to v1.0 manufacturing process, supporting clinical manufacturing and then transferred to a different manufacturing site, and implemented as v1.2 manufacturing process. The comparability of the results obtained to support the site transfer has been shown.

A summary of LVV method changes has been provided in a tabular format and the impact of the change of method on functional comparability has been sufficiently addressed.

A prospective comparability assessment evaluating the initial versus the proposed commercial manufacturing process is described by the applicant and includes vector analytical and functional comparability. The results show that the manufacturing processes are either consistent or showing an improvement for the commercial process.

Characterisation

Structural and functional characterisation of the LVV was performed using vector lots manufactured at all facilities used during the development.

The integrity and identity of the CAR coding sequence has been confirmed. Vector function in T cells has been investigated. Data provided indicates a consistency in vector manufacturing.

Vector process-related impurities are evaluated through a combination of release and characterisation testing. Data on the frequency of CAR+/EGFRt+ and on vector copy number (VCN) have been submitted as part of the LVV characterisation studies and considered satisfactory.

Specification (LVV)

The specifications for the unprocessed bulk vector harvest (BVH), the BLV and the FLV are provided and are considered acceptable. The specifications include general tests, identity, potency, purity / impurities, and safety related tests.

Overall, the justifications provided are deemed sufficient to justify the current specifications set by the applicant.

Analytical methods

A description of the analytical methods used for release testing of the lentiviral vector has been provided and deemed acceptable. All non-compendial methods have been validated according to ICHQ2(R1). For the compendial methods, no formal validation is required but suitability/verification has been demonstrated.

Batch analysis

The batch history and the batch data of BLV and FLV lots produced have been provided along with information on the cell banks used to produce the vectors lots. This is considered sufficient.

Reference materials

There are no reference standards for the LVV. However, a vector control lot that has been fully characterised and is used as an assay control.

Container closure system

A full description of the BLV and FLV container closure system have been provided and their appropriateness is justified.

Stability (LVV)

Long-term stability studies are ongoing and include multiple FLV lots. These studies incorporate batches from each manufacturing site and are being conducted with primary lots manufactured using the proposed commercial manufacturing process and sites and supportive lots including material produced using the clinical manufacturing processes. Stability studies were evaluated according to the specifications in place at the time of testing.

Stressed stability studies were performed to demonstrate the stability indicating profile of the FLV.

Based on the available stability data, a shelf life up to 12 months at -80°C ± 10°C is accepted for the FLV.

PART 2: Autologous CD8+ and CD4+ T cells transduced with the LVV to express an anti-CD19 CAR

General Information (transduced cells)

The assigned INN (lisocabtagene maraleucel) covers both active substances, i.e., the CD8+ and CD4+ T cells transduced with a LVV to express an anti-CD19 CAR. The company codes JCAR017 and liso-cel are also used by the applicant to describe the active substances/finished product.

The active substances consist of purified human autologous CD8+ and CD4+ T cells transduced with a LVV containing an expression cassette for the anti-CD19 CAR and the EGFRt. The CAR construct (see below Figure 1) accounts for a single chain antibody fragment of murine origin derived from the mouse monoclonal anti-CD19 antibody FMC63, an extracellular spacer element of human origin, the CD28 as TM domain, the 4-1BB and CD3ζ as signaling domains. Reference is also made to the presence of the EGFRt on the CAR T cell surface.

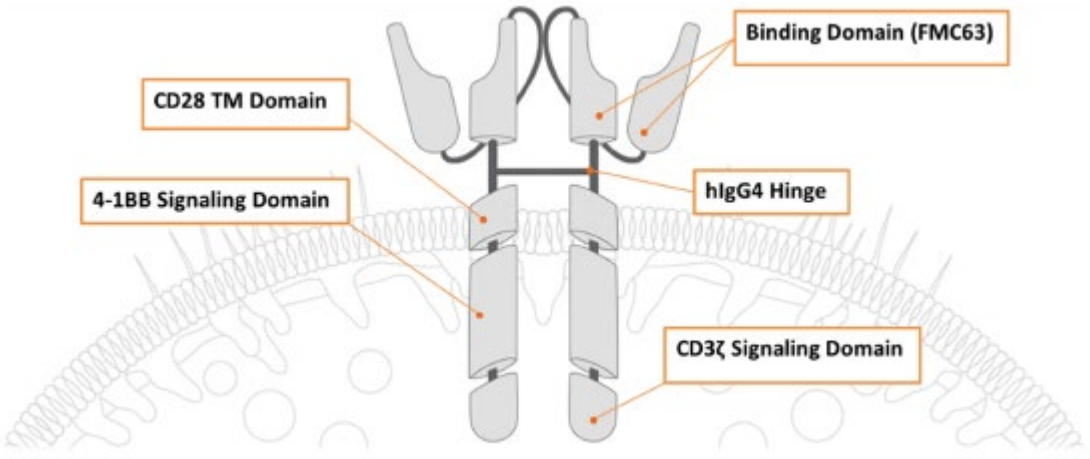


Figure 1: Schematic diagram of the JCAR017 CAR

Manufacture, process controls and characterisation (transduced cells)

Description of manufacturing process and process controls

Selection and cryopreservation of CD8+ and CD4+ cell intermediates is carried out at the facility in Germany. The cell intermediates are then shipped to the Juno Therapeutics Inc. Manufacturing Plant (JuMP, USA), where the manufacture of the active substances and finished products takes place.

The name, address and responsibilities of each site involved in the active substance manufacture have been provided. Appropriate evidence of GMP compliance has been provided. During the procedure a major objection was raised due to the lack of valid EU GMP certificate for JuMP. Following an inspection, the relevant GMP certification was provided and the major objection is considered resolved.

The manufacturing process covers unit operations that start with leukapheresis wash and includes selection, activation, transduction, expansion and harvest.

CPPs, IPCs, and processing times have been presented with their associated targets or ranges. Sampling points for release testing have been included as well. In general, the aim of each unit operation has been

addressed, and the procedures performed within each unit operation has been adequately described. Excess cryopreserved intermediates may be generated, which would be forward processed in the instance of a processing failure with the first bag.

No reprocessing is allowed.

Controls to monitor cell viability along the manufacturing process have been summarised. An explanation for the processing times stated in the unit operations has been provided.

During the procedure a major objection was raised due to insufficient information and data confirming the suitability of the transduction unit operation. In response to the major objection evidence of suitable control of the transduction step has been provided. Nevertheless, the transduction step is considered as complex and there is currently limited experience. Satisfactory and consistent performance of the transduction step is critical to active substance/finished product quality and consequently for the benefit/risk profile of the product. Therefore, in order to further assess the consistency of product quality and clinical outcomes, the applicant should submit batch analysis and corresponding clinical safety and effectiveness data from a minimum of thirty (30) lots of Breyanzi finished product used to treat patients included in a non-interventional study based on secondary use of data from existing registries, according to an agreed protocol. Based on this data the applicant should also provide an evaluation on the need for a revision of the finished product specifications. Interim reports should be provided after approximately 15 lots and any significant out of trend results should be reported immediately (**Annex II condition,** Due date: Final report by 31 December 2026).

Based on the information received and the commitment to provide the data as indicated above, the major objection was considered resolved.

The description of microbial contamination controls within the manufacturing process has been provided. However, during the procedure a major objection was raised in relation to deficiencies in the microbiological control strategy. In response, satisfactory measures have been implemented by the applicant to improve the microbiological control strategy. Sterility testing at the level of finished product release has also been adjusted to fully comply with Ph Eur 2.6.27. Consequently, the major objection was considered resolved.

Control of materials

The leukapheresis starting material is collected at qualified sites as described in the dossier.

For the leukapheresis starting material and cryopreserved material (CMAT) release Ph. Eur. 2.6.27 compliant sterility testing will be performed. The applicant has provided validation reports for the microbiological control of the leukapheresis starting material and the CMAT, which are suitable.

The leukapheresis collection procedure has been sufficiently described.

As requested, the applicant has established a release test panel for the leukapheresis starting material.

The applicant has also provided the lists of tests performed for adventitious agents and confirmed the following points:

- patient screening and leukapheresis collection (procurement) adhere to national requirements of Member States;
- relevant epidemiological practices are adhered to;
- the testing for viral markers is performed by qualified laboratories;
- donor's serum and or plasma is tested for adventitious agents as per directive 2006/17/EC;
- the adventitious agents' tests are performed with EC-marked kits, as per directive 2006/17/EC.

The applicant has detailed their strategy for the selection of the leukapheresis collection centres. The overall leukapheresis collection procedure will be performed according to written procedures as provided by the applicant. In addition, leukapheresis starting material testing and cell processing laboratories comply with EU Directives 2004/23/EC and all the daughter directives. Furthermore, periodic reviews of the apheresis centres are performed as well. The approach is overall sufficiently detailed and is endorsed.

Media, buffer, and reagent preparations have been adequately described.

Control of critical steps and intermediates

With respect to the control of critical steps and intermediates, overall, the control strategy is presented in an acceptable way. CPPs with the associated acceptable range as well as IPCs with corresponding acceptance criteria/action limits, have been presented. IPCs mainly focus on TNC. Non-CPPs and processing times have been described.

The cryopreserved CD8+ and CD4+ selected materials (CMAT) are identified as intermediates. As requested, a minimum set of release specifications has been put forward for the intermediates.

CD4+ and CD8+ intermediates stability has been directly and indirectly assessed through finished product manufacturing from intermediates stored for various timepoints**.**

Process validation

In view of the continuous active substance/finished product manufacturing process, the process validation is described in the finished product section.

Manufacturing process development

In view of the continuous active substance/finished product manufacturing process, the manufacturing process development is described in the finished product section.

Characterisation

In terms of characterisation, an extensive set of studies were performed, covering the characterisation of 1) JCAR017 CAR structure and function, 2) JCAR017 phenotype and function, 3) JCAR017-associated mechanism of action, 4) the exploratory correlative analysis between JCAR017 quality attributes and clinical outcome in terms of efficacy, safety, and pharmacokinetics as reported in study 017001.

Characterisation data has been collected throughout development. Overall, the characterisation data provided show homogeneity between the two cell components and has been provided for a relevant number of batches.

Shared considerations were provided for the CD8+ and CD4+ active substances on the structural and functional characterisation of the CAR. The information provided, covering the CAR amino acid sequence, size and structure determination including primary structure as well as functional features of the CAR binding and activation domains, reassure about the CAR intended structure and functions.

In terms of phenotypic and functional characterisation, the data suggests that the two cell components show a high degree of purity. The applicant has provided the requested information on the materials' phenotypic composition.

Extensive characterisation has been provided also in terms of (VCN)/transduced T cell, CAR protein expression on the surface of cells and %CD3+CAR+.

The claim of a consistent CAR expression/cell is supported by characterisation data.

Data showing IFNγ secretion by the CD8+ and CD4+ cell components upon antigenic stimulation has been presented. During the procedure a major objection was however raised as the suitability of IFNγ

secretion as potency assay was questioned. The IFNγ secretion has subsequently been justified as an acceptable surrogate marker for potency determination.

With regard to the CD8+ cell component, it is acknowledged that no correlation has been found between the IFNγ secretion (or cytolytic activity) and the intended clinical outcome. However, this is an effect observed nearly for all such complex CAR T cell-based products. Therefore, in light of the data and justifications provided, the use of the IFNγ secretion assay can be supported as a surrogate potency test for release.

Concerning the CD4+ cell component, the applicant has evaluated the functional profile of multiple cytokines that support the intended mechanism of action of the CD4+ cell component. The evaluation is based on correlative analysis data from a clinical study and recent published T cell literature.

Consequently, the major objection was considered resolved.

Characterisation of impurities has been conducted. All lots selected for testing were conforming and manufactured with a commercially representative process.

For the process-related impurities, the data or considerations provided by the applicant are assessed against exposure limits per dose.

Adequate safety margins are in place for process-related impurities.

The derivation of a permitted exposure for protamine sulphate is calculated from the therapeutic value of 50 mg/day, which is deemed acceptable.

As far as the product-related impurities are concerned, the approach adopted by the applicant takes into account residual cell types. Overall, the approach is extensive and endorsed. It is recognised that the characterisation has been performed on a relevant number of batches.

Short summaries of qualification reports for all impurities characterisation methods, has been provided. Impurity characterisation methods appear suitable for their intended use.

Characterisation data has been extensively provided for study batches. However, differences have been noted between the US study 017001 vs the EU study BCM-001 results, which therefore has requested further insights on the quality standpoint. Comparison of quality attributes and correlations with efficacy response were provided for 017001 vs BCM-001 batches. The data are supportive of no substantial differences between the two sets of batches from the quality standpoint.

Specification (transduced cells)

As the active substance cell components are immediately processed to finished product, the specifications as well as analytical procedure, validation of analytical procedure, batch analysis, justification of specification, and container closure system are described under the finished product section.

Stability (transduced cells)

As the active substance cell components are immediately processed to finished product, no active substance stability data have been submitted, which is acceptable.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product consists of two separate autologous cell suspensions, i.e. 1) a cryopreserved autologous CD8+ T (killer) CAR+ cell suspension and 2) a cryopreserved autologous CD4+ T (helper) cell suspension. The two cell component are presented in separate vials. The finished product is intended for intravenous administration.

The finished product is composed of ≥5.1 x 10^6 anti-CD19 CAR+ viable T cells/vial (up to 4 vials/cell component), CryoStor CS10 (a cryopreservative solution containing 10% dimethylsulfoxide (DMSO)), Multiple Electrolytes Injection Type I, and human albumin solution. The Multiple Electrolytes Injection, Type I contains sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, N-acetyl-DL-tryptophan, caprylic acid and water for injections.

The Albumin (Human), 25% Solution Octapharma is an EU authorised medicinal product. Multiple Electrolytes Injection, Type 1 is compliant with USP/Ph. Eur. For the CryoStor CS10, which is the only non-compendial excipient used in the finished product formulation, all the requested clarifications and information with respect to its quality for its intended use has been provided by the applicant which is deemed acceptable.

The calculated dose volume is patient specific and is reported on the Release for Infusion (RFI) certificate provided to the clinical sites together with the finished product in the delivered package, and accounts for up to 18.4 mL/cell component. The target flat dose is 100x10^6 CAR+ viable T cells (range 44x10^6 - 120×10^6 cells), accounting for a CD4:CD8 cell component target ratio of 1:1.

The formulation development has been described.

Manufacturing process development

Across the product development, four finished product manufacturing process versions (v1-v4) have been used. Process v4 represents the commercial process and commercial site, namely Juno Manufacturing Plant (JuMP) (Bothell, WA, USA). The manufacturing process foreseen for the treatment of EU patients in the commercial setting accounts for the manufacture of the CD4+ and CD8+ cell intermediates at the facility in Germany and their subsequent shipment to JuMP for the finished product manufacture.

Patients administered with finished product v1 were not included in the efficacy analysis set. Therefore, absence of a comparability exercise versus subsequent product versions is acceptable. Patients receiving finished product v2 are included in the efficacy analysis set. The applicant claims that no process changes were associated with the technology transfer that had the potential to impact CQAs; therefore, no prospective comparability was performed. This is endorsed.

Implementation of manufacturing process v3 accounted for changes in the formulation. Therefore, the applicant conducted a process v2 versus process v3 retrospective comparability exercise. A conclusion of comparability is supported. Significant manufacturing changes have been introduced between process v3 and v4. Comparability has been addressed. Relevant shifts/differences are noted in both comparability studies for QAs for the v3 vs v4 finished product, yet compliant to the applicant's established acceptance criteria, i.e., release specifications. In addition, analysis of clinical efficacy, safety and PK data by manufacturing process versions shows consistent results across manufacturing process versions. It can be therefore concluded that, despite the relevant shifts observed the clinical performance of process v3 vs v4 finished product can be considered overall comparable.

In addition, it is concluded that sufficient data has been provided to support the CMAT manufacturing site in the EU commercial setting.

Process characterisation

As far as process characterisation is concerned, a process parameter risk assessment was performed with the aim to identify parameters having a potential impact on relevant finished product and process performance attributes. This risk assessment was then used to prioritise evaluation of parameters and their impact on the relevant attributes within process characterisation studies.

Overall, it can be agreed with the applicant that process characterisation studies showed consistent production of finished product across the range process parameters tested. All characterisation conditions generated finished product compliant with release specifications, providing reassurance on consistency of manufacture.

The main elements that informed the commercial process control strategy are represented by the classification of critical raw materials, establishment of CQAs, design and execution of process characterisation studies, and classification of process controls.

Container closure system

The container closure system consists of cryopreservation vials made of cyclic olefin copolymer. The commercial container closure system complies with Ph. Eur. 3.2.2 Plastic Containers and Closures for Pharmaceutical Use.

The product has been tested for its compatibility with the container closure system (vials), the syringe needle and the syringe used to withdraw the thawed product from the retrieval port, using conditions and preparation procedures representative to those used in clinical trials and proposed for commercial use. According to the data provided, it can be agreed that 1) the CD8+ and CD4+ cell components preserve their intended quality when held for 2 hours between 15°C and 25°C in 5 mL cryopreservation vials, 2) are compatible with a 20G needle. The applicant's conclusions according to which the total time from the removal of the finished product from the LN2 shipper/freezer to the administration should not exceed 2h, is endorsed. The SmPC includes the following statement "once Breyanzi components have been drawn into syringes, proceed with administration as soon as possible".

Manufacture of the product and process controls

The names and addresses of the facilities involved in the finished product manufacture are provided along with the respective responsibilities. Upon shipment of the cryopreserved CD4+ and CD8+ cell intermediates from Germany (EU), the active substance/finished product manufacture, packaging as well as release and stability testing is performed at JuMP (USA). During the procedure a major objection was raised due to the lack of valid EU GMP certificate for JuMP. Following an inspection, the relevant GMP certification has now been provided and the major objection is considered resolved. QP release/certification in the EU is performed by Celgene Distribution B.V. in the Netherlands.

The finished product manufacturing process encompasses harvest buffer exchange and formulation, fill, and cryopreservation of finished product. The manufacturing process is continuous and transitioning from active substance to finished product manufacture occurs without any holding steps.

CPPs have been defined for the above unit operations, while no IPCs have been established. Processing time have been set in the formulation, fill and cryopreservation unit operation.

The target dose volume is provided by the applicant, to the administration site, with the minimum number of finished product vials that are necessary to achieve the calculated dose volume. The applicant

confirmed that Juno Therapeutics Inc., Manufacturing Plant (WA, USA) is responsible for the storage of excess finished product vials until the finished product has been administered to the patient.

The process validation strategy includes three stages: process design, process qualification, and continued process verification. The PPQ studies were considered appropriately designed. All acceptance criteria for the CPPs, IPCs and CQAs with acceptance criteria were met.

To account for variability, the PPQ study design included multiple sources of cell starting material, multiple LVV manufacturers and multiple LVV lots.

The selected tests and acceptance criteria established for cryopreserved material have been justified. Questions raised during the procedure in relation to the process validation have been adequately addressed. Validation data demonstrates filter suitability for their intended use in a worst-case scenario.

Extractable and leachable risk assessment, studies and conclusion are adequate.

Appropriate shipping validation studies have been performed.

Product specification

In general, the proposed finished product specifications are reasonable and cover relevant CQAs. The quality parameters taken into account for each cell component include appearance, identity, purity, strength, potency and safety.

The release specifications for the container closure system have been provided and are deemed acceptable.

During the procedure a major objection was raised in relation to the lack of a risk evaluation for the potential presence of nitrosamine impurities. In response, the applicant confirmed that the risk of the presence of nitrosamine impurities in the finished product had been evaluated in accordance with the published Art. 5(3) Referral on Nitrosamines (https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf). The relevant documentation was provided as requested. The risk of nitrosamine impurities is considered negligible and no specific controls are considered necessary in this regard. The major objection was considered resolved.

Analytical methods

For each quality attribute tested at release, the applicant has provided a summary of the analytical method and the corresponding analytical method validation report.

Batch Analysis

Batch analysis data for clinical lots manufactured throughout development has been provided. Results for multiple batches were submitted, covering the various manufacturing process versions and sites. The great majority of lots are within the specifications set at the time of production and comply also with the proposed commercial specifications. Batch analysis results show consistency of production well within the validated ranges.

Stability of the product

The finished product lots used in primary and supportive stability studies are representative of the commercial process and of the container closure system proposed for the commercial setting.

The claimed shelf-life of 13 months at ≤-130°C in vapor phase of liquid nitrogen (LN2) is based on data for both CD8+ and CD4+ cell components. The stability data collected support the 13 months expiry date proposed by the applicant.

The testing panel applied for the stability studies is considered acceptable.

Based on the data provided, a shelf-life claim of 13 months at ≤-130°C is considered acceptable.

Adventitious agents

TSE and viral safety aspects for the LVV and active substance/finished product, have been adequately addressed.

In the context of the traceability aspects, the applicant declares that a full donor traceability system is in place for the human plasma-derived product used in the manufacture of the finished product.

The applicant has clarified that leukapheresis product from patients with active HIV or HCV infection would not be accepted for product manufacture. This is controlled through the infectious diseases testing specification established for the CMAT.

GMO

Breyanzi contains autologous genetically modified T cells. An environmental risk assessment in accordance with Directive 2001/18/EC has been presented with respect to the risk of release of GMO into the environment.

Considering the overall information provided, it can be agreed that the environmental risk associated with Breyanzi can be considered negligible.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Breyanzi is a combination product composed of two active substances (autologous CD8+ and CD4+ T cells transduced with a lentiviral vector to express an anti-CD19 CAR).

Information on development, manufacture and control has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory performance in clinical use.

Nonetheless, considering that 1) limited clinical experience has been gained with the proposed overall commercial manufacturing process and 2) consistent performance of the transduction step is critical to finished product quality, safety and efficacy, the applicant is requested to further assess the consistency of product quality and clinical outcomes by providing additional batch analysis and corresponding clinical safety and effectiveness data post-approval (see Annex II condition).

A number of major objections were raised during the procedure:

MO1 related to deficiencies in the microbiological control strategy. In response, the applicant provided satisfactory clarifications on the microbiological control strategy, and the sterility method was aligned with the Ph. Eur. as requested. Consequently, the major objection was considered resolved.

MO2 related to the lack of a EU GMP certificate for the active substance/finished product manufacturing and release/stability testing site Juno Therapeutics Inc. Following an inspection, the relevant GMP certificate was provided and the major objection considered resolved.

MO3 related to concerns around the suitability of the proposed transduction approach. Additional data and justifications, including validation data, were provided in response. These were considered acceptable and considering also the commitment from the applicant to provide further data as outlined in the Annex II condition below, the major objection was considered resolved.

MO4 related to deficiencies in the data submitted to support the suitability for of the proposed potency test (IFN-γ secretion). It was acknowledged that IFNγ secretion is not an ideal potency assay, and that there is a lack of satisfactory correlation with efficacy. However, based on the additional justifications provided by the applicant, the proposed potency assay was considered acceptable and the major objection resolved.

MO5 related to the absence of a risk evaluation on potential nitrosamine impurities. Following submission of the requested documentation the major objection was considered resolved. The risk of nitrosamine impurities is considered negligible.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

The CAT/CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:

In order to further assess the consistency of product quality and clinical outcomes, the MAH shall submit batch analysis and corresponding clinical safety and effectiveness data from a minimum of thirty (30) lots of Breyanzi finished product used to treat patients included in a non-interventional study based on secondary use of data from existing registries, according to an agreed protocol. Based on this data the MAH should also provide an evaluation on the need for a revision of the finished product specifications. Interim reports should be provided after approximately 15 lots and any significant out of trend results should be reported immediately (Annex II condition. Due date: Final report by 31 December 2026).

At the time of the CAT/CHMP opinion, there were a number of unresolved quality issues which are not expected to have an impact on the benefit/risk ratio of the product. These points are put forward and agreed as recommendations for future quality development (see below "Recommendations for future quality development").

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

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT/CHMP recommended some points for further investigation including completing the characterisation and testing of the viral vector and the finished product.

The CHMP endorses the CAT assessment regarding the recommendation(s) for future quality development.

2.5. Non-clinical aspects

2.5.1. Pharmacology

2.5.1.1. Primary and secondary pharmacodynamic

In vitro experiments to evaluate genomic integration profile of the self-inactivating (SIN) lentiviral vector encoding the CAR and the non-functional truncated epidermal growth factor receptor (EGFRt)transduced in Autologous CD4+ and CD 8+ T cells, demonstrated no preferential integration at loci associated with enhanced risk of transformation.

The in vitro studies focus on the characterisation of JCAR017, in terms of affinity and specificity of the FMC63 scFv binding domain to CD19, the cytotoxic T cell killing of CD19 positive target cells, cytokine production and JCAR017 cell proliferation. JCAR017 FMC63 binding domain specific interaction with a discontinuous epitope of human CD19 was reported. The specificity of JCAR017 binding to human CD19-expressing target cells and the absence of species cross-reactivity was further demonstrated by a flow cytometry binding assay, that confirmed the absence of activity against CD19-expressing mouse cells.

The rationale to choose CD19, expressed mainly on normal and malignant B-cells, as target for JCAR017 was proved by a bioinformatics analysis on databases of human normal and tumour tissues, including haematological malignancies.

The activation of JCAR017 upon human CD19-engagement was evaluated.

The downstream 4-1BB and CD3ζ regions of the CAR construct were reported to undergo activation by co-culture of CAR mutant-expressing Jurkat reporter cells and CD19-expressing tumour cells.

JCAR017 T cells were evaluated for proliferation, activation, cytokine production and acquisition of killing capability of target cells.

Both CD4+ cell component and CD8+ cell component JCAR017 T cells were reported to proliferate specifically in response to co-culture with several CD19-expressing cell lines, including FL and PMBCL-derived cells, in terms of cytokine production (IFN-γ, IL-2 and TNF-α) and up-modulation of CD69 and CD25 markers.

A viability assay (RPT-001115) with anti-idiotypic stimulation of JCAR017 CD4 and/or CD8 cells showed that the combination of 1:1 CD4+:CD8+ JCAR017 subsets provided a benefit to total cell growth as compared to CD8+ subset alone. This assay did not include other ratios besides the 1:1 ratio. In addition, the assay measured total viability in the 1:1 subgroup and did not discriminate between CD4 viability and CD8 viability when the 1:1 ratio was used.

Cytolytic activity of JCAR017 T cells against a variety of CD19+ FL and PMBCL cell lines, upon co-culture with each target cell line, was also reported. Likewise, JCAR017 cells derived from NHL patients showed a high degree of specific cytolytic activity against CD19+ tumour cells, after 4-day culture.

Regarding the characterisation of co-expression of CAR and EGFRt, the performed flow cytometry analysis confirmed this parameter.

The in vivo pharmacology studies were performed in immune-deficient NOD/SCID IL-2Rγnull mice engrafted i.v. with 5.0E+05 human CD19+ Raji Burkitt's lymphoma cells engineered to express a red-shifted firefly luciferase (rFLuc) transgene and green fluorescent protein (GFP), for non invasive assessment of disseminated lymphoma growth by in vivo bioluminescence imaging (study RPT-0433). The results demonstrated that JCAR017 cells, obtained from healthy and patient donors, were able to reduce tumour burden and increase mice survival, in a dose-dependent manner, through all the tested

periods (0-100 days), in contrast with the control group (died by day 10-11). JCAR017 precommercial v3.0 and proposed commercial v4.0 processes evaluation in tumour-engrafted NOD/Scid mice showed antitumour efficacy of both products, in terms of tumour burden reduction and mice survival, in a dose dependent manner. However, it is important to note that differences between v3.0 and v4.0 processes in mice survival, mostly at medium and high doses, are reported as significant:

a)	v3.0 HD1 vs. v4.0 HD1	2 x 106	p <0.001
b)	v3.0 PtD1 vs. v4.0 PtD	1 5 x 105	p 0.002
c)	v3.0 PtD1 vs. v4.0 PtD1	1.25 x 105	p 0.009
d)	v3.0 HD2 vs. v4.0 HD2	5 x 1055	p 0.003
e)	v4.0 HD2 vs. v3.0 HD2	2 x 106	p<0.001

With regard to JCAR017 PK evaluation, the monitoring over-time of circulating CD8+ JCAR017 cells demonstrated that these cells, at the high dose, peaked at Day 8 whereas at the medium and low doses peaked on Day 14, dependent from donors and manufacturing processes. Circulating CD4+ JCAR017 cells displayed a more variable trend across the manufacturing processes and donor sources. While high dose HD1 CD4+ JCAR017 v3.0 remained very high at all time-points, the v4.0 counterpart did not exhibit any expansion. Likewise, HD2 CD4+ JCAR017 v4.0 were very high at all time-points, but the v3.0 one did not expand at any time. In addition, both CD4+ JCAR017 v3.0 and v4.0 did not display almost any expansion at low and medium doses**.**

To assess all the parameters and the efficacy of cetuximab treatment in depleting JCAR017 T Cells in vivo, a series of in vivo studies were performed by means of a Raji xenograft mouse model. The studies Raji-1806 and Raji-1809 (RPT-001479) were undertaken to demonstrate the in vivo elimination of JCAR017 after cetuximab administration (0.25 or 0.125 mg/mouse), by assaying the elimination or reduction in CAR T numbers in peripheral blood, spleen, or bone marrow (primary endpoints) as well as increased tumour burden and reduced cetuximab-treated animals' survival (secondary endpoints). In Raji-1806 study, CAR T cells (0.5E+06 for both CD4+ and CD8+) were found expanded within circulation and were detectable within lymphoid tissues on Day 13 post infusion. Cetuximab (0.5 mg/mouse, intraperitoneally) was administrated on Days 7, 9, 11, and 13 reducing significantly CAR T numbers in blood, spleen and bone marrow. This study was not suitable for evaluating tumour growth and survival parameters because no reduction in tumour burden was observed in 6 out of 8 JCAR107-treated mice, reflecting the low survival similar observed in JCAR017-not treated Raji xenograft mice. The Raji-1809 study demonstrated that cetuximab administered on Days 12, 14, 16, 18, 20, 22, and 24 (starting at the peak time CAR T expansion) reduced significantly numbers of CAR T cells in blood and spleen but not in bone marrow. Conversely to the previous study, this report showed faster tumour growth and reduction in numbers of JCAR017 in cetuximab-treated versus vehicle mice.

PK data were gathered after single (Report CC-DISC-DMPK-3291 cetuximab administered at 5 mg or 20 mg/kg IV or 20 mg/kg IP for the dose selection) or repeated (RPT-002100; cetuximab 0.125 or 0.25 mg/Kg mouse, intravenously on different days) cetuximab administration.

In RPT-002100, it is noted that reference clinical PK information for the cetuximab (i.e., mean steady-state peak and through concentrations) are referenced from the FDA-approved SmPC (2019) or from the paper Luo FR et al, 2005, which does not provide updated information.

Importantly, the analysis of cetuximab PK in the mouse serum (after both single and repeated dose administration was supported by an ELISA with an assay range from 7.81 (LLOQ) to 1000 (ULOQ) ng/ml of Cetuximab (Report CC-DISC-DMPK-3415). As consequence, the performance of assays has implied the study sample dilution since the amount of cetuximab found in the mouse serum is far above the assay ULOQ. The results show that the dilution factors reported in report RPT-002100 and CC-DISC-

DMPK-3291 (i.e., ≤600), are outside the validated range of dilutions (i.e., 1:800 to 1:12,800 dilution) that was established in report CC-DISC-DMPK-3415 to address the ELISA assay dilution integrity. In this regard, it should be noted that the dilution integrity should cover the dilution(s) applied to the study samples (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

Overall, according to the results provided in study RPT-002100 report, the mouse PK data after the first (out of six) administered cetuximab dose may be considered in line with cetuximab clinical levels observed at the steady state. However, human steady state levels appear to be far below as compared to those observed in the mouse approaching the steady state (i.e., mouse PK data immediately prior to the final cetuximab dose), in correspondence of which assessment of cell ablation has been performed and data has been provided (i.e., day 21). Furthermore, ablation data has been provided at day 13 with no corresponding PK information, thus hampering the assessment of the data relevance. Of note, a trend of cell ablation in the mouse at earlier time points after cetuximab administration, including immediately prior to the administration of the second cetuximab dose, should be discussed possibly also taking also into account corresponding mouse cetuximab PK data.

To perform the NC Study RPT-002100, the applicant set-up and validated a flow cytometry assay for the detection of human JCAR017 cells in mouse whole blood specimens.

2.5.1.2. Safety pharmacology programme

The autologous cell-based JCAR017 T products lack species cross-reactivity thus in all NC studies performed safety pharmacology was deemed not practical and of negligible utility. Overall, no safety pharmacology studies were conducted.

2.5.1.3. Pharmacodynamic drug interactions

NC studies to test drug interactions were performed to support future use in those patients that may require adjunct CAR T therapy for the treatment of B-cell lymphomas in association with cancer therapies.

The first study intended to evaluate the effects of durvalumab, an anti-PD-L1 Ab (20 µg/mL), on the activation status of JCAR017 cells, supporting their association in a therapeutic regimen.

BTKi (ibrutinib and acalabrutinib) were evaluated for their effects on in vitro JCAR017 function. The results indicated no detrimental effects of both drugs on JCAR017 performance**.**

The efficacy of JCAR017 in combination with Ibrutinib or Acalabrutinib was evaluated also in vivo in NOD-SCID IL2Rγnull mice engrafted with 5 x 105 Nalm-6 Firefly Luciferase (FfLuc)-green fluorescent protein (GFP) lymphoblastic leukaemia cells. The results showed that the combination of JCAR017 with ibrutinib or acalabrutinib enhanced mice survival and was significantly more effective at expanding numbers of CAR-T cells and limiting numbers of tumour cells than treatment with JCAR017 alone.

Studies on the interactions between the immunomodulatory drugs CC-122 and lenalidomide and JCAR017 seem to show strong donor-dependent effects in terms of immune parameters variability (e.g., cytokine production like IFN-γ, IL-2, and TNF-α, or surface marker expression).

In the experiment regarding the IDO1-specific inhibitor epacadostat, IDO1 expression in a tumour cell line was reported to be driven by JCAR017 via IFNγ secretion, resulting in tryptophan depletion, and in turn abrogation of CAR T-cell proliferation that could be restored by the addition of epacadostat.

2.5.2. Pharmacokinetics

Pharmacokinetic studies

Because of JCAR017 product typology, conventional non-clinical pharmacokinetic studies were not conducted, which is appropriate. Nevertheless, the in vivo persistence of JCAR017 cells was investigated in the report RPT-0433, and PK data were discussed in section of primary pharmacodynamics in vivo studies.

Absorption, metabolism, excretion

JCAR017 is an autologous cell-based product administered by intravenous infusion. As such, absorption, metabolism, and excretion studies were not performed.

Pharmacokinetic drug interactions

The lack of pharmacokinetic drug interactions studies is justified, given the autologous human cell therapy nature of JCAR017 and the lack of suitable nonclinical models.

2.5.3. Toxicology

JCAR017 T product is an autologous T-cell based treatment characterised by the lack of species cross-reactivity. In this light, traditional toxicity, including single and repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance studies were deemed of negligible utility and thus were not conducted.

2.5.3.1. Genotoxicity

Genotoxicity of JCAR017 product was assessed by Genomic mapping of lentiviral integration sites in JCAR017 cryopreserved drug product. The results demonstrated that JCAR017 construct did not change the integration patter, which resulted similar to that of wildtype HIV-1, according to literature data.

2.5.3.2. Carcinogenicity

Consistent with regulatory guidance under "Nonclinical Evaluation for Anticancer Pharmaceuticals" (ICH S9, 2009) carcinogenicity studies were not conducted. However, to determine carcinogenicity-linked parameters, a non-conventional in vitro study (8398350) was performed to assess IL-2 independent CAR017 T cell proliferation by evaluation of cell counts and CAR T cell characterisation via flow cytometry.

Taken together, the applicant provided data supporting the absence of a carcinogenicity potential of JCAR017 T cells, since most samples in the absence of IL-2, after 60 days of culture, resulted below the LLOQ for cell concentration. However, the characteristics of the JCAR017 cells assessed by immunophenotyping (purity, proliferation, and identity) was incomplete, thus it is not possible to conclude that purity and identity of JCAR017 T cells was comparable at Day 1 and Day 61.

2.5.4. Ecotoxicity/environmental risk assessment

Human cells are not able to proliferate in the environment and the applicant has sufficiently substantiated that no shedding is expected from patients. The risk for non-target people to come into contact with the product is negligible as assured by sufficient risk minimisation measures, i.e., administration in qualified centres, appropriate product disposal, instructions on handling (including use of individual personal protective equipment by HCPs), recommendations regarding donation of cells/tissues/blood/organs from treated patients, chain of identity and custody in place. Furthermore, the applicant has demonstrated

that the risk of RCL generation post-administration is negligible and that presence of residual transduction competent LVV in JCAR017 is unlikely.

Considering the overall applicant's discussion, it can be agreed that the environmental risk associated with Breyanzy can be considered negligible.

2.5.5. Discussion on the non-clinical aspects

Due to the intrinsic specie-specific characteristics of cellular immunotherapy products, full non-clinical studies have not been possible. In particular, suitable animal models are not available for accurately assessing the non-clinical characteristics of a human cell-based product such as JCAR017. Therefore, the non-clinical studies were conducted to demonstrate the proof of principle of the therapy, and to identify the principal effects by in vitro assays and in vivo immunocompromised rodent models employing human tumour xenografts.

The in vitro studies included in the dossier provide an appropriate characterisation of JCAR017, in terms of affinity and specificity of the FMC63 scFv binding domain to CD19, the cytotoxic T cell killing of CD19 positive target cells, cytokine production and JCAR017 cell proliferation.

The results support that JCAR017 is specific for human CD-19 binding and lacks species cross-reactivity, in particular towards mouse and non-human primate. A bioinformatics analysis confirmed the rationale to choose as target for JCAR017 CD19, expressed mainly on normal and malignant B-cells. Upon human CD19-engagement, JCAR017 T cells were reported to undergo proliferation, activation, cytokine production (IFN-γ, IL-2 and TNF-α) and acquisition of killing capability of target cells.

The lack of conventional in vivo studies and the use of immune-deficient Raji Burkitt's lymphoma-bearing NOD/SCID IL-2Rγnull mice model are justified and appropriate to investigate autologous cell-based products. JCAR017 (precommercial [v3.0] and proposed commercial process [v4.0]) were assayed for antitumour activity, evaluated as tumour growth inhibition and mice survival enhancement, and for in vivo expansion. The reported data demonstrated that the potency of JCAR017 was dependent on dose and donor source but differences in antitumour effects were observed between JCAR017 v3.0 e v4.0 manufactured from the same donor. Similarly, CD4+cell component and CD8+ cell component showed variability for in vivo expansion in a donor- dose- and manufacturing process-dependent manner. While variance from donor to donor is expected, some donor variance between JCAR017 precommercial (v3.0) and commercial processes (v4.0) is reported in terms of mice survival and circulating cell numbers.

JCAR017 lots utilised in Report RPT-001114 and Report RPT-001115 were manufactured using Process v4.0, the proposed commercial process. NC data in Report RPT-001115 do not provide knowledge on how each T cell subset (CD4+ cell component vs CD8+ cell component) was impacted by the combination of both (1:1) when an increased viable cell count was observed upon JCAR017 stimulation. Moreover, since only the 1:1 ratio was tested throughout the non-clinical development, NC data cannot provide support for other ratios observed in the clinic.

In vivo studies were also undertaken to demonstrate the cetuximab capability to deplete JCAR017 cells. All these results support the cetuximab capability to deplete JCAR017 cells even if it should be considered that the cetuximab activity may be under-estimated in the Raji xenograft model lacking NK cells. This feature does not allow CAR-T antibody depletion via ADCC. Also, although the analysis of cetuximab PK in the mouse serum showed that cetuximab dose may be considered in line with cetuximab clinical levels observed at the steady state, mouse approaching the steady state (i.e., mouse PK data immediately prior to the final cetuximab dose, when cell ablation was performed)- displayed very high levels of cetuximab with respect to human steady state levels.

In order to detect JCAR017 cells within the in vivo experiments, the set-up, the validation and the qualification of a flow cytometry assay were carried out. The assays resulted appropriately performed and permitted the identification of JCAR017 cells as CD3+EGFRt+, CD3+EGFRt+ID+ or CD3+ID+ cells, even though the methodology is not complete in all parts. An additional study to evaluate antibody titrations, included in RPT-002100, supports that the used antibody volume did not affect the specificity of the flow cytometry panel and did not generate non-specific binding or fluorescent spillover as well as demonstrate that the FM2 control was suitable and comparable to individual FMO for anti-EGFR PE and anti-ID AF647 antibodies.

Studies related to pharmacodynamic interactions of JCAR017 with standard-of-care therapeutics, including programmed cell death protein-1 ligand antibody (durvalumab), immunomodulatory drugs (CC-122 [investigational drug] and lenalidomide [Revlimid]) and Bruton tyrosine kinase inhibitors (ibrutinib and acalabrutinib), were performed in vivo and in vitro. The provided data support the absence of detrimental effects of durvalumab, ibrutinib and acalabrutinib on JCAR017 performance. Regarding the donor-dependent effects of CC-122 and lenalidomide on JCAR products, although cytokine directionality is preserved, the increase of IFN-γ, IL-2 and TNF-α production in some cases is very limited. In addition, although changes in surface marker expression may support potentiated effector differentiation, low CD28 expression is recommended to be deeper investigated. As well, the induction of IDO in malignant B-cells cultured with JCAR products is recommended to be better elucidated.

In genotoxicity studies, the applicant demonstrated that JCAR017 construct did not change the integration patter similar to that of wildtype HIV-1. The advantage to use SIN-LTR construct relied on a low potential to activate neighbouring genes, thus abolishing the risk of insertion-mediated genotoxicity and oncogenic insertional transformation. Overall, the collected data support a very low likelihood for T cell transformation induced by lentiviral insertional mutagenesis.

The carcinogenicity study, performed to assess IL-2 independent CAR017 T cell proliferation, excluded the prevalence of JCAR017 T cells with a malignant potential, supporting the absence of a carcinogenicity potential for JCAR017.

Given the absence of a relevant animal model for assessing the safety of JCAR017, no studies were conducted to assess potential effects of JCAR017 on fertility, embryonic development, prenatal and postnatal development, or juvenile development.

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

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

2.5.6. Conclusion on the non-clinical aspects

Overall, the studies provided in the non-clinical package are sufficient to demonstrate the key structural, phenotypic and functional characteristics of JCAR017.

Specifically, primary pharmacodynamic studies provide adequate evidences on the affinity and specificity of JCAR017 towards CD19-target cells and on their activation in terms of proliferation, cytokine production and lysis of target cells as well as on JCAR017 antitumour effects.

The secondary pharmacodynamic studies demonstrated the specie-specificity of JCAR017 and the efficacy of their cetuximab-mediated ablation.

From the toxicology point of view, the data sustained the lack of insertion-mediated genotoxicity and oncogenic insertional transformation as well as the absence of JCAR017 carcinogenicity potential.

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

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 1. Overview of clinical studies submitted in the MAA

Type of Study	Study Identifier; Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	No. of Subjects Enrolled[a]; Treated[b]; Planned[c] (n; n; N)	Subject Population	Study Status; Type of Report
Uncontrolled	017001; 5.3.5.2	• Safety • Antitumor activity (ORR)	Phase 1, open-label, single-arm, multicohort, multicenter, seamless design trial	JCAR017; DL1: 50×10^6 CAR+ Tcells DL2: 100×10^6 CAR+ Tcells DL3: 150×10^6 CAR+ Tcells; intravenous	1 or 2 doses; additional cycles or retreatment allowed as defined in the protocol	369 (344 DLBCL, 25 MCL); 286 (269 DLBCL, 17 MCL); ≥ 274	R/R CD19+ B-NHL; DLBCL: ≥ 2 prior therapies, Or MCL: ≥ 1 prior therapy	Ongoing: Full CSR (data cutoff 12 Aug 2019);
Uncontrolled	JCAR017-BCM-001; 5.3.5.2	Efficacy (ORR) • Cohort 1 (Europe) • Cohort 3 (Japan)	Phase 2, open-label, single-arm, multicohort, multicenter trial	JCAR017; 100×10^6 CAR+ Tcells; intravenous	Single dose	57 enrolled (total); Cohort 1: 27 treated; 34 planned Cohort 3: 10 treated; 10 planned	R/R CD19+ B-NHL; ≥ 2 prior therapies	Ongoing; CSR (data cutoff 13 Sep 2019);

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Clinical Pharmacology data on JCAR017 derived from studies 017001 and BCM-001. Study 017001 was conducted in US in adult patients with R/R B-cell non-Hodgkin lymphoma (NHL) and BCM-001 enrolled patients with aggressive B-cell NHL and was conducted in Europe and Japan to evaluate the feasibility of manufacturing JCAR017 drug product for delivery in Europe.

Cellular kinetic parameters were determined in peripheral blood using non-compartmental methods.

In study 017001, non-compartmental PK parameters such as Cmax (peak level of expansion), AUC0-28, and Tmax were calculated and summarised for subjects who had a PK measurement on Day 29 or later. PK values and persistence (qPCR and flow cytometry) were summarised by scheduled visit. Data were summarised by disease cohort (DLBCL, MCL) and dose regimen.

In study BCM-001, the PK study endpoints by PCR are Cmax, tmax, and AUC, including maximum expansion, expansion rate (defined as Cmax/Tmax) and duration of persistence of JCAR017 in peripheral blood. The AUC calculated is the Area under the curve (AUC) from JCAR017 infusion through 28 days after infusion (i.e., from Day 1 to Day 29; (AUC0-28). By flow cytometry, the parameters are Cmax, tmax, and AUC, and persistence of JCAR017 in peripheral blood (up to 2 years after JCAR017 infusion).

A population pharmacokinetics (PK) modelling and simulation exercise of systemic JCAR017 transgene levels based on data from Study 017001 was performed to support the development of JCAR017.

The objectives of this analysis were to develop a population pharmacokinetic (PK) model to characterise the kinetics of JCAR017 transgene to permit estimation of the systemic exposures to JCAR017; and to understand covariates that might influence JCAR017 kinetics in individual subjects.

The population PK analysis was performed using data from subjects who were treated with a single dose of JCAR017 in Study 017001, excluding data from subjects who were on the 2-dose schedules and data after retreatment or additional cycles in subjects who were on single-dose schedule and received retreatment or additional cycles of JCAR017.

The PK data of JCAR017 from Study 017001 were analysed using a nonlinear-mixed effects modeling approach as implemented in NONMEM, version 7.3.0.

The population PK model was developed in a stepwise manner, including base structural model selection, covariate analysis, and model evaluation with goodness-of-fit criteria, visual predictive checks, and the bootstrap re-sampling test for robustness.

The final form of the structural model for JCAR017 transgene includes the four, classical phases of cellular growth: lag, growth, stationary, and decline (Madigan, 1997) and the addiction of a lag phase to the initial cellular expansion phase improved model fit.

A total of 2.085 post-infusion PK observations were included in the Population PK Analysis Set. Of these, 221 (10.6%) were below the limit of detection (LOD) and were flagged as missing. This primarily occurred in the extreme tail of the post-treatment times.

Population-predicted (PRED) and individual-predicted (IPRE) JCAR017 transgene levels versus observed (DV) JCAR017 transgene levels for the structural model shows that there is an agreement for individual-predicted versus individual observed values.

The final popPK model included the following covariates: 1) Age on Cmax and Tdbl; 2) SPD per IRC prior to LDC on HLα; 3) Tocilizumab and/or corticosteroid use (for the treatment of CRS or iiNT) on Cmax and HLα; 4) Manufacturing process version (proposed commercial process versus original and pre-commercial processes) on Tlag.

No formal biopharmaceutics studies (including bioavailability, bioequivalence, or in vitro-in vivo correlation studies) and no clinical studies to evaluate the PK and tolerability in healthy subjects have been conducted because JCAR017 is a genetically modified autologous T-cell immunotherapy product being developed for subjects with large B-cell lymphoma.

Traditional PK analyses are not relevant for this CAR T cell product and overall, the proposed strategy to describe cellular kinetics based on expansion and persistence is acceptable.

Bioanalytical methods

Real-time quantitative polymerase chain reaction (qPCR) was employed either to quantify the presence of replication-competent virus (RCL) or the residual vector copy number (VCN) in CAR-T cells in patients at different times of treatment.

The expansion and persistence of the two CAR T-Cells (CD4+EGFRt+ and CD8+EGFRt+) and CD19 positive B Cells in patient samples was also evaluated by flow cytometry analysis. Whole blood was harvested with ETDA as anticoagulant and cells labelled with a panel of fluorophore-conjugated antibodies to determine the relative percentage and absolute counts of the populations of interest.

The immunogenicity of the extracellular domain of JCAR017 was evaluated analyzing the INF-gamma released from T cells, by an interferon (INF) gamma enzyme-linked immunospot assay, and the production of anti-therapeutic antibody (ATA). The formation of ATA against the extracellular domain of JCAR017 was evaluated in plasma and serum by an ECL-based immunoassay in studies 017001 and BCM-001. According to guidelines for the detection of ATA a multi-tiered approach for immunogenicity was considered which included a screening, a confirmatory assay, and a titre assay.

Cytokine levels were analysed in patients receiving JCAR017 to address the severity of cytokine release syndrome (CRS) with sandwich immunoassays.

Expansion and persistence (ADME)

Expansion

In study 17001, CAR T-cell expansion was observed across all dose levels tested (DL1S, DL2S, DL3S, with no clear relationship between administered dose and maximum observed concentration (Cmax) or AUC through 28 days after infusion (ie, from Day 1 to Day 29) (AUC0-28). After an additional cycle or retreatment Cmax and AUC0-28 appeared to be lower compared with those after the first dose (DL1D).

Table 2. Pharmacokinetics Summary by Assigned Dose Regimen, DLBCL Cohort (qPCR PK Analysis Set, study 17001)

Parameter Statistic	DL2S N = 176	DL1S N = 44	DL1D[a] N = 6	DL3S N = 41
n[b]	166	40	6	39
Transgene				
C_{max} (copies/µg)				
Median	25098.5	20958.2	8734.0	20005.2
Q1, Q3	9806.3, 79118.5	5634.7, 71868.6	4785.0, 17573.6	5278.2, 71017.7
t_{max} (day)				
Median	11.0	14.0	1.0	10.0
Q1, Q3	10.0, 14.0	12.0, 19.5	0.0, 3.0	7.0, 14.0
AUC_{0-28} (day*copies/µg)				
Median	229062.6	186994.0	106443.8	166162.7
Q1, Q3	96750.8, 689751.7	41717.3, 510264.9	53022.5, 125118.6	52416.1, 754593.3

AUC_{0-28} = area under the concentration-time curve through 28 days after infusion (ie, from Day 1 to Day 29); C_{max} = maximum observed concentration; DL1D = Dose Level 1, 2 dose; DL1S = Dose Level 1, Single Dose; DL2S = Dose Level 2, Single Dose; DL3S = Dose Level 3, Single Dose; DLBCL = diffuse large B-cell lymphoma; N = number of subjects in the population; n = number of subjects analyzed; PK = pharmacokinetic; Q = quartile; qPCR = qualitative polymerase chain reaction; t_{max} = time to maximum concentration

[a] PK parameters for DL1D were based on data after the second infusion.
[b] Number of subjects who had PK parameters. Noncompartmental PK parameters were calculated for subjects who had PK measurement on Day 29 or later.
Data as of the 12 Aug 2019 cutoff
Source: 017001 ClinPharm Report Table 14.2.10.2.1.1

In study BCM-001, the PK study endpoints obtained by PCR are Cmax, tmax, and AUC, including maximum expansion, expansion rate (defined as Cmax/Tmax) and duration of persistence of JCAR017 in peripheral blood. The cellular kinetic profile shows an initial rapid expansion (proliferation and multiplication) phase achieving maximal expansion (Cmax) around Day 10. Cmax and AUC0-28d were 66% and 33% higher respectively in cohort 3 (Japanese sites) relative to cohort 1, and a higher median Tmax of 12 days was observed in cohort 3.

Table 3. Summary of JCAR017 Transgene Pharmacokinetic Parameters by Cohort (qPCR PK Analysis Set)

Parameter Statistic	Cohort 1 N = 25	Cohort 3 N = 10	Total N = 35
n[a]	22	10	32
C_{max} (copies/µg)			
Median	28004.0	46561.5	29414.5
Q1, Q3	8817.0, 91948.0	6837.0, 71743.0	7827.0, 82206.0
t_{max} (day)			
Median	10.0	12.0	10.0
Q1, Q3	7.0, 16.0	9.0, 15.0	9.0, 15.5
AUC_{0-28} (day*copies/µg)			
Median	298106.0	398123.9	325344.6
Q1, Q3	87422.5, 745570.4	59182.7, 572674.8	76953.4, 640981.9

AUC_{0-28} = area under the concentration-time curve through 28 days after infusion (ie, from Day 1 to Day 29); C_{max} = maximum concentration; N = number of subjects in the population; n = number of subjects analyzed; PK = pharmacokinetic; Q1, Q3 = first and third quartiles; qPCR = quantitative polymerase chain reaction; t_{max} = time to maximum concentration.

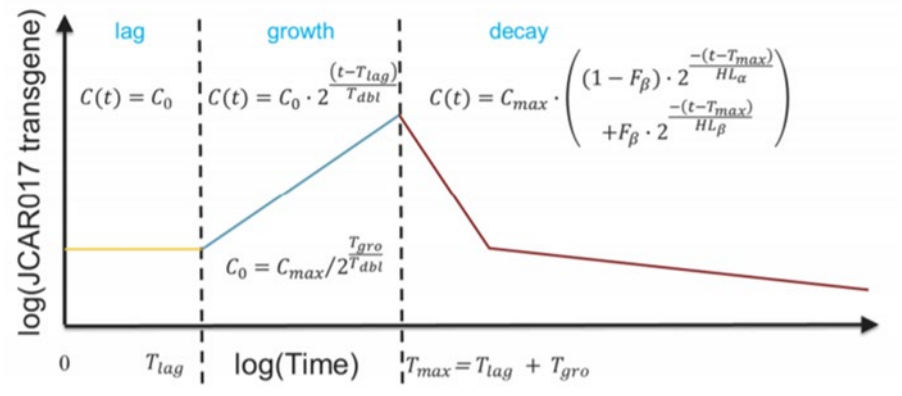
[a] Number of subjects who had PK parameters. Noncompartmental PK parameters were calculated for subjects who had PK measurement on Day 29 or later.

Note: The qPCR PK Analysis Set includes subjects in the JCAR017-treated Set who have both baseline and on-study PK measurements as assessed by qPCR.

Data cutoff date: 13 Sep 2019

Sources: Table 14.1.1, Table 14.2.7.2.1

Data on cellular kinetic are available in the popPK model and showed that JCAR017 transgene levels are stable for approximately 3 days after dose (Tlag 2.53 days (60.2% BSV), followed by an expansion lasting approximately 7 days where the JCAR017 transgene levels increase approximately 100-fold, followed by two phases of declining JCAR017 transgene levels with alpha-phase (HLα) and beta-phase (HLß) half-life estimates of 5.07 (95.5% BSV) and 564 days, respectively. The fraction of peak JCAR017 transgene levels appearing in the beta-phase (Fβ) was estimated 0.665%. There is no correlation between the dose administered and expansion of the cells and, moreover, a very high variability in the exposure parameters is shown.



C_0 = initial transgene levels; C_{max} = maximum transgene levels; F_β = fraction of C_{max} that appears in the β or terminal phase; HL_α = initial (α phase) decline half-life; HL_β = terminal (β phase) half-life; T_{dbl} = doubling time during growth phase; T_{gro} = growth phase duration; T_{lag} = lag phase duration; T_{max} = time to maximum transgene levels

Figure 2: JCAR017 Transgene Model

Persistence

Long-term persistence of CAR+ T cells in peripheral blood up to 2 years was noted. A threshold for expansion or persistence that correlates with response or response duration remains to be identified even if long-term persistence provide evidence for durable efficacy.

In Study 017001, the majority of subjects treated demonstrated long-term persistence of CAR+ T cells based on transgene detection in peripheral blood with 77% on Day 90 and with durable persistence of JCAR017 transgene for 45% of subjects up to 2 years after JCAR017 infusion (Day 730).

Table 4. Persistence of JCAR017 Transgene by Dose Level, DLBCL Cohort (qPCR PK Analysis Set, study 17001)

Visit	Persistence, x/n (%)				
	DL1S N = 44	DL2S N = 176	DL3S N = 41	DL1S + DL2S + DL3S N = 261	DL1D[a] N = 6
Day 29	38/39 (97)	158/161 (98)	40/40 (100)	236/240 (98)	5/6 (83)
Day 60	31/32 (97)	110/133 (83)	26/30 (87)	167/195 (86)	4/4 (100)
Day 90	20/25 (80)	85/111 (77)	21/27 (78)	126/163 (77)	3/3 (100)
Day 180	14/18 (78)	47/81 (58)	11/15 (73)	72/114 (63)	2/3 (67)
Day 270	11/16 (69)	36/65 (55)	5/7 (71)	52/88 (59)	2/3 (67)
Day 365	6/9 (67)	28/54 (52)	1/4 (25)	35/67 (52)	2/3 (67)
Day 545	8/13 (62)	15/28 (54)	0/0	23/41 (56)	2/3 (67)
Day 730	6/12 (50)	3/8 (38)	0/0	9/20 (45)	2/3 (67)

DLBCL = diffuse large B-cell lymphoma; DL1D = Dose Level 1, 2-dose regimen; DL1S = Dose level 1, single-dose regimen, DL2S = Dose Level 2, single-dose regimen, DL3S = Dose Level 3, single-dose regimen; N = number of subjects in the population; n = number of subjects for evaluation; PK = pharmacokinetics; qPCR = quantitative polymerase chain reaction; x = number of subjects persistent

Note: The qPCR PK Analysis Set includes subjects in the JCAR017-treated Analysis Set who have both baseline and on-study PK measurements as assessed by qPCR. The denominator at each time point is the number of evaluable subjects.

[a] Persistence for DL1D were based on data after the second infusion.

Data cutoff: 12 August 2019

Source: Table 14.2.10.5.3.1

In Study BCM-001, in cohort 1, transgene persistence was observed in 95% of subjects on Day 29 and 63% (5 of 8 subjects) on Day 90. In cohort 3, persistence of JCAR017 transgene was observed in 100% of subjects (10 of 10 subjects) on Day 29 and 100% (7 of 7 subjects) on Day 90. 33% on day 180. No important difference in persistence was observed across cohorts through Day 90.

Manufacturing process aspects

JCAR017 manufacturing process suffered changes during the course of the development as well as the manufacturing of the viral vector. The proposed commercial manufacturing process version 4 (v4), was derived from iterative improvements and optimisation of the precommercial processes, designated v2 and v3.

The Clinical Outcomes Across Manufacturing Process Versions (**CLOVER**) analysis was performed on the DLBCL qPCR PK Set (DL1S and DL2S), in order to evaluate the impact of manufacturing process changes on clinical and PK outcomes. Key safety, efficacy, and pharmacokinetic (PK) outcomes were compared between the precommercial processes (v2 and V3) and the proposed commercial process (v4). In addition, within the proposed commercial process, the clinical and PK outcomes data for subjects receiving v4 product manufactured with lentiviral vector from two different vector manufacturing sites (vector manufacturing processes v.1.0 and v.1.2 - see quality section above) were also compared.

The persistence of JCAR017 transgene was one of the objectives in the CLOVER report in order to assess

if differences occurred based on manufacturing process and vector manufacturing site. The persistence of JCAR017 transgene in the peripheral blood is defined as a transgene count greater than or equal to the limit of detection (LOD) of 5 copies per reaction. No definitive difference in persistence was observed between v2, v3 and v4 through Day 545. Persistence data with v4 were limited on Day 730 due to the shorter follow-up for v4 subjects. No definitive difference in persistence was observed between v4 vector manufacturing sites through Day 270. Comparisons of persistence data after Day 270 were limited due to the small number of subjects with available data for vector manufactured as v.1.2 as well as their shorter follow-up.

Non-conforming products

Of the 344 subjects in the DLBCL Cohort who underwent leukapheresis, 25 subjects received nonconforming product and were not included in the DLBCL Cohort JCAR017-Treated Analysis Set. Nine (9) of these subjects were assigned to DL1S and 16 were assigned to DL2S. A nonconforming product was defined as any product wherein a cell component did not meet a release specification limit. However a nonconforming product was allowed to be released under the following conditions: 1) only specified attributes that were out of specification would have been considered for an "exception release" recommendation and excluded failures due to any product safety attribute; 2) only a single out-of-specification attribute may have been considered for exception release, as long as it fell within the limits outlined within the JCAR017 PPDP; 3) agreement on the acceptable benefit-risk assessment. Ten (10) patients in Study 017001 received CD8+ cell component only, 3 received CD4+ cell component only, 12 received both cell components with one cell component not meeting one of the following specifications: potency (5), purity (1), sterility (1), viability (5). In cases where the subject was treated with only one drug product cell component (CD8+ or CD4+ CAR+ T cells), they were infused with half of the assigned dose, using the conforming cell component. In the Study BCM-001, 6 patients received both non-conforming cell components.

Dose-proportionality

The relationship between log-transformed cellular kinetic parameters Cmax, AUC0-28d, and total cell JCAR0017 dose are explored using scatter plot and linear regression in the DOVER report (study 017001). In the phase 1 study 017001, JCAR017 was administered at 4 dose levels: DL1S=50 x 10^6 CAR+T cells, single dose regimen (N=45), DL2S= 100 x 10^6 CAR+T cells, single dose regimen (N=177), DL3S= 150 x 10^6 CAR+T cells, single dose regimen (N=41) and DL1D= 50 x 10^6 CAR+T cells, 2 dose regimen (N=6). The second dose was administered 14 days after the first dose. No difference is shown in the exposure in terms of Cmax and AUC0-28 after administration of three different single dose levels.

Considerable inter-subject variability in PK parameters was observed in both studies (see section below for the target population). As reported in the popPK the BSV (between subjects variability) for the Cmax was 93%.

Time-dependency

According to the SmPC, the product is intended for administration of a single one time dose only.

In the report JCAR017-017001-ClinPharm, JCAR017 transgene PK parameters for the DLBCL Cohort after retreatment (N = 15) or an additional cycle (N = 7) are provided. In the 2-dose schedule (DL1D), the second dose did not provide a distinguishable increase in Cmax and AUC0-28 from the first dose. Cmax and AUC0-28 after an additional cycle or retreatment appeared to be lower compared with those after the first dose.

Target population

The proposed target population for Breyanzi treatment includes adult patients with relapsed or refractory large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell

lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after at least two prior therapies. PK data is available for DLBCL cohort only in Study 017001 and for adult subjects with aggressive B-cell NHL enrolled in BCM-001 study.

JCAR017 accounts for a combination pack including the CD4+ cell component and CD8+ cell component administered in sequence. The infusion foresees the administration of a 1:1 CD4+:CD8+ cell components ratio.

The volume of each cell component to administer is calculated by dividing the target dose by the viable cell concentration (in cell per ml) and the transduction frequency. The transduction frequency was reported in a different way within the indirect method (based on surface expression of EGFRt as a surrogate for CAR expression) and direct method (based on anti-idiotype antibody to directly measure surface expression of CAR). A transition to measurement of transduction frequency with direct CAR detection was initiated within the proposed commercial manufacturing process (v4).

The indirect method was used for all but 2 (261/263) subjects in study 017001. For the mentioned 2 subjects, the direct method was used. Since the indirect method overestimate the transduction frequency, this results in a variability in the calculation of the administered dose used in study 017001 compared to the dose calculated with the direct method. A dosing variance explanatory report (**DOVER**) was performed to assess the clinical impact of variability of administered dose and CD4+:CD8+ cell components ratio using analyses that characterise relationships between key clinical efficacy and safety outcomes and PK parameters from Study 017001 and both the administered dose and the CD4+:CD8+ cell components ratio of JCAR017.

The administered dose in 245/263 subjects in study 017001 was retrospectively calculated with the transduction frequency measured with the direct method. This results in a median administered dose of 50.1 × 10^6 CAR+ viable T cells (range: 43.9 × 10^6, 56.0 × 10^6) for DL1S, 91.1 × 10^6 CAR+ viable T cells (range: 45.3 × 10^6, 120.0 × 10^6) for DL2S, and 128.9 × 10^6 CAR+ viable T cells (range: 86.6 × 10^6, 156.0 × 10^6) for DL3S. Consequently, the ratio CD4+:CD8+ was also recalculated and ranged from 0.73 to 2.20, varying from the target of 1:1, although for 94% ranged between 0.73 and 1.3. In terms of PK parameters, the linear regression analyses showed a potential association between PK parameters and the CD4+:CD8+ ratio. However, a 0.2 increase in CD4+:CD8+ ratio would translate in a decrease of Cmax and AUC0-28 of just 23% and 22%.

Special populations

In Study 017001 the relationship between PK parameters (Cmax, AUC0-28 and Tmax) and baseline characteristics such as age, race, sex, body weight, BMI was evaluated in the DLBCL Cohort in the qPCR PK analysis set. Gender, race, sex, body weight and BMI did not demonstrate to have a significant relationship with the PK parameters.

Study BMC-001 enrolled European and Japanese subjects administered with 100x10^6 CAR-T cells dose; although data are merely descriptive, the Cohort 2 (Japanese) showed median values of Cmax and AUC0-28 higher than Cohort 1, but the Q1 and Q3 values are completely included in those of Cohort 1.

According to the results based on the latest data (cut-off date: 19Jun2020 for both studies), patients aged 65-74 were 77 in Study 017001 and 17 in Study BCM001; patients aged 75-84 were 24 in Study 017001 and 0 in BCM001; only one patient aged 85+ was enrolled in Study 017001. Patients <65 years old (N=145) had a 2.93-fold and 2.35-fold higher median Cmax and AUC0-28d, respectively, compared to patients ≥ 65 years old considering data from Study 017001. The SmPC was updated accordingly.

Other baseline characteristics were evaluated to assess a possible relationship with JCAR017 PK. Subjects with a high baseline tumour burden (measured by the sum of product of the perpendicular diameters [SPD] or high serum lactate dehydrogenase [LDH; ≥ 500 U/L] prior to the start of lymphodepletion)

showed increase in some or all PK parameters. Subjects with an SPD per IRC prior to LDC of ≥ 50 cm2 (N = 59) had a 2.46-fold and 2.88-fold higher median Cmax and AUC0-28, respectively, compared to subjects with an SPD per IRC prior to LDC of < 50 cm2 (N = 174). Subjects with an LDH prior to LDC of ≥ 500 U/L (N = 47) showed a longer Tmax (14 vs 11 days) compared with subjects with < 500 U/L (N = 198).

No dedicated studies were performed in impaired renal and hepatic subjects and it is acceptable due to the nature of the medicinal product.

No data are available in children since the intended indication is only in adult patients.

Drug-drug interactions

No in vitro and in vivo studies were performed with JCAR017 due to the nature of the product.

In Study 017001 the effect of tocilizumab and/or corticosteroid use for treatment of CRS or iiNT on PK parameters was evaluated.

Subjects treated with tocilizumab (N = 47) had a 4.15-fold and 4.06-fold higher median Cmax and AUC0-28, respectively, compared to subjects who did not receive tocilizumab (N = 198) (Cmax, 78,748.2 vs. 18,963.5 copies/µg, p < 0.0001; AUC0-28, 662,966.5 vs. 163,410.4 day*copies/µg, p < 0.0001). Median tmax of subjects with and without tocilizumab was 10.0 and 12.5 days, respectively (p = 0.2724).

Subjects who received corticosteroids (N = 46) had a 4.39-fold and 3.90-fold higher median Cmax and AUC0-28, respectively, compared with subjects who did not receive corticosteroids (N = 199) (Cmax, 85,563.5 vs. 19,481.9 copies/µg, p < 0.0001; AUC0-28, 647,537.1 vs. 166,162.7 day*copies/µg, p < 0.0001). Median tmax of subjects with and without corticosteroids was 11.0 and 12.0 days, respectively (p = 0.6665).

2.6.2.2. Pharmacodynamics

JCAR017 is a CD19-directed genetically modified autologous cellular immunotherapy consisting of purified CD8-positive and CD4-positive T cells.

CAR binding to CD19 expressed on the cell surface of tumour and normal B cells induces activation and proliferation of CAR T cells, release of pro-inflammatory cytokines, and cytotoxic killing of target cells.

Biomarkers

Pharmacodynamic variables including soluble biomarkers, C-reactive protein (CRP), ferritin, B-cell aplasia (defined as CD19+ B-cells < 3% of peripheral blood lymphocytes) and serum immunoglobulins (Ig) were summarised descriptively.

Soluble biomarkers

In the study 017001, peripheral blood plasma samples were collected at different points. Plasma samples were collected prior to lymphodepleting chemotherapy (LDC), immediately prior to JCAR017 infusion, and at various timepoints after JCAR017 infusion. Only the samples collected up to Day 29 were analysed in Clinical Pharmacology Report.

A total of 41 soluble biomarkers were measured as an exploratory endpoint. In Study 017001, soluble biomarkers in plasma, such as interleukin-6 (IL-6), IL-8, IL-10, macrophage inflammatory protein 1 alpha (MIP1alpha, tumour necrosis factor alpha (TNF alpha, and interferon gamma (IFN gamma, generally peaked within 14 days after JCAR017 infusion and returned to baseline (defined as the last

assessment prior to JCAR017 infusion) levels within 28 days after infusion. Peak levels of 11 soluble biomarkers were positively associated with Cmax and AUC0-28.

CRP and Ferritin

Serum CRP and ferritin are both acute phase reactants and the baseline values have been associated with increased risk of CRS and iiNT after JCAR017 administration (Siddiqi, 2017).

C-reactive protein and ferritin were measured at the clinical laboratory at each clinical study centre.

In the study 017001, serum CRP was elevated on Day 1 prior to infusion and decreased approximately 80% within the first 28 days after infusion. Serum ferritin was elevated at baseline and levels remained relatively unchanged during the first 28 days after JCAR017 infusion.

In Study BCM-001, in Cohort 1, serum CRP was elevated on Day 1 prior to infusion and decreased approximately 90% within the first 28 days after infusion. Similar observations were observed in Cohort 3 within the first 21 days after JCAR017 infusion. Serum ferritin was elevated at baseline and levels remained relatively unchanged during the first 28 days after JCAR017 infusion for Cohort 1 and Cohort 3 (CSR BCM-001, Section 11.6.3).

B-Cell Aplasia

B-cell aplasia was evident at baseline n 92% of the DLBCL Cohort with a single dose schedule in Study 017001, in 98% of subjects on Day 29, in 93% on Day 90, in 86% on Day 180, and in 73% on Day 365, without a relevant difference among the different dose levels in Study 017001.

In Cohort 1 of BCM-001, B-cell aplasia was evident in 93% at baseline, 100% on Day 29, in 100% on Day 90, in 86% on Day 180, and in 75% on Day 270.

No apparent difference in B-cell aplasia was observed across studies. B-cell aplasia data in Study BCM-001 were limited after Day 180 due to the median on-study follow-up time of 3.38 months.

In Study 017001, hypogammaglobulinaemia (ie, immunoglobulin G [IgG]<500mg/dL) was present in 49% of the DLBCL Cohort with a single-dose schedule in the JCAR017 at baseline, in 58% on Day 29, and in 61% on Day 365. No clear difference in hypogammaglobulinaemia was observed among the different dose levels in Study 017001. In Cohort 1 of Study BCM-001, the percentage of subjects with hypogammaglobulinaemia was 56% at baseline, 65% on Day 29 and 63% on Day 180.

Immunogenicity

Formation of ATA to the extracellular domain of JCAR017 was evaluated in plasma samples for Study 017001 using an electrochemiluminescence immunoassay. The same assay format was used for Study BCM-001 with serum as matrix. In both studies a multi-tiered approach was used to evaluate ATA that included a screening assay, a confirmatory assay, and a titre assay.

In Study 017001 prevalence and incidence of ATA was 11% and 14%, respectively.

There were no clear differences in the prevalence and incidence of ATA among the different dose levels.

Cmax and AUC0-28 were higher in subjects who had pre-existing ATA compared with subjects who did not have pre-existing ATA; similarly, Cmax was higher for subjects who had treatment-induced or treatment-boosted ATA compared with subjects who did not have treatment-induced or treatment-boosted ATA and the same trend although less pronounced was observed for AUC0-28. However, these PK parameters exhibited considerable inter-subject variability with a wide range of values and it should also consider that the number of subjects who had pre-existing ATA, treatment-induced or treatment-boosted ATA, is smaller compared to subjects who did not have pre-existing ATA or subjects who did not have treatment-induced or treatment-boosted ATA.

There were no clear differences in efficacy and safety outcomes between subjects with or without pre-existing ATA. Similarly, no clear differences in safety were observed between subjects with or without treatment-induced or treatment-boosted ATA.

It is of note that higher ORR and CR rate were observed in subjects who had treatment-induced or treatment-boosted ATA.

The presence of ATAs against JCAR017 is similar between the pre-commercial (v2 and v3) processes versus proposed commercial process (v4) and between vector manufacturing sites.

Updated immunogenicity results from Studies 017001 and BCM-001 based on longer follow-up data (data cut-off date: 19 Jun 2020), including the analyses to investigate the potential relationship between ATA status and efficacy, safety and PK in Study 017001 were submitted with Day120 LoQs responses and compared with the original results based on earlier cutoff date (data cut-off date: 12 Aug 2019 for Study 017001 and 13 Sep 2019 for Study BCM-001). Overall, treatment induced ATA (induced or boosted by the treatment) was low, and they were slightly higher in 017001 (15.6%) than in BCM-001 study (9.1%) at the DCO 19 Jun 2020.

Expansion parameters (Cmax and AUC0-28) based on qPCR were summarised by prevalence and incidence of ATA in the DLBCL Cohort of Study 017001. The results were consistent with those in the original analyses COD: 12 Aug 2019). Patients who had pre-existing ATA had a higher Cmax (prevalence of ATA: transgene Cmax 44867.0 copies/µg, incidence of ATA: transgene Cmax 31172.5 copies/µg) and AUC0-28 (prevalence of ATA: transgene AUC0-28 403257.0 day*copies/µg; incidence of ATA: transgene AUC0-28 214156.2 day*copies/µg) (as determined by qPCR or flow cytometry) in study 017001 (DLBCL cohort).

At the updated COD, there was no apparent relationship between the incidence of ATAs (treatment-induced or treatment-boosted) and the Cmax and AUC0-28.

For patients with treatment-induced antibodies, persistence data indicate a steeper decline after D28 in subjects who develop ATAs than in subjects who did not; similar results were observed using qPCR and flowcytometry.

Replication-competent virus

A replication-incompetent self-inactivating (SIN) lentiviral vector has been used (see quality and pre-clinical part). Replication-competent lentivirus (RCL) testing was performed using qPCR to detect viral vector envelope sequences on DNA obtained by a peripheral blood draw. Testing for RCL used an analytically-qualified qPCR-assay that was performed at a central laboratory. RCL in the blood was tested in 208 subjects for the DLBCL Cohort in the JCAR017-treated Analysis Set in the Study 017001, in 12 on Day 90 and 7 on Day 180 in Cohort 1 and in 5 on Day 90 and 3 on Day 180 in Cohort 3 of the Study BCM-001. No RCL has been detected in any of the tested samples.

False Positive HIV Tests

Treatment with lentiviral-derived CAR T cells has been reported to result in false positive human immunodeficiency virus (HIV) PCR nucleic acid amplification test results (Ariza-Heredia, 2017; Laetsch, 2018). Lentiviral vectors, such as those used for manufacturing JCAR017, contain portions of the HIV viral genome that are integrated into the genomes of cells transfected by these vectors. Human immunodeficiency virus nucleic acid amplification tests and HIV viral load testing can be falsely positive and may not reflect true HIV infection. Such false positive screening tests can most often be resolved using a fourth generation HIV screening assay that detects both HIV-1 antibodies and p24 antigens. SmPC contains statement that treatment with lentiviral-derived CAR T cells has the potential to interfere with HIV serology testing.

Relationship between plasma concentration and effect

Pharmacokinetic-Pharmacodynamic Relationships

Relationships between PK parameters (log10 transformed Cmax, log10 transformed AUC0-28, and untransformed tmax) and baseline or peak levels of soluble biomarkers, CRP, and ferritin were evaluated in subjects in the DLBCL Cohort on a single-dose schedule in the qPCR PK Analysis Set. After adjustment for multiplicity, the following relationships were observed at the $p < 0.05$ level: 1) AUC0-28 versus baseline transforming growth factor β3 (TGFβ3) and tumour necrosis factor (TNF)-α ; 2) tmax versus baseline IL-5, IL-7, IL-15, and ferritin; 3) Cmax versus peak levels of IFN-γ, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, TNFα, monocyte chemoattractant protein (MCP) 1, macrophage inflammatory protein (MIP) 1α, and MIP1β; 4) AUC0-28 versus peak levels of chemokine (C-C motif) ligand 17 (CCL17), IFNγ, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, TNFα, MCP1, MIP1α,MIP1β, vascular cell adhesion molecule 1 (VCAM1), and ferritin; 5) tmax versus peak levels of IL-7, vascular endothelial growth factor (VEGF)-D, and ferritin.

No relationships were observed with $p < 0.05$ between any baseline soluble biomarkers and Cmax.

Pharmacokinetic-Efficacy Relationships

All analyses were based on subjects for the DLBCL Cohort with a single-dose schedule that were in both the JCAR017-treated Efficacy Analysis Set and the qPCR PK Analysis Set. Efficacy variables examined for their relationship to JCAR017 PK parameters included BOR, DOR, and PFS per IRC.

As general comment, higher Cmax and AUC0-28 were associated with CR and/or PR and longer PFS. Responders (N=179) had 3.55-fold and 2.72-fold higher median Cmax ($p < 0.0001$) and AUC0-28 ($p < 0.0001$), respectively, than non-responders (N=53). Median tmax of responders and non-responders was 11.0 and 14.0 days, respectively. Complete responders (N=133) had 1.65-fold and 1.51-fold higher median Cmax (p=0.0175) and AUC0-28 (p=0.0707), respectively, than non-complete responders (N=99). Median tmax of complete responders and non-complete responders was 11.0 and 14.0 days, respectively. A unit of log10 increase in Cmax and AUC0-28 was associated with a 25% and 22% reduction in the hazard of relapse or death for DOR, respectively. A unit of log10 increase in Cmax and AUC0-28 was associated with a 41% and 38% reduction in the hazard of relapse or death for PFS, respectively.

Pharmacokinetic-Safety Relationships

Safety variables examined for their relationship to JCAR017 PK parameters included CRS and iiNT as well as tocilizumab and corticosteroids used to treat CRS or iiNT. All analyses were based on subjects in the DLBCL Cohort on a single-dose schedule that were in the qPCR PK Analysis Set. Higher Cmax and AUC0-28 were associated with higher incidence of any grade CRS, any grade iiNT, Grade ≥ 3 iiNT, Grade ≥3 infection and tocilizumab and/or corticosteroid usage for the treatment of CRS or iiNT. Subjects with any grade CRS (N=99) had 2.29-fold and 2.36-fold higher median Cmax ($p = 0.0003$) and AUC0-28 ($p<0.001$), respectively, than subjects without any grade CRS (N=146). The number of subjects with Grade≥3 CRS analysed in the qPCR PK Analysis Set was too small (N=5) to establish a relationship with PK. Subjects with any grade iiNT (N=72) had a 3.34-fold and 3.77-fold higher median Cmax ($p<0.001$) and AUC0-28 ($p<0.001$), respectively, compared with subjects who did not have any grade iiNT (N=173). Subjects with Grade ≥3 iiNT (N=20) had a 5.04-and 5.92-fold higher median Cmax (p=0.0002) and AUC0-28 ($p<0.001$), respectively, compared with subjects with Grade 0-2 iiNT (N=225). Subjects with Grade ≥3 infection (N=18 for subjects treated at DL2S) had a 3.05-fold and 2.72-fold higher median Cmax and AUC0-28, respectively, compared with subjects with Grade 0-2 infection (N=150 for subjects treated at DL2S). As similar trend was observed for subjects treated at DL3S. For subjects treated at

DL1S this trend was not observed, however sample size of subjects with grade ≥ 3 infection was considered too small (n = 3) to allow a definite conclusion. Subjects treated with tocilizumab (N=47) had a 4.15-fold and 4.06-fold higher median Cmax (p<0.001) and AUC0-28 (p<0.001), respectively compared with subjects who did not receive tocilizumab (N=198). Similarly, subjects who received corticosteroids (N=46) had a 4.39-fold and 3.90-fold higher median Cmax (p<0.001) and AUC0-28 (p<0.001), respectively, compared with subjects who did not receive corticosteroid (N=199).

Pharmacodynamic-Efficacy Relationships

Baseline and peak levels of 41 soluble biomarkers, CRP, and ferritin were evaluated for their possible relationship with BOR (responders vs. non-responders) in the DLBCL Cohort with a JCAR017 single-dose schedule of the JCAR017-treated Efficacy Analysis Set.

Pharmacodynamic-Safety Relationships

A total of 41 soluble biomarkers were evaluated for their possible relationship with CRS and iiNT in the DLBCL Cohort with a JCAR017 single-dose schedule of the JCAR017-treated. Baseline levels of ICAM1, IL-6, MIP1α, SAA1, and TNFα were associated with CRS. Baseline levels of ICAM1, IL-6, IL-10, MIP1α, SAA1, TNFα, and VCAM1 were associated with iiNT. Baseline levels of IL-6, IL-8, IL-10, and MIP1α were associated with Grade≥3 iiNT. Subjects with any grade CRS (N = 110) had a 3.23-fold and 1.83-fold higher median baseline CRP and ferritin levels, respectively, compared with subjects who did not have CRS (N = 152) (CRP, 53.9 vs. 16.7 mg/L, p = 0.0008; ferritin, 745.5 vs. 406.6 µg/L, p = 0.0267). Subjects with any grade iiNT (N = 79) had a 3.01-fold and 1.85-fold higher median baseline CRP and ferritin levels, respectively, compared with subjects who did not have iiNT (N = 183) (CRP, 59.6 vs. 19.8 mg/L, p=0.0068; ferritin, 782.0vs. 421.6 µg/L, p = 0.0584). Subjects with Grade ≥ 3 iiNT (N = 26) had a 2.91-fold and 3.32-fold higher median baseline CRP and ferritin levels, respectively, compared with subjects with Grade 0–2 iiNT (N = 236) (CRP, 68.4 vs. 23.5mg/L, p=0.0557; ferritin, 1521.5vs. 458.5 µg/L, p = 0.0128)

Mechanism of action

Breyanzi is a CD19-directed genetically modified autologous cellular immunotherapy administered as a defined composition to reduce variability in CD8+ and CD4+ T cell dose. The CAR is comprised of a murine FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. CD3 zeta signalling is critical for initiating T-cell activation and antitumour activity, while 4 - 1BB (CD137) signalling enhances the expansion and persistence of Breyanzi.

CAR binding to CD19 expressed on the cell surface of tumour and normal B cells induces activation and proliferation of CAR T cells, release of pro-inflammatory cytokines, and cytotoxic killing of target cells.

2.6.3. Discussion on clinical pharmacology

Bioanalytical methods

Real-time quantitative polymerase chain reaction (qPCR) was employed either to quantify the presence of replication-competent virus (RCL) or the residual vector copy number (VCN) in CAR-T cells in patients at different times of treatment. Overall, considering the heterogeneity of human samples, their limited availability for technical replicates and the outlier criteria applied to samples falling between QC1 an LLOQ, the method was adequately validated.

The ISR was only performed for study 017001 samples. Only 3% of the number of samples have been reanalysed (instead of 5% min) and the concentration obtained by reanalysis are within 35% of their mean for at least 67% of the repeats instead of 30% as required in the guideline on bioanalytical method validation. Although the results are not in accordance with the EMA Guideline, this issue will not be pursued considering that Breyanzi is not plasma protein bound, no back conversion from unknown metabolites is expected and no effect of sample inhomogeneity or concomitant medications is expected. Therefore, the method accuracy and precision can be confirmed without ISR.

The expansion and persistence of CAR T-Cells and CD19 positive B Cells in patient samples was also evaluated by flow cytometry analysis. This method poses particular validation challenges due to the complexity of cellular measures, the lack of reference materials, and the fact that data are not derived from a calibration curve. Although analytical parameters met the acceptance criteria, some clarifications were requested regarding the impact of haemolyzed, lipemic, or clotted samples and additionally, interference coming from protein-based immunotherapies targeting cell surface molecules on flow cytometry selectivity/specificity. No validation was performed in this regard, but visual inspection was used to identify and exclude compromised samples. Since no significant difference is observed between PK parameters obtained by qPCR and flow cytometry analyses, the risk of relevant interference is considered limited.

When the two methods for CAR-T measure are compared it is noted that CAR-T expansion measured with qPCR analysis and flow cytometry correlates only partially. Although peak values are reached at 12 days for qPCR and 11 days for flow cytometry the persistence of transgene/CAR-T population is measured consistently only with qPCR. Flow cytometry analysis in study BCM-001 shows that effective expansion of CAR-T+ population is reached only partially, and many patients display CAR-T low values (LOD of 0.1 cells/µL of blood with at least 25 events) at 11 days which drop after few days, as compared with published studies on CAR-T drug products (Demaret et al. Clinical cytometry 2020; Kalos et al. Sci Transl Med. 2011). Differences between the two methods rely on the small sample size and/or on different sensitivity for the qPCR and flow cytometry assays. Based on the fact that the trend of the two assays was similar and that pharmacokinetic analyses in both studies 017001 and BCM-001 were based principally on qPCR for transgene expression, which is more reliable, while the flow cytometry assessments were used only as exploratory and supportive data, the data are considered validated.

An interferon (INF) gamma enzyme-linked immunospot assay was used for the detection of INF-gamma producing T-cells in response to the extracellular domain (ECD) of JCAR017 in order to test its immunogenicity (Report JCAR017-dmpk-2949). Some problems were evidenced regarding the linearity of the assay, nevertheless the evidenced lack of linearity is not considered limiting according to the following considerations: data provided show that patient samples exhibit very low or undetectable levels of cytokine release from a single cell; cellular immunogenicity analysis for this product is considered exploratory and not intended to support any interpretation of the clinical observations.

The formation of anti-therapeutic antibody (ATA) against the extracellular domain of JCAR017 was evaluated in plasma and serum by an ECL-based immunoassay in studies JCAR017 and BCM-001. The bioanalytical methods were found suitable for their intended use for most aspects. Further characterisation data for the positive controls used (JCAR017 anti-idiotype monoclonal antibody and affinity purified rabbit polyclonal anti-JCAR017 ECD antibody) were provided and clarified that different method for the characterisation of the affinities of the positive controls have been used due to the nature of the positive control (polyclonal Ab vs. monoclonal Ab). A dissociation constant (Kd) was determined for JCAR017 anti-ID monoclonal antibody (0.327 nM), whereas, given that the rabbit polyclonal anti-JCAR017 positive control contains multiple clones with varying specificities, an EC50 is considered more appropriate. The EC50 value (0.37 nM) is an average of the different clones that are present in the polyclonal preparation.

It has been clarified that the median of the NC replicates (n=3) was used to calculate the PSCP to reduce the need for formal outlier evaluation.

Long-term stability data for the positive control spiked at HPC and LPC have been provided. The vast majority of the study samples from studies 017001 and BCM-001 were covered by the provided data. It is agreed that long-term frozen storage stability evaluation of the surrogate PC is unnecessary.

The applicant has further discussed the reliability of the cut points used for study sample analysis in the study JCAR017-BCM-001 and the false positive error rate is inside the recommended 2-11% range.

The method for cytokines measurement meets the criteria for precision, accuracy, dynamic range, sensitivity, matrix effect, specificity and stability.

Pharmacokinetics

Following infusion, JCAR017 exhibited an initial expansion followed by a bi-exponential decline which is common for the different CAR T cells products currently available. The bi-phasic decay was identified by means of the transgene model, decay which can be missed with a non-compartmental approach using a short interval data (e.g. 28 days). It was observed that the AUC0-90 is only slightly higher than median AUC0-28 in Studies 017001 and BCM-001 (ration AUC0-90/AUC0-28= 1.24 and 1.14, respectively) and that further increases in AUC was not observed from AUC0-90 to AUC0-180 (ratio AUC0-180/AUC0-90 = 1.04 in Study 017001 and 1.02 in Study BCM001), and from AUC0-180 to AUC0-270 (ratio AUC0-270/AUC0-180 = 1.01 in Study 017001 and 1.02 in Study BCM001). It confirms that the proposed exposure period (Days 1 – 29) captured sufficiently the cell expansion phase and adequately reflected the overall exposure.

Only 3% (7/247) of subjects in Study 017001 and 2% (1/44) of subjects in Study BCM-001 had tmax longer than 28 days. Of these 7 subjects in Study 017001, 4 subjects had tmax of 29 days and one subject had tmax of 30 days. Thus, most subjects in both studies had tmax within the first month. The potential of a second peak of expansion after day 29 can be excluded based on the data available. The relationship between Cmax and efficacy or safety endpoints was evaluated in Study 017001 and the results included Cmax occurring after Day 29 and took them into consideration.

Population PK analysis

The cellular kinetics model report is only explorative and considered of low regulatory impact. The objectives were to characterise the kinetics of JCAR017 transgene to permit estimation of the systemic exposures to JCAR017 and to understand covariates that might influence JCAR017 kinetics in individual subjects.

Population-predicted (PRED) and individual-predicted (IPRE) JCAR017 transgene levels versus observed (DV) JCAR017 transgene levels for the structural model shows that there is an agreement for individual-predicted versus individual observed values. However, it is noted that this is not completely true for population predicted versus individual observed values. This suggest that the model predictions are in agreement with those that it is observed in a single individual, but it could not be able to give a good prediction on the overall population. This can be due to the high variability in cell expansion between individuals.

In the final model the population-predicted (PRED) and individual-predicted (IPRE) JCAR017 transgene levels versus observed (DV) JCAR017 transgene levels and conditional weighted residuals (CWRES) versus time after dose and population-predicted (PRED) showed a better agreement between the model predictions and observations respect to the basal model and this is likely due to the introduction of covariates into the model that partially contain the high inter-subject variability.

The final popPK model included several covariates as described above

The modelling is adequately described and the proposed application are mostly related to exclusion of significant covariate effects on relevant PK parameters. For descriptive purposes, the steps described for model building and evaluation are considered overall State of the art and consistent with the requirements in the EMA guideline.

The Visual Predictive Check indicate that the model adequately describes the clinical data, with only a tendence to slightly under predict the higher concentration of JCAR017 transgene at later time point after infusion. The effect of covariates is overall well contained within the residual between-subject variability.

Manufacturing process aspects

From a PK point of view, data from v2 and v3 process were compared to v4 data and, although v4 seems to show lower exposure in terms of Cmax and AUC0-28, the exposure ranges are largely overlapped and a large CV is observed. Further comparison of data from v3 process (without data from v2) to v4 data was conducted, supporting similar PK expansion and persistence parameters with overlapping IQR and ranges. Regarding the exposure reached in v4 process, with both vector manufacturing process v1.0 and v1.2,Cmax and AUC0-28 for v1.2are lower than with v1.0, but also in this case the variability is high, the number of subjects treated with v1.2were low and no conclusion can be drawn on the actual impact of the vector manufacturing process on JCAR017 exposure. In study BCM-001, lower Cmax an AUC0-28 was also observed with the commercial vector subgroup (N=7, Cmax 17201 copies/µg, median Tmax 14 days and median AUC0-28 108043 day*copies/µg) compared to the v1.2vector subgroup (N=29, Cmax 29275 copies/µg, Tmax 19 days and AUC0-28 265403 day*copies/µg), but also in this case IQRs were overlapping and the sample sizes were very small, not allowing to make a definite conclusion on differences in PK parameters for product manufactured using different vectors.

The available PK parameters with the commercial vector were also lower compared to the v1.0 vector (28817 copies/µg, 11 days and 244238 day*copies/µg).

Comparison between PK data from subjects receiving conforming product and subjects receiving the nonconforming product, showed that mean Cmax and AUC0-28 for subject treated with nonconforming product are lower, however the range of exposure in both categories are very large and overlapped. From a PK point of view, this data is not informative to point out a difference in exposure between subjects treated with conforming product and those treated with nonconforming product.

Dose-proportionality

Based on data available on 4 dose levels administered in Study 017001, no difference is shown in the exposure in terms of Cmax and AUC0-28 after administration of three different single dose levels. A high variability in Cmax and AUC0-28 is observed within each dose level. This high variability is linked to the capacity of JCAR017 to proliferate and no conclusion can be drawn on the dose-proportionality. Some subjects (N=6) were administered with a second dose after 14 days, without a second LDC, and the Cmax and AUC0-28 seems to be lower after the second dose, however due to low number of subjects and the high variability, it cannot be possible to clearly determine the effect of a second dose. Fifteen and seven subjects were retreated and had additional cycles; in this case subjects repeat the complete LDC. In these subjects JCAR017 median Cmax and AUC0-28 are lower compared to the single administration, however the low number of subject and the unknown burden of the disease prior the retreatment/additional cycle did not permit to draw conclusion on the effect of additional cycles.

Considerable inter-subject variability in PK parameters was observed in both studies. As reported in the popPK the BSV (between subjects variability) for the Cmax was 93%.

Target population

For patients with relapsed or refractory large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after at least two prior therapies, the proposed regimen is a single dose of Breyanzi contains a target of 100 x 10^6 CAR-positive viable T cells (consisting of CD8+ cell component and CD4+ cell component), suspended in one or more vials of each cell component. JCAR017 accounts for a combination pack including the CD4+ cell component and CD8+ cell component administered in sequence. The infusion foresees the administration of a 1:1 CD4+:CD8+ cell components ratio.

Based on DOVER data in study 017001 the recalculated by direct CAR detection ratio CD4+:CD8+ ranged from 0.73 to 2.20, varying from the target of 1:1. For 94% of patients the ratio ranged between 0.73 and 1.3 and for 89% between 0.8 and 1.2. In terms of PK parameters, the retrospective linear regression analyses showed a potential association between PK parameters and the CD4+:CD8+ ratio. A 0.2 increase in CD4+:CD8+ ratio would translate in a decrease of Cmax and AUC0-28 of 24% and 22%. Although the high variability was observed in PK, it should be noted that similar retrospective analyses also showed a potential relationship between higher CD4+:CD8+ cell components ratio and a shorter DOR and PFS (see section Clinical Efficacy). Therefore, a more precisely defined range for the ratio of CD4+:CD8+ cells composition is considered of added value to optimise efficacy outcomes, although it should be noted that a wider range than the 1:1 target range do not translate in a significant effect on PK parameters.

Special populations

The Cmax and AUC0-28 showed a decrease with increasing age, however, as per product characteristics, there is a high variability. This trend can be in part explained by the physiological decrease in immunological responses in elderly.

Interactions

Based on qPCR PK analysis set (N=245), the applicant analysed the effect of tocilizumab and/or corticosteroid administration on JCAR017 PK. The PK analysis did not distinguish between subjects receiving only tocilizumab from subjects receiving only corticosteroids, therefore the net effect of the two medicinal products on JCAR exposure is not clear. The submitted analysis suggests that the administration of tocilizumab as well as the administration of corticosteroids increase the exposure of JCAR in term of Cmax (4.15-fold for tocilizumab and 4.39 for corticosteroids) and AUC0-28 (4.06 with tocilizumab and 3.90 with corticosteroids). These results should be carefully considered since the showed effect is biased by other factors impacting on the JCAR exposure. First of all, as reported in PD section of this AR, subjects with any grade CRS (N=99) had 2.29 and 2.36-fold higher median Cmax and AUC0-28, respectively than subjects without any grade CRS (N=146).

Moreover, also the tumour burden showed a significant effect on PK parameters. A higher burden of the disease at baseline increases the risk of CRS and consequently the possibility to be administered with tocilizumab and/or corticosteroids. Therefore, the higher exposure seen in subjects treated with tocilizumab/corticosteroids is also influenced by other concomitants factors also having impact on JCAR PK parameters. A sound conclusion cannot be drawn on the actual effect of tocilizumab on JCAR017 PK and therefore no specific recommendations can be given in the SmPC section 5.2.

Pharmacodynamic

B-cell aplasia

B-cell aplasia (ie, CD19+ B-cells <3% of peripheral blood lymphocytes), an on-target effect of anti-CD19 CAR T-cell therapies, may be seen as CAR T cells persist long term, functioning as a surrogate marker of CAR T-cell persistence and activity.

Immunogenicity

Due to the small number of subjects who had pre-existing ATA, treatment-induced or treatment-boosted ATA, it is not possible to consider the relationship between ATA status and efficacy, safety as conclusive.

Overall, treatment induced ATA (induced or boosted by the treatment) was low, and they were slightly higher in 017001 (15.6%) than in BCM-001 study (9.1%) at the DCO 19 Jun 2020.

It is difficult to interpret how ATAs (regardless of knowledge on neutralizing capacity) would impact clinical outcomes.

The cytokine profile (study 017001) over time indicates that there is a trend toward higher cytokine levels (IFN-γ) in patient without treatment-induced ATA or treatment-boosted ATA during treatment than patients who did not. The relevance of this data for PK/efficacy/safety outcomes is difficult to predict and overall relationship between cytokines change and outcomes are inconclusive.

In the data provided with a data cut off of 19 June 2020, a pattern of lower ORR (55.6% vs 74.9%) and CR rate (44.4% vs 53.4%), but longer DOR was observed in subjects who had pre-existing ATA compared with subjects who did not have pre-existing ATA.

A different pattern of higher ORR (95.0 % vs 69.9%) and CR rate (82.4% vs 47.6%) and longer DOR were observed in subjects who had treatment-induced or treatment-boosted ATA compared with subjects who did not have treatment-induced or treatment-boosted ATA.

No apparent relationship between pre-existent ATA or treatment-induced/boosted ATAs and AESI was observed, but the data are currently very limited.

Regarding the discussion on neutralizing potential of ATAs, given the absence of evidence that the emergence of ATA impacts exposure, safety, or efficacy, the late emergence of the ATA relative to the tmax, the lack of an endogenous counterpart, and the use as a single dose strategy, a NAb assay has not been implemented to date for liso-cel. However, as the relevance of the long-term kinetics of liso-cel persistence becomes clear, the applicant will explore the optimal assay format for NAb assays in future trials.

In regard to the cellular immune responses to JCAR017, an interim bioanalytical Sample Analysis Report for interferon gamma ELISPOT (Cellular Immunogenicity) for JCAR017-BCM-001 study was provided. No further validation data have been provided for the interferon (IFN) gamma enzyme-linked immunosorbent (ELISPOT) assay that detects T cells that are specific to the extracellular domain of liso-cel while a number of validation issue have been reported in the D80 AR (e.g. a high intra-assay variability for the D1637+JACR017-CAR-ECD peptides positive control). Given that the cellular immunogenicity was an exploratory endpoint of study BCM-001, the issue is not pursued.

In conclusion, there are no sufficiently informative data either on cellular immunogenicity or on potential neutralizing activity of treatment-emergent or treatment-boosted ATAs, or long-term impact of immunogenicity on clinical endpoints. The overall number of patients with detected ATAs is low precluding meaningful analysis and conclusions cannot be drawn. Therefore, an uncertainty still remains regarding the impact of cellular and humoral immunogenicity (ATA) on the PK, efficacy and safety following initial treatment when for pre-existent ATA or treatment-induced/boosted ATAs, and in case of re-treatment.

The studies in which immunogenicity will be further characterised are listed in Part IV (Plans for post-authorisation efficacy studies) of the RMP, and include the ongoing studies 017001, JCAR017-BCM-001 and JCAR017-BCM-003.

The applicant commits to explore the feasibility of developing a neutralizing antibody (NAb) assay and if successful to validate this assay. Up to then all ATA confirmed positive samples will be banked and will be Nab characterised in case a validated Nab assay has been established. Results of ATA status and Nab characterisation, as well as corresponding bioanalytical reports will then be included in/attached to the (amended) final clinical study reports of the corresponding studies.

Depending on the outcome, the applicant is expected to additionally provide an updated integrated analysis of the immunogenicity of Breyanzi (impact on PK, efficacy and safety) within one of the post-approval procedures (e.g., with final clinical study reports, when submitted). This should include the validation report of the developed neutralizing antibody assay and the final bioanalytical reports including all the results of immunogenicity samples (in all immunogenicity assays).

Pharmacokinetic-Safety Relationships

It is not known whether activity of CAR-T cells could be affected by immunosuppressive mechanisms due to corticosteroids use or due to inhibition of IL-6 signalling as one the main inflammatory cytokines. Preclinical studies do not suggest that IL-6 is directly involved in CAR-T lysis of tumour cells (Singh et al, 2017). The impact of corticosteroids on early expansion is not excluded, as well as on persistence or durability of immune responses (Brudno et al, 2019). The applicant further discussed potential effect of tocilizumab and/or corticosteroids on JCAR017 activity by comparing response rates between subjects who received tocilizumab and/or corticosteroid for CRS or iiNT and those who did not (data cut-off date of 19 Jun 2020). Although response rates are slightly lower in the subset of patients who have received tocilizumab and/or corticosteroid for CRS or iiNT, 95% CIs were overlapping, indicating no significant difference. With regard to time-to-event endpoints, median DOR, PFS and OS for the subgroup of patients treated with tocilizumab and/or corticosteroids (8.0, 3.0 and 10.0 months, respectively) were shorter compared to the subgroup of patient which did not received tocilizumab and/or corticosteroids (20.5, 9.0 and 45.2 months, respectively). While for DOR and OS, the 95% CIs for the median were overlapping, this was not the case for the 95% CIs for median PFS. However, K-M curves and 95%CIs for probability of continued DOR and PFS at 6 months up to 24 months and for probability of OS at 18 months up to 24 months were overlapping and showed similar plateaus indicating long-term benefit for a proportion of the subjects. Further, subjects with higher tumour burden at baseline are more likely to develop CRS and iiNT and thus are more likely to be treated with tocilizumab and/or corticosteroids. Such potential for selection was confirmed by comparing the baseline patient and disease characteristics between both groups. With no clinically meaningful differences in prior treatment history and baseline patient characteristics, there were clinically meaningful (≥ 20%) differences in baseline disease characteristics, with an increased frequency of subjects with pre-LDC LDH ≥ 500 U/L, pre-LDC SPD ≥ 50 cm^2, and baseline CRP ≥ 20 mg/L in the treated group compared with the not-treated group, indicating patients in the treated group had an increased tumour burden and inflammatory state. An additional post-hoc analysis comparing efficacy outcomes of subjects with elevated markers of tumour burden (pre-LDC SPD ≥50 cm^2, pre-LDC LDH ≥500 U/L) and inflammation (baseline CRP ≥ 20 mg/L) compared to those without, regardless of tocilizumab and/or corticosteroid use showed a similar trend to that seen in the treated versus not-treated subgroups, with numerically shorter median DOR and OS, indicating that the potential differences observed between tocilizumab and/or corticosteroids treated patients is likely due to selection bias and cannot be attributed to treatment with tocilizumab and/or corticosteroids alone.

Pharmacokinetic-Pharmacodynamic Relationships

No differences were observed in peak or baseline levels of cytokines, known to be potentially associated with expansion or safety as described in literature (including median peak levels of INF-γ, IL-6, MIP-1β, IL-15 and TNF-α and baseline levels of IL-6 and TNF-α) between patients with C_{max} or AUC_{0-28} above or below median.

Pharmacodynamic-Efficacy Relationships

No soluble biomarkers were associated with BOR. Baseline and peak levels of CRP and ferritin were also not associated with BOR.

Pharmacodynamic-Safety Relationships

In all cases, the number of subjects with Grade ≥ 3 CRS analysed in the JCAR017-treated Analysis Set was too small (N=6) to draw clear conclusion of a relationship between PD biomarkers and Safety signals.

2.6.4. Conclusions on clinical pharmacology

Considering the cellular nature of JCAR017 and the expected high variability, pharmacology was well characterised. The immunogenicity will be further characterised in the ongoing studies 017001, JCAR017-BCM-001 and JCAR017-BCM-003 that are listed in Part IV (Plans for post-authorisation efficacy studies) of the RMP. The applicant commits to explore the feasibility of developing a neutralizing antibody (NAb) assay, to validate this assay and to provide the results within the updated clinical study reports (including an updated integrated analysis of the immunogenicity).

The CAT considers the following measures (recommendation) necessary to address the issues related to pharmacology:

The applicant is recommended to investigate the feasibility of developing a neutralizing anti-body (NAb) assay, to validate this assay and to provide the results within the updated clinical study reports (including an updated integrated analysis of the immunogenicity).

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

2.6.5. Clinical efficacy

Introduction

The applicant targeted an indication "*for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after at least two prior therapies*".

To support this marketing authorisation application (MAA) efficacy data from the DLBCL Cohort of Study 017001 (US) and Cohort 1 and 3 of Study JCAR017-BCM-001 (EU/Japan) have been submitted (see Table below).

Table 5. Study details

Study ID		No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Efficacy Endpoint
017001 DLBCL cohort		14 / US	Phase 1, multi-cohort, uncontrolled open-label study	DL1, DL2 and DL3	To evaluate safety and activity	Enrolled patients N=341 N=269 in the DLBCL treated set	Median FU 11.5 months	M/F 174/95 Median Age 63 years	r/r DLBCL after at least 2 lines of therapy and/or ASCT	ORR by IRC
JCAR017-		11 / EU	Phase 2,	DL2	To determine	Enrolled	Median FU	M/F	r/r DLBCL,	ORR by IRC

BCM-001 cohorts 1 and 3		(Austria, Belgium, Finland, France, Italy, Spain, Switzerland) and Japan	single-arm, multi-cohort, open-label study		efficacy	patients N=58 N=37 (27 in EU and 10 in Japan) in the JCAR017-treated set	4.9 months	24/13 Median age 58 years	HGBL and FL3b after at least 2 lines of therapy and/or ASCT	

To contextualise the results observed in uncontrolled trials 017001 and BCM-001 the applicant has also conducted a Systematic Literature Review (SLR), including randomised and non-randomised studies published between 01 Jan 2003 and 02 Dec 2019, and a global, non-interventional, retrospective, multi-centre, observational study (NDS-NHL-001; n=407) evaluating efficacy outcomes of unselected patients with R/R large B-cell lymphoma treated in real-world (RW) clinical oncology settings.

The efficacy and safety of JCAR017 in transplant-eligible patients with aggressive large B-cell lymphoma who have failed one prior line of systemic therapy is investigated in ongoing Phase 3 study JCAR017-BCM-003 (TRANSFORM). No data from study BCM-003 have been submitted in this application for MA.

2.6.5.1. Dose response study(ies)

Dosing recommendations were mainly based on results from Phase I Study 017001.

Dosing assumptions and dose groups in study 017001

The starting dose planned for Study 017001 (50×10^6 CAR+ T cells [DL-1]) was equivalent to 0.5×10^6 CAR+ T cells/kg for a 100-kg adult and 1×10^6 CAR+ T cells/kg for a 50-kg adult. Study 017001 allowed for dose escalation to 2 higher dose levels (100×10^6 CAR+ T cells [DL2] and 150×10^6 CAR+ T cells [DL3]) if safety and efficacy data from the lower doses were acceptable. Dose de-escalation to 25×10^6 CAR+ T cells was also available if the toxicity was unacceptable. Dosing started at DL1S, then proceeded to DL1D (2 doses of 50×10^6 CAR+ T cells given 14 days apart), DL2S (single dose of 100×10^6 CAR+ T cells), and DL3S (single dose of 150×10^6 CAR+ T cells).

Dose finding results

DL1S, DL1D, and DL2S met the safety threshold as per the modified continual reassessment method (mCRM) algorithm and were considered likely efficacious by the criteria defined in the protocol (i.e. p[CR >0.25] > 0.9). Of the 139 subjects in the DLBCL Treated Set who were evaluable for DLTs, DLTs were noted in 9 subjects: 6 subjects received treatment at DL1S, 2 subjects at DL2S, and 1 subject at DL3S. DLTs occurring in more than one subject were encephalopathy (N=4; three of which were Grade 3 and had resolved, and the fourth of which was Grade 4 and not resolved at the time of death due to disease progression) and thrombocytopenia (N=2; both Grade 4, both with outcomes of recovering/resolving). One Grade 5 DLT was noted (an event of diffuse alveolar damage).

There was no evidence of increased toxicity with DL2S compared to DL1S, the preliminary DOR observed with DL2S appeared to be longer and point estimates of CAR T-cell expansion appeared higher in DL2S.

A target single dose of 100×10^6 CAR+ T cells (DL2S) was then selected for the DLBCL Cohort dose confirmation (DC) group.

CD4+:CD8+ cell components ratio variability

The protocol-defined target CD4+:CD8+ cell components ratio was 1:1 for all dose levels, and no other CD4+:CD8+ cell components ratios were prospectively tested. The volumes needed to achieve target dose and ratio were calculated using the indirect CAR detection method for all but 2 subjects. However, based on the administered dose retrospectively calculated using the direct CAR detection method, that

actual ratio varied: the median CD4+:CD8+ cell components ratio was 0.99 (range: 0.81, 1.20) for DL1S, 1.01 (range: 0.73, 2.20) for DL2S, and 1.00 (range: 0.82, 1.60) for DL3S. The CD4+:CD8+ cell components ratio administered to approximately 94% of subjects in the DLBCL Cohort included in the JCAR017-treated Analysis Set was clustered within a range from 0.7 to 1.3.

Dose recommendations

Results of multivariable analysis

No clear effect of manufacturing process version, dose, or CD4+:CD8+ cell components ratio was observed on clinical response endpoints, except for a potential association between higher CD4+:CD8+ cell components ratio and shorter DOR (for a 0.2 increase in CD4+:CD8+ cell components ratio HR=1.266; 2-sided p-value=0.0155).

Results of univariate analyses

Efficacy analyses in the DLBCL Treated Analysis Set at any dose level (N=256) showed that the administered dose of CAR+ viable T cells over the range studied had no relationship with best objective response (BOR), DOR and PFS. Responses, including CRs, were seen in all assigned dose regimens tested, and no evidence of a relationship between assigned dose regimen and depth of response was observed.

With respect to safety, the logistic regression model showed a potential relationship between increased dose and a higher all-grade CRS rate. The OR for all-grade CRS in the logistic regression model was 1.01 (95%CI 1.00, 1.02; p=0.0705). The estimated probability of having all-grade CRS over administered doses from the logistic regression model was 0.33 (95%CI 0.24, 0.45), 0.44 (95%CI 0.38, 0.51) and 0.56 (95%CI 0.40, 0.71) at cell doses of 50 x 10^6, 100 x 10^6, and 150 x 10^6, respectively. The finding from the logistic regression model is similar to the CRS incidence summary by assigned dose levels where DL3S shows over 20% higher incidence of all-grade CRS relative to DL1S and DL2S (40% at DL1S, 37% at DL2S and 63% at DL3S); this difference was limited to low-grade events as no such difference was observed for Grade ≥3 CRS events. Results of the logistic regression analysis did not show a clear relationship between administered dose and all-grade Investigator-identified neurologic toxicity (iiNT, OR 1.01, 95%CI 0.99, 1.02; p=0.3085) or Grade ≥ 3 iiNT (OR 0.99, 95%CI 0.97, 1.00; p=0.1271). A potential relationship was also observed between increased dose and a higher Grade ≥3 infection rate. The odds ratio for having Grade ≥3 infection from the logistic regression model was 1.01 (95%CI 1.00, 1.03). The estimated probability of having Grade ≥3 infection over administered doses from the logistic regression model is 0.073 (95%CI 0.035, 0.147), 0.138 (95%CI 0.099, 0.188), and 0.244 (95%CI 0.116, 0.444) at administered cell doses of 50 x 10^6, 100 x 10^6, and 150 x 10^6, respectively. This finding is similar to the incidence of Grade ≥3 infection TEAEs by assigned dose levels where DL1S was 8.9%, DL2S was 11.3%, and DL3S was 22.0%.

Results of univariate CD4+:CD8+ ratio analyses

Linear regression analysis indicated a potential association between PK parameters and the CD4+:CD8+ cell components ratio, indicating that a 0.2 increase in the CD4+:CD8+ cell components ratio would decrease Cmax and AUC0-28 by 23% and 22%, respectively (see also the PK Section above). The 0.2 increment in CD4+:CD8+ cell components ratio was chosen because it was felt to reflect a meaningful increment given the range of ratios administered during the trial.

Logistic regression analysis was also performed to evaluate the relationship between CD4+:CD8+ cell components ratio and the probability of response. The odds ratio was 1.32 (95%CI 0.94, 2.01; p=0.1155), indicating no clear relationship between higher CD4+:CD8+ cell components ratio and probability of response.

The Cox proportional model showed that the DOR HR for a 0.2 increase in CD4+:CD8+ cell components ratio was 1.307 (95%CI 1.089, 1.569; p=0.0040), indicating a potential association between higher CD4+:CD8+ cell components ratio and shorter DOR. With respect to PFS, the HR for a 0.2 increase in CD4+:CD8+ cell components ratio was 1.173 (95%CI 1.001, 1.374; p=0.0486).

With respect to safety, logistic regression analysis was performed to evaluate the relationship between CD4+:CD8+ cell components ratio and the probability of CRS, iiNT. Results indicated that there was no clear relationship between CD4+:CD8+ cell components ratio and the incidence of all-grade CRS (OR: 1.10-, 95%CI 0.84, 1.45), all grade iiNT (OR: 1.24, 95%CI 0.93, 1.65), and grade ≥3 iiNT (OR: 1.29; 95%CI 0.87, 1.81).

Justification of Recommended Dose Range

A dose range of 44 to 120 × 10^6 CAR+ T cells is recommended in the SmPC to reflect the clinical experience at assigned DL1 and DL2.

In Study 017001, subjects were assigned to 3 discrete dose levels (DLs), yet within each DL the actual administered dose varied within a range (see Table below).

Table 6. Assigned Dose Level and Administered Dose in Studies 017001 and BCM-001

Study	Assigned Dose Level (CAR+ T Cells)	Administered Dose (range) (CAR+ T Cells)	Number of Liso-cel-treated Subjects
017001	Dose Level 1[a] (50×10^6)	$44 – 104^b \times 10^6$	51
	Dose Level 2 (100×10^6)	$45 – 120 \times 10^6$	178
	Dose Level 3 (150×10^6)	$87 – 156 \times 10^6$	41[c]
BCM-001 Cohort 1	Dose Level 2 (100×10^6)	$71 – 103 \times 10^6$	36

CAR+ = chimeric antigen receptor positive.
[a] Includes 6 subjects assigned to receive Dose Level 1, double dose (DL1D).
[b] One subject assigned to DL1D received a dose of 104×10^6 CAR+ T cells in error due to an incorrect manual transcription of the overall dose level value (as opposed to the target cell dose) by the Sponsor on the release dosage assignment form, which has since been automated.
[c] 7 subjects received a dose below and 34 received a dose above 120×10^6 CAR+ T cells.
Data cutoff date: 04 Jan 2021.
Sources: CSR BCM-001 Table 14.3.1.1.3 and D180 017001 Table 14.3.1.1.8.a

The efficacy and safety outcomes at the recommended dose range of 44 to 120 x 10^6 CAR+ T cells (i.e. at assigned DL1+DL2) were compared to efficacy and safety outcomes at the dose ranges that represent administered doses 20% above and below the target dose of assigned DL1 or DL2, the lower, mid, and upper boundaries of the recommended dose range, and the dose range of the total population assigned to DL1+DL2+DL3.

The upper and lower limits of the recommended dose range (44 to 120 × 10^6 CAR+ T cells) were selected based on the following reasons:

- Clinical efficacy and safety outcomes were consistent across the recommended dose range of 44 to 120 x 10^6 CAR+ T cells at assigned DL1+DL2 and are similar to the clinical outcomes for the dose range of the total population (44 to 156 x 10^6 CAR+ T cells).

- A numerically higher incidence of all-grade CRS, all-grade iiNT, and Grade ≥ 3 infection was observed at assigned DL3 (150 x 10^6 CAR+ T cells) when compared with lower assigned DLs, consistent with the results from the retrospective logistic regression modelling. Therefore, the recommended dose range excludes subjects assigned to the highest administered doses (DL3) in Study 017001.

Justification of Recommended CD4+:CD8+ cell components Ratio Range

The recommended CD4+:CD8+ cell components ratio for JCAR017 is 1:1; to reflect the clinical experience in study 017001 a 0.8 – 1.2 CD4+:CD8+ cell components range was included in the product specifications. The upper and lower limits of the CD4+:CD8+ ratio range are justified for the following reasons:

- Clinical efficacy and safety data for liso-cel at the recommended dose range 44 to 120 x 10^6 CAR+ T cells at assigned DL1+DL2 were consistent across the entire range of administered CD4+:CD8+ ratio range of 0.7 to 2.2.

- Retrospective analyses of key clinical efficacy and safety outcomes versus administered CD4+:CD8+ cell components ratio as a continuous variable demonstrated that there was no clear relationship between CD4+:CD8+ cell components ratio (range 0.7 to 2.2) and the majority of key clinical outcomes (BOR, incidence of CRS, and iiNT), yet associations could not be excluded between higher CD4+:CD8+ cell components ratio and shorter DOR and PFS. Information on CD4+:CD8+ cell components ratios <0.8 is limited.

Lymphodepleting chemotherapy (LDC)

Administration of JCAR017 was preceded by LDC with fludarabine (30 mg/m^2) plus cyclophosphamide (300 mg/m^2) (flu/cy) for 3 days. This regimen was selected to optimise cellular expansion, persistence, and antitumour activity of the CAR T cells, as well as to limit toxicity and retain antitumour activity.

2.6.5.2. Main study(ies)

The efficacy of JCAR017 was investigated in Phase 1 study 017001 and Phase 2 study JCAR017-BCM-001.

Study 017001

Study 017001 is an open-label, multicentre, multicohort, seamless design, Phase 1 study to determine the safety, antitumour activity, and PK of JCAR017 in adult subjects with R/R B-cell NHL. Study design is summarised in Figures below.

Figure 3: Study 017001 design

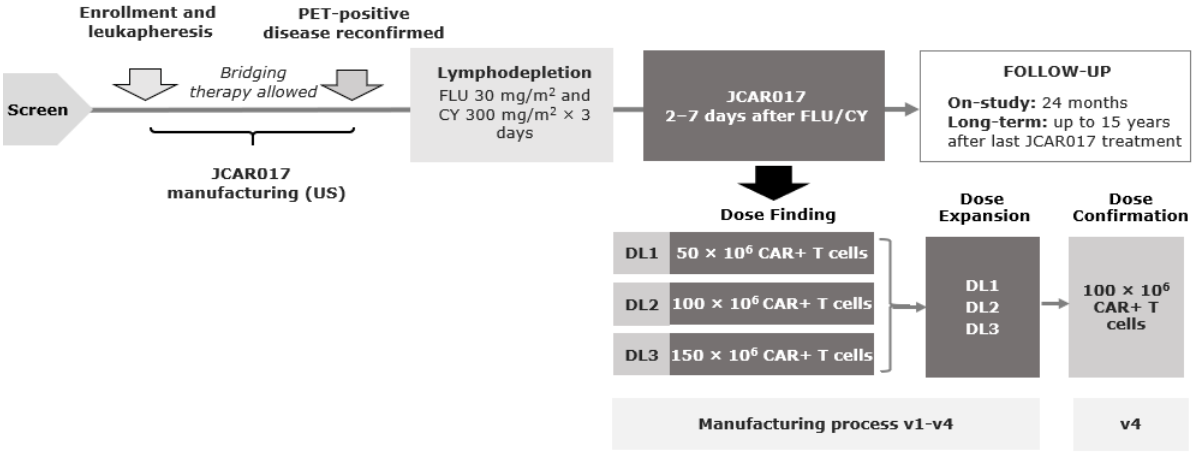
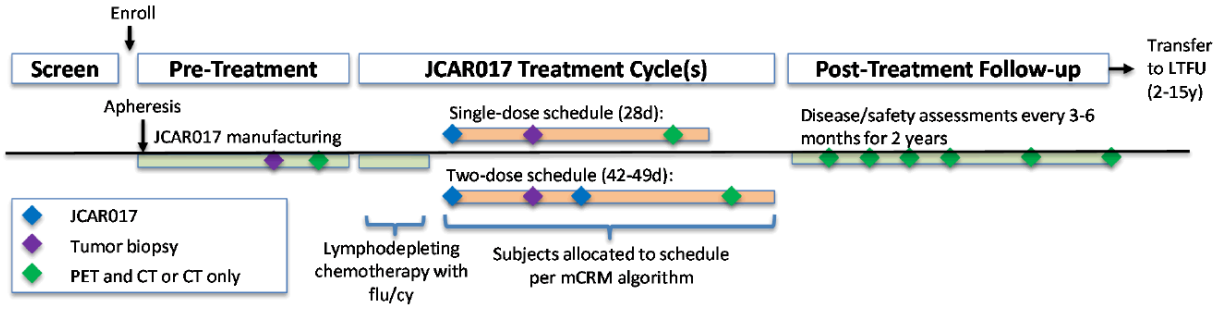


Figure 4: Study 017001 design (periods)



CT = computed tomography; d = days; flu/cy = fludarabine/cyclophosphamide; LTFU = long-term follow-up; mCRM = modified continual reassessment method; PET = positron emission tomography; y = years.

Subjects could be enrolled in one of the following 2 disease-specific cohorts: the diffuse large B-cell (DLBCL) and the mantle cell Lymphoma (MCL) Cohort. Data from the MCL Cohort are not part of this MAA.

The study design included dose finding (DF), dose expansion (DE), and dose confirmation (DC) groups.

Consistent with the principles of seamless oncology trial design (Prowell, 2016) for therapies with adequate preliminary evidence of a promising benefit-risk profile, a DC group for the DLBCL Cohort further assessed the safety and efficacy of JCAR017 at the recommended regimen.

In Study 017001, subjects were treated with JCAR017 product manufactured using one of the 4 different manufacturing processes (version [v] 1, v2, v3, and v4), with v4 representing the proposed commercial process. After transition to v4, the LVV used to manufacture JCAR017 product was initially supplied as v.1.0, and then subsequently supplied as v.1.2 The LVV manufactured as v.1.0 was used for the majority of the JCAR017 clinical experience in study 017001.

Study BCM-001

Study BCM-001 is an open-label, single-arm, multicohort, multicentre, Phase 2 study to determine the efficacy and safety of JCAR017 (administered as a single dose of 100 × 10^6 CAR+ T cells) in adult subjects with R/R aggressive B-cell NHL and to demonstrate the feasibility of manufacturing JCAR017 in Europe. As of the 13 Sep 2019 data cut-off date, the study was ongoing. The study design is summarised in Figures below:

Figure 5: Study BCM-001 design

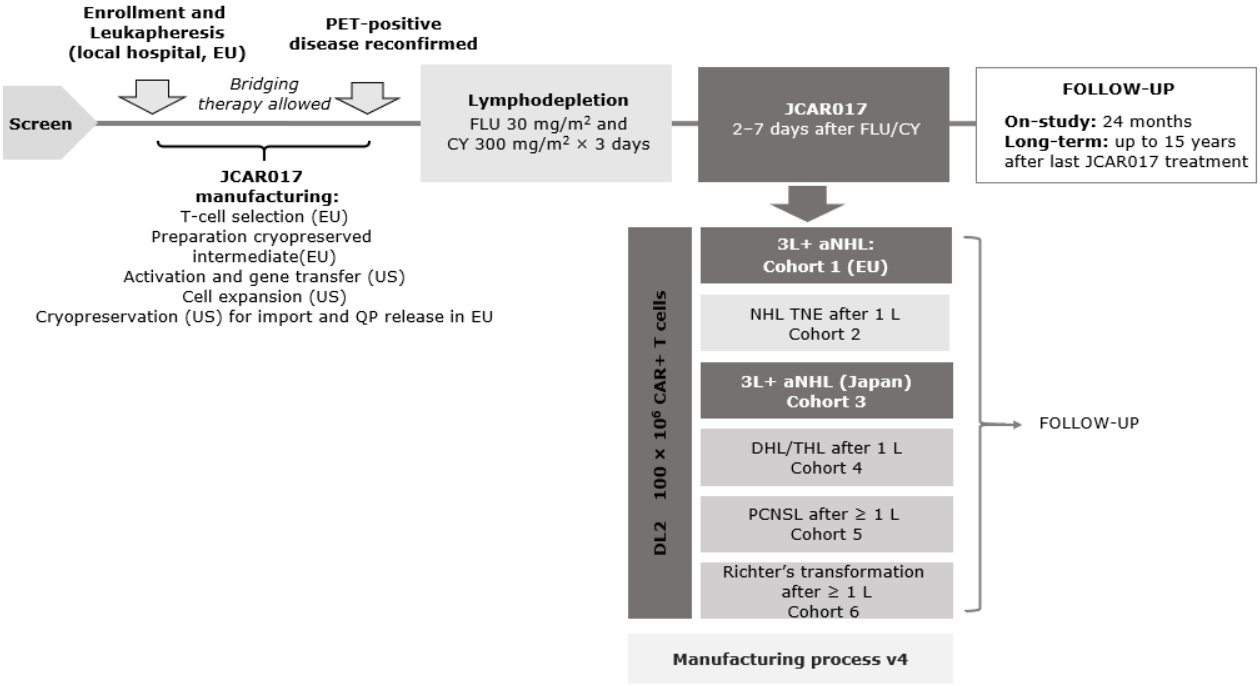
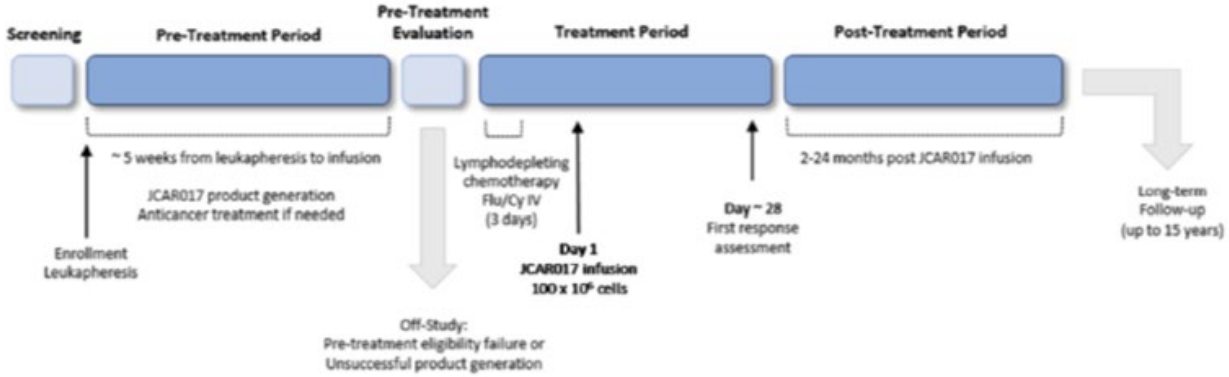


Figure 6: BCM-001 design (periods)



Flu/Cy = fludarabine/cyclophosphamide; IV = intravenous.

Subjects could be enrolled into one of 6 cohorts, including the following 2 cohorts in DLBCL relapsed or refractory after at least 2 prior treatments (3L+ R/R DLBCL): Cohort 1 enrolling subjects in Europe (EU), and Cohort 3 enrolling subjects in Japan. No additional cohort had enrolled subjects as of the 13 Sep 2019 data cut-off date.

In Study BCM-001 JCAR017 was manufactured using the proposed commercial process (v4). The LVV used to manufacture JCAR017 product was initially supplied as v1.2, and later as the final commercial version transferred.

Methods

- **Study participants**

Study 017001 – DLBCL cohort

Main inclusion criteria

- Age ≥18 years

- Relapsed or refractory (R/R) B-cell NHL of the following histologies:

    - DLBCL not otherwise specified (NOS; including transformed DLBCL from follicular lymphoma and other indolent histology [transformed iNHL] such as chronic lymphocytic leukaemia [CLL]/small lymphocytic lymphoma [SLL], marginal zone lymphoma [MZL], and other lymphomas [including Waldenström macroglobulinaemia]), high grade lymphoma (HGL) with MYC and BCL2 and/or BCL6 rearrangements and DLBCL histology, primary mediastinal B-cell lymphoma (PMBCL), and Grade 3b follicular lymphoma (FL3B).

- Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have R/R disease after at least 2 lines of therapy or after autologous haematopoietic stem cell transplant (auto-HSCT).

- Histological confirmation of diagnosis at relapse

- PET-positive disease as per the Lugano Classification (Cheson, 2014)

- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (note, ECOG status of 2 was also allowed until Protocol Amendment 5)

- Adequate organ function, defined as: adequate bone marrow function to receive LDC; serum creatinine ≤1.5 × age-adjusted upper limit of normal (ULN) OR calculated creatinine clearance (Cockcroft and Gault) >30 mL/min/1.73 m^2, alanine aminotransferase (ALT) ≤5 × ULN and total bilirubin <2.0 mg/dL (or <3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver); adequate pulmonary function, defined as NCI CTCAE Grade ≤1 dyspnoea and oxygen saturation (SaO2) ≥92% on room air; adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥40% as assessed by echocardiogram or multi-gated acquisition (MUGA) scan performed within 1 month of determination of eligibility

- Subjects who received previous CD19-targeted therapy must have had CD19-positive lymphoma confirmed on a biopsy since completing the prior CD19-targeted therapy

Main exclusion criteria

- Subjects with central nervous system (CNS)-only involvement by malignancy (subjects with secondary CNS involvement were allowed on study)

- Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis

- Active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection at the time of screening; subjects with uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate antibiotics or other treatment at the time of leukapheresis or JCAR017 administration

- Presence of acute or chronic graft-versus-host disease (GVHD)

- History of any one of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease

- History or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

- Therapeutic doses of corticosteroids (defined as >20 mg/day prednisone or equivalent) within 7 days of leukapheresis or 72 hours prior to JCAR017 administration. Physiologic replacement, topical, and inhaled steroids were permitted; Low dose chemotherapy (e.g., vincristine, rituximab, cyclophosphamide ≤300 mg/m^2) given after leukapheresis to maintain disease control had to be stopped ≥7 days prior to LDC and cytotoxic chemotherapeutic agents not considered lymphotoxic within 1 week of leukapheresis. Lymphotoxic chemotherapeutic agents within 2 weeks of leukapheresis. Immunosuppressive therapies within 4 weeks of leukapheresis and JCAR017 administration. Oral chemotherapeutic agents, including lenalidomide and ibrutinib, were allowed if at least 3 half-lives had elapsed prior to leukapheresis

- Donor lymphocyte infusions (DLI) within 6 weeks of JCAR017 administration, radiation within 6 weeks of leukapheresis. Allogeneic haematopoietic stem cell transplant (allo-HSCT) within 90 days of leukapheresis

- Prior CAR T-cell or other genetically modified T-cell therapy, with the exception of prior JCAR017 treatment in this protocol for subjects receiving retreatment

Study BCM-001 – Cohorts 1 and 3

Main inclusion criteria

- age ≥18 years

- ECOG PS of 0-1 (Cohort 1) or 0-2 (Cohort 3)

- Cohort 1: subjects with DLBCL NOS (de novo or tFL), HGL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (DHL/THL) and FL3B per WHO 2016 classification (Swerdlow, 2016), after ≥2 lines of therapy including an anthracycline and rituximab (or other CD20-targeted agent)

- Cohort 3 (Japan only): subjects who met eligibility criteria for either Cohort 1 or transplant ineligible subjects included those who were deemed ineligible for HDCT and HSCT due to age, PS, or comorbidity. At the very least, subjects must have met one of the following criteria: age ≥70 years, ECOG PS ≥2, impaired pulmonary function (DLCO ≤60%), impaired cardiac function (LVEF <50%), impaired renal function (CrCl <60 mL/min) or impaired hepatic function (AST/ALT >2 × ULN, bilirubin >2 mg/dL or cirrhosis, Child-Pugh B or C)

- Subjects with secondary CNS lymphoma involvement may have enrolled

- Histological confirmation of diagnosis at last relapse

- PET-positive disease as per Lugano criteria (Cheson, 2014)

- Adequate organ function (as per study 017001)

Main exclusion criteria

- Any significant medical condition, laboratory abnormality, or psychiatric illness, which placed the subject at unacceptable risk if participating in the study. Subject had any condition that confounded the ability to interpret data from the study

- Subjects with T cell rich/histiocyte rich large B-cell lymphoma, primary cutaneous large B-cell lymphoma, PMBCL, Epstein-Barr virus positive DLBCL of the elderly and Burkitt lymphoma

- Treatment with any prior gene therapy product or CD19-targeted therapy

- Previous history of or active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection. Uncontrolled systemic fungal, bacterial, viral, or other infection (including tuberculosis) despite appropriate antibiotics or other treatment at the time of leukapheresis or JCAR017 infusion

- Presence of acute or chronic GVHD or active autoimmune disease requiring immunosuppressive therapy

- History of any one of the following cardiovascular conditions within the past 6 months: heart failure NYHA class III or IV, cardiac angioplasty or stenting, myocardial infarction, unstable angina or other clinically significant cardiac disease

- History or presence of clinically relevant CNS pathology such as epilepsy, seizure, aphasia, stroke, cerebral oedema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

- Tumour invasion of venous or arterial vessels and/or dep venous thrombosis (DVT)/pulmonary embolism (PE) within 3 months of ICF signature and/or DVT/PE that required ongoing therapeutic levels of anticoagulation

- For prohibited medications see the exclusion criteria for study 017001 above.

- **Treatments**

Leukapheresis

Leukapheresis was performed on each subject to collect a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of the JCAR017 investigational product. If JCAR017 could not be manufactured, the subject could have had additional leukaphereses: subjects were required to continue to meet eligibility requirements.

Anticancer Treatments between Screening and Lymphodepleting Chemotherapy

If deemed necessary by the treating physician, anticancer treatment was allowed for disease control during JCAR017 manufacture (e.g., after screening while waiting for leukapheresis, or after leukapheresis and prior to LDC). The subject was required to continue to have PET-positive disease and meet eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of LDC.

Criteria for Initiating Lymphodepleting Chemotherapy and JCAR017 Treatment

In study **017001**, as of Amendment 6, subjects could not receive JCAR017 if they experienced a significant worsening in clinical status compared with that during eligibility screening. In case of delayed infusion because of clinical instability, LDC could be repeated if appropriate.

In study **BCM-001**, as a result of the urgent safety measure in December 2018, neither LDC nor JCAR017 treatment should have been administered if there was a worsening of ECOG PS to 2, rapid clinical deterioration, or evidence of rapid PD. Subsequent to Protocol Amendment 2, subjects who were TNE may have had ECOG PS 2; however, subjects should have been clinically stable, recovered from prior toxicities, and not have evidence of rapid PD or rapid clinical deterioration prior to receiving LDC or JCAR017 infusion.

Lymphodepleting Chemotherapy

Subjects were treated with fludarabine (30 mg/m^2/day for 3 days) plus cyclophosphamide (300 mg/m^2/day for 3 days) prior to treatment with JCAR017. Dose reductions of either/both agents were allowed at the discretion of the investigator and/or in compliance with approved labels for these products. Lymphodepleting chemotherapy could start 5 to 10 days prior to JCAR017 infusion.

JCAR017 Premedication

Subjects were premedicated with 500 to 650 mg acetaminophen orally (PO) and 25 to 50 mg diphenhydramine hydrochloride or, per the current Product Administration Manual, equivalent antihistamine (PO or IV) 30 to 60 minutes prior to JCAR017 administration. These medications were to have been repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Premedication with steroids was not allowed.

JCAR017 Dose and Schedule

In study **017001** JCAR017 was administered according to the dose regimen to which a subject was assigned. The dose levels (DLs) allowed in this study were:

- DL-1: 25×10^6 CAR+ T cells

- DL1: 50×10^6 CAR+ T cells (single-dose and 2-dose regimens [DL1S and DL1D, respectively])

- DL2: 100×10^6 CAR+ T cells (single-dose regimen only [DL2S])

- DL3: 150×10^6 CAR+ T cells (single dose regimen only [DL3S])

In the single-dose schedule, JCAR017 was given 2 to 7 days after completion of LDC.

In study **BCM-001** JCAR017 was administered as 100×10^6 CAR+ T cells on Day 1.

JCAR017 Administration

JCAR017 was administered as separate IV infusions that consisted of CD8+ CAR+ and CD4+ CAR+ T cells (JCAR017 CD8+ cell component administered first, followed by the JCAR017 CD4+ cell component). Subjects were monitored during and after each IV administration of JCAR017 components. JCAR017 was delivered in an outpatient setting at the investigator's discretion.

Recommended Supportive Care, Additional Treatment, and Monitoring

Prophylactic treatment/measures were strongly recommended for subjects at risk for TLS, per institutional standard of care. The use of red blood cells and platelet transfusions, and/or colony-stimulating factors was permitted per institutional standard of care. The use of prophylactic or empiric anti-infective agents (e.g., trimethoprim/sulfamethoxazole for pneumocystis pneumonia [PCP] prophylaxis, broad spectrum antibiotics, antifungals, or antiviral agents for febrile neutropenia) was permitted per institutional standard of care.

Steroids at therapeutic doses (>20 mg/day of prednisone or equivalent) were prohibited until lack of response, subsequent therapy for lymphoma, or 1 year following JCAR017 treatment. Therapeutic doses were allowed in life-threatening situations and for other medical conditions when indicated, or after loss of detectable JCAR017 cells.

- **Objectives**

Study 017001 – DLBCL Cohort

Primary:

- To evaluate the safety of JCAR017 in adult subjects with relapsed or refractory (R/R) B-cell NHL

- To assess the antitumour activity of JCAR017 (measured as overall response rate [ORR])

Key Secondary:

- To assess the rate of complete response (CR) and durability of antitumour activity (measured as duration of response [DOR]) of JCAR017

- To estimate the progression-free survival (PFS) and overall survival (OS) of subjects treated with JCAR017

Other Secondary/Exploratory:

- To assess health-related quality of life (HRQoL) and health economics and outcomes research

- To assess the effect of JCAR017 attributes on safety, PK, and antitumour activity

- To assess the effect of tumour and tumour microenvironment on JCAR017 PK and pharmacodynamics

Study BCM-001 – Cohorts 1 and 3

Primary:

- To determine the efficacy, defined as ORR, of JCAR017 in subjects with aggressive B-cell NHL

Secondary:

- To evaluate other measures of efficacy of JCAR017 (e.g., complete response rate [CRR], event-free survival [EFS], PFS, OS, DOR)

- To characterise the PK profile of JCAR017 in the peripheral blood measured using quantitative polymerase chain reaction (qPCR) detection for the JCAR017 vector sequence

- To describe changes in HRQoL using the European Organisation for Research and Treatment of Cancer Quality of Life C30 (EORTC QLQ-C30), the European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L), and the Functional Assessment of Cancer Therapy – Lymphoma "Additional concerns" subscale (FACT-LymS)

- **Outcomes/endpoints**

Primary efficacy endpoint: Objective response rate (ORR) as the proportion of subjects with a BOR of either CR or PR per IRC assessment based on the Lugano 2014 criteria. The BOR was the best disease response recorded from the time of JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy, or HSCT. In the IRC analysis, a non-PD was assigned as a BOR by the IRC when PET was not evaluable or not done for all the post-baseline assessment time points and the best response based on CT-staging evaluation was CR, PR or SD. In such a case, a subject was considered as a non-responder in the calculation of ORR.

The secondary efficacy endpoints included the following:

- CR rate (CRR), defined as the proportion of subjects with a BOR of CR per IRC assessment based on the Lugano 2014 criteria (Cheson, 2014)

- DOR defined as the time from first response (CR or PR) to PD or death per IRC assessment based on the Lugano 2014 criteria.

- PFS, defined as the time from first infusion of JCAR017 to PD, per IRC assessment based on the Lugano 2014 criteria, or death

- PFS ratio, defined as the ratio of PFS on the most recent line of therapy prior to JCAR017 to the PFS on JCAR017 per investigator assessment (study 017001 only). The PFS on JCAR017 was based on Investigator assessment. The PFS to the most recent line of therapy prior to JCAR017 was the time from the start date of the most recent line of therapy prior to JCAR017 to the date of disease progression or informed consent if date of progression was entirely missing

- EFS, defined as the interval from the date of JCAR017 infusion to the earliest of the following events: death from any cause, PD per IRC assessment, or starting a new anticancer therapy (study BCM-001 olny)

- OS, defined as the time from treatment with JCAR017 to the date of death

- Measurement of HRQoL changes as assessed using the EORTC QLQ-C30 and the EuroQol 5-dimensions 5-levels (EQ-5D-5L, study 017001 only) or the Functional Assessment of Cancer Therapy – Lymphoma "Additional Concerns" Subscale (FACT-LymS, study BCM-001 only).

Efficacy assessments

Based on the Lugano criteria, radiographic disease assessments by PET and/or diagnostic quality CT scans were performed pre-treatment, after any anticancer therapy for disease control (if applicable), at the end of the treatment cycle, and approximately 1 (only in study BCM-001) 3, 6, 9, 12, 18, and 24 months following the last dose of JCAR017 or until disease progression or treatment with additional anticancer therapy. For subjects with secondary CNS involvement, brain MRI scans and repeated CSF assessments were performed using flow cytometry. Positron emission tomography scans were not required after a subject achieved a CR unless PD was suspected on follow-up CT scan. Assessment of bone marrow involvement by lymphoma was by PET scan only. Disease response was determined according to the Cheson (2014) recommendations. Treatment decisions and assessment of the probability of CR for mCRM were performed using assessment of response as per the Investigator.

- **Sample size**

Study 017001

Based on a meta-analysis using random-effects model on data from 8 published studies of NCCN recommended regimens for patients with R/R aggressive large B-cell NHL, the estimated ORR was 30% (95%CI 24 to 38) and CR is 19% (95%CI 13 to 26). For the primary analysis in Study 017001, based on the null hypothesis of ORR ≤40% and an alternative hypothesis of ORR >40% with the effect size of 25% (ORR=65%), a sample size of 75 subjects in the PAS was to provide ~98% power to demonstrate statistical significance at a 1-sided significance level of 0.021 based on an exact test.

For the efficacy endpoint of CR rate, based on the null hypothesis of CR rate ≤20% and an alternative hypothesis of CR rate >20% with the effect size of 20% (CR rate=40%), 75 subjects in the PAS was to provide ~96% power to demonstrate statistical significance at a 1-sided significance level of 0.021 based on an exact test. In chemorefractory patients predefined ORR rate of 30% and a CR rate of 10% were based on the retrospective SCHOLAR-1 study (Crump, 2017).

The maximum planned sample size for the DF + DE phases was 174 subjects. The maximum planned sample size for the DF phase was 114 subjects. The planned sample size for a DC group was at least 100 subjects to ensure at least 75 subjects in the PAS.

Study BCM-001

Determination of the null hypothesis was based on results from the retrospective SCHOLAR-1 study (Crump, 2017).

Cohort 1: a sample size of 34 subjects treated with JCAR017 conforming product provided at least 90% power to reject the null hypothesis of response rate less than 40% assuming the target response rate of 70% using an exact binomial test with an overall 2-sided significance level of 0.05 considering a formal interim analysis with the first 10 subjects treated with JCAR017 conforming product being followed for at least 3 months after JCAR017 infusion to test the superiority of JCAR017. The primary analysis for Cohort 1 was planned after at least 34 subjects treated with JCAR017 conforming product were treated

with JCAR017 and the last subject had been followed for at least 6 months or until death, PD, or withdrawal from study.

- **Randomisation**

Not applicable.

- **Blinding (masking)**

Not Applicable.

- **Statistical methods**

Study 017001 Efficacy Analysis sets

Screened Set: all subjects who signed informed consent.

Eligible Set: all subjects who signed informed consent and met all inclusion/exclusion criteria.

Leukapheresed (Intent-to-treat - ITT) Set: all subjects who had signed informed consent, who met all inclusion/exclusion criteria, and who underwent leukapheresis. In case of protocol deviations where subjects underwent leukapheresis without having met all inclusion/exclusion criteria, the subjects were still included in the Leukapheresed Set.

Primary Analysis Set (PAS) for the DLBCL Cohort: subjects in the DF, DE, and DC groups who failed at least 2 therapies in the DLBCL Cohort with DLBCL NOS (de novo or tFL), or HGL with DLBCL histology, treated at the recommended regimen (DL2S). Subjects in the PAS must have had PET-positive disease present before JCAR017 administration based on IRC assessment. The diagnosis per investigator assessment was used to determine inclusion in the PAS. This set was used for the primary efficacy analysis.

JCAR017-treated Analysis Set: all subjects who received at least 1 dose of JCAR017 cell product. In case a subject received multiple JCAR017 doses, the first dose of JCAR017 should have been conforming product, which met specification at the time of product release. The DLBCL Cohort JCAR017-treated Analysis Set is defined the "DLBCL Treated Set."

JCAR017-treated Efficacy Analysis Set: the JCAR017-treated Efficacy Analysis Set included all subjects in the DLBCL Cohort and JCAR017-treated Analysis Set who had PET-positive disease present before JCAR017 administration based on IRC assessment. The DLBCL Cohort JCAR017-treated Efficacy Analysis Set is referred as the "DLBCL Efficacy Set."

Per Protocol Analysis Set (PP): a subset of the PAS, including subjects who were compliant with the major requirements of the study protocol. The PP Analysis Set was used in sensitivity analyses of the primary and secondary efficacy endpoints.

Study BCM-001 Efficacy analysis set

Screened Set: all subjects who signed informed consent.

Enrolled Set: all subjects who signed informed consent, passed all eligibility criteria, and underwent leukapheresis

JCAR017-treated Set: all subjects who received JCAR017

Efficacy Evaluable Set: all subjects who received JCAR017 and who had a baseline assessment and at least one post-JCAR017 disease assessment.

Efficacy Analyses (studies 017001 and BCM-001)

For binary endpoints, such as ORR, the frequency distribution (n,%) was provided. The point estimate together with 2-sided exact 95% confidence interval (CI) were provided. For time-to-event endpoints such as DOR, EFS, PFS, and OS, the Kaplan-Meier (KM) product limit method was used to estimate the survivorship function. Event rates at specific time points were estimated from the KM curves. Medians together with 2-sided 95% CI were calculated.

ORR and CRR: ORR and CRR were calculated along with the 2-sided 95% exact Clopper-Pearson confidence intervals (CIs).

DOR and PFS: the KM method was used to estimate the median DOR and PFS and the DOR/PFS rate at 6, 12, 18, and 24 months along with the 95% CIs. Censoring reasons: completed the study, discontinued the study, received retreatment, received a new anticancer therapy, proceeded to HSCT, experienced an event after missing at least 2 consecutive scheduled disease assessments.

OS: the OS analysis included all available survival information with long-term follow-up data. Data from surviving subjects were censored at the last time that the subject was known to be alive. The KM method was used to estimate the OS rate at Months 6, 12, 18, and 24, and the median OS along with the 95%CI.

EFS (only for study BCM-001): the KM method was used to estimate the rate of EFS at Months 1, 3, 6, 9, 12, 18, and 24, and Q1, median, and Q3 of EFS. Two-sided 95% CI for median was also provided.

Health-Related Quality of Life

The EQ-5D-5L, EORTC QLQ-C30, and FACT-LymS (only in study BCM-001) were used to assess the subject's global health status, physical, social, emotional, and functional well-being as well as lymphoma-related quality of life.

In study 017001, PROs were evaluated in all subjects in the DLBCL Treated Set after implementation of Protocol Amendment 4. The main objectives were to examine 4 key prespecified domains (global health status, physical functioning, fatigue, and pain; selected for their clinical relevance in this patient population) using the EORTC QLQ-C30. Exploratory objectives included use of the EQ-5D-5L to examine health utility index and EuroQol visual analogue scale (EQ-VAS) scores.

The EORTC QLQ-C30 and EQ-5D-5L were assessed at baseline, Day 29 (Month 1), Months 2, 3, 6, 9, 12, 18, 24/end of study, and at disease progression/relapse. Analyses up until Month 18 were included in this analysis, as <10 subjects responded to the questionnaires after that point.

In study BCM-001 four domains from the EORTC QLQ-C30 (fatigue, physical, and cognitive functioning; and global health/QoL) and the FACT-LymS were analysed to assess the impact of JCAR017 treatment on HRQoL.

The EORTC QLQ-C30 and FACT-LymS were assessed at screening and baseline (pre-treatment evaluation visit), during treatment (Day 1 and Day 29), and posttreatment (Days 60, 90, 180, and 270 post-JCAR017 infusion). The results were analysable up until Month 3, as <10 subjects responded to the questionnaires after this time.

EORTC QLQ-C30: A predefined change of at least 10 points on the scale score was required to be considered clinically meaningful.

EQ-5D-5L: A predefined change ranging from ≥0.08 to ≤-0.1 points on the scale score was required to be considered clinically meaningful (Pickard, 2007).

FACT-LymS: The MID for the FACT-LymS score ranges from 3 to 5 points (Hlubocky, 2013). There are no established RDs for the FACT-LymS; therefore, the MID value of 3 (+3 for improvement and -3 for deterioration) will be used as both the MID and RD.

Sensitivity Analyses

Sensitivity analyses of primary and secondary efficacy endpoints in study 017001 were performed based on: (1) the Leukapheresed Set, (2) the PP Analysis Set and/or PP DLBCL Analysis Set, (3) the disease histology determined by central pathology review, (4) the response determined by Investigator. A subject in the Leukapheresed Set who did not receive cell product was considered not evaluable (i.e., a non-responder) for the sensitivity analysis of ORR and CR rate.

Sensitivity analyses for DOR, PFS and EFS: sensitivity analyses were performed in study 017001 (1) without censoring HSCT and (2) in alignment with EMA guidelines (EMA, 2012), without censoring new anticancer therapy, HSCT and missing at least 2 consecutive scheduled disease assessments.

Interim analysis

Study 017001

An interim analysis (IA) and a primary analysis based on the PAS were planned. The one-sided significance levels for the interim and primary analyses were 0.01 and 0.021, respectively, using the interpolated spending function. The overall one-sided type I error was 0.025. Since the IA was not performed, all the alpha was preserved for the primary analysis.

Study BCM-001

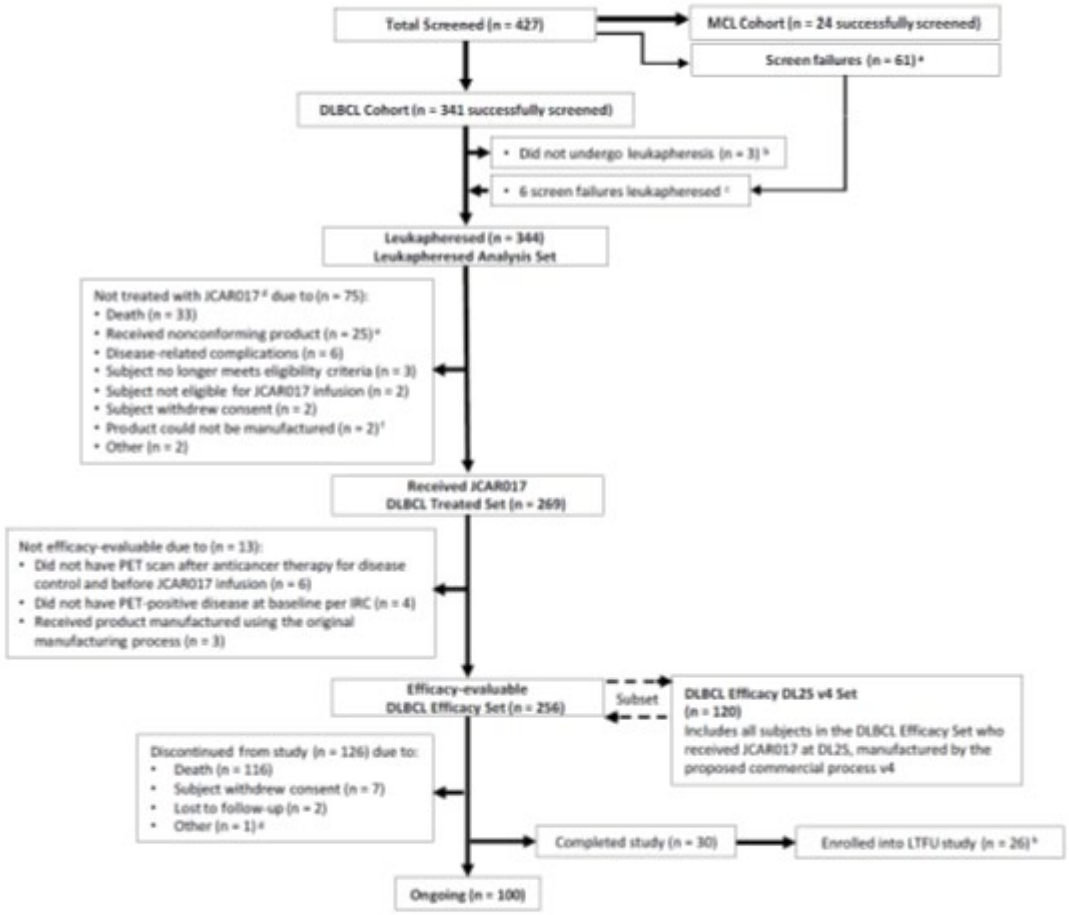
A formal IA was performed with the first 10 subjects in Cohort 1 treated with JCAR017 conforming product being followed for at least 3 months to test the superiority of JCAR017. An interpolated spending function was used as efficacy boundary for the interim analysis with a significance level of 0.01. The IA did not reject the null hypothesis of ORR.

Results

- **Participant flow**

Study 017001 Participant flow

Figure 7. study 017001: Subject Disposition in the DLBCL Cohort



CLOVER = Clinical Outcomes Across Manufacturing Process Versions; CSR = clinical study report; DL2S = Dose Level 2, Single Dose; DLBCL = diffuse large B-cell lymphoma; IRC = Independent Review Committee; LFTU = long-term follow-up; MCL = mantle cell lymphoma PET = positron emission tomography; SCS = Summary of Clinical Safety; v4 = version 4 (proposed commercial manufacturing process).

[a] For details on screen failures, see CSR 017001 Section 10.1.1.1.
[b] For details on successfully screened subjects who did not undergo leukapheresis, see CSR 017001 Section 10.1.1.3.
[c] Six subjects who underwent leukapheresis were retrospectively determined to have not met study eligibility criteria. These subjects were included in the Leukapheresed Set, the DLBCL Treated Set, and the DLBCL Efficacy Set, as applicable, see CSR 017001 Section 10.1.1.2.
[d] For details on subjects who underwent leukapheresis but did not receive JCAR017, see CSR 017001 Section 10.1.1.4.
[e] Subjects who received nonconforming product are discussed in Section 3.3.
[f] The source of these data is the off-study case report form. For a complete accounting of manufacturing failures, see CSR 017001 Section 10.2.2.2. For a complete accounting of deaths, see CSR 017001 Section 12.5.2.1.
[g] Subject discontinued from the study 2 years after JCAR017 infusion due "health status and mental status" (verbatim text from case report form, see CSR 017001 Listing 16.2.1.1).
[h] Enrolled into Study GC-LTFU-001 as described in Section 1.1.1.4 (SCS GC-LTFU-001 Listing 16.2.1).
Data cutoff date 12 Aug 2019.

Seven subjects (6 in the DLBCL Cohort and 1 in the MCL Cohort) were screened and considered to have met eligibility criteria at leukapheresis by the Investigator, underwent leukapheresis, and continued in the study, but were found later to have not met entry criteria at leukapheresis. All of these were considered protocol deviations. Subjects who were enrolled underwent leukapheresis as soon as possible thereafter.

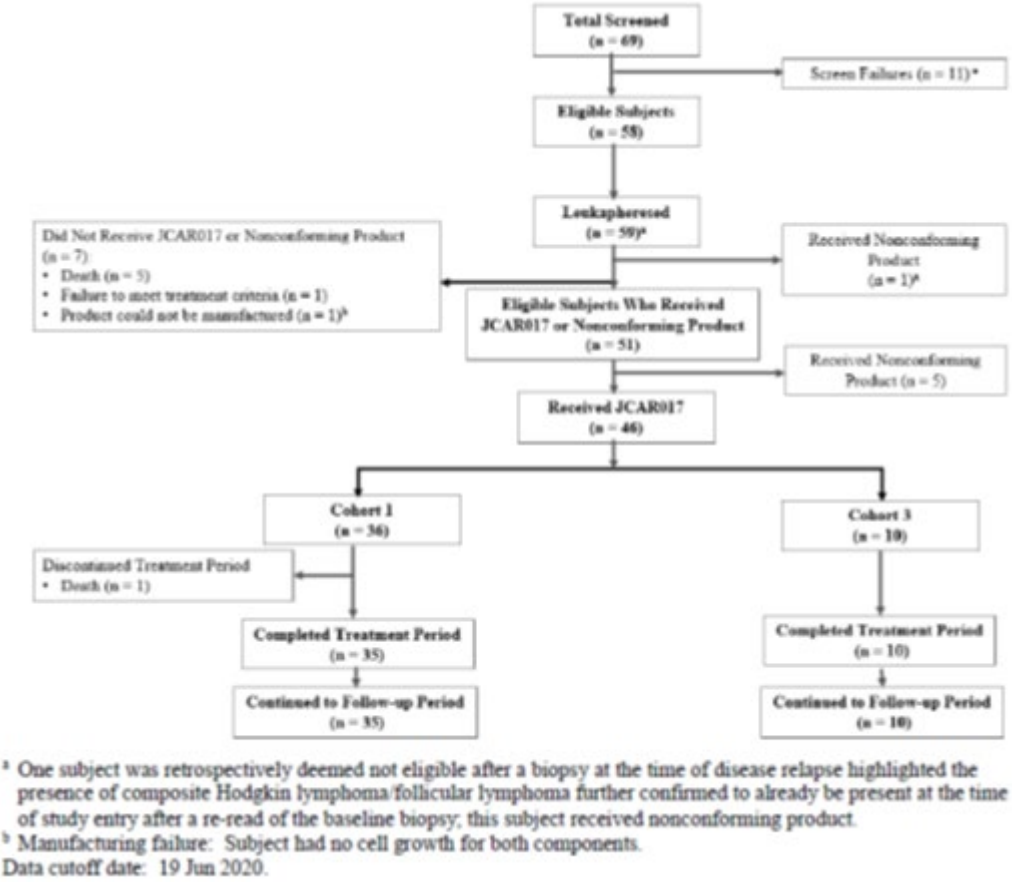
Three subjects in the DLBCL Cohort, who were successfully screened, did not undergo leukapheresis: one subject withdrew consent prior to leukapheresis, one subject died prior to leukapheresis, and one subject had not yet undergone leukapheresis at the time of the data cut-off. One additional subject who was not categorised into either the DLBCL Cohort or the MCL Cohort, was successfully screened, discontinued from the study prior to being assigned a cohort, and did not undergo leukapheresis.

Updated analysis (data cut-off date of 19 Jun 2020)

The updated analysis includes data from 1 additional subject treated with JCAR017 at DL2S.

Study BCM-001 Participant flow (data cut-off 19 Jun 2020)

Figure 8. Subject Disposition



[a] One subject was retrospectively deemed not eligible after a biopsy at the time of disease relapse highlighted the presence of composite Hodgkin lymphoma/follicular lymphoma further confirmed to already be present at the time of study entry after a re-read of the baseline biopsy; this subject received nonconforming product.
[b] Manufacturing failure: Subject had no cell growth for both components.
Data cutoff date: 19 Jun 2020.

Among the 35 (97.2%) subjects in Cohort 1 who continued to the Posttreatment Period, 13 (36.1%) subjects were still ongoing at the cut-off date while 22 (61.1%) subjects had discontinued from the Posttreatment Period for the following reasons: Alternative treatment (n = 1), Withdrawal by subject (n = 5), Death (n = 10), Other reasons (n = 6). Among the 10 (100.0%) subjects in Cohort 3 who continued to the Posttreatment Period, 4 (40.0%) subjects were still ongoing at the cut-off date while 6 (60.0%) subjects had discontinued from the Posttreatment Period for the following reasons: Death (n = 4), Withdrawal by subject (n = 2).

- **Recruitment**

Study 017001

The first subject signed an Informed Consent Form (ICF) for Study 017001 on 06 Jan 2016. The first leukapheresis for this study occurred on 11 Jan 2016, and the first infusion of JCAR017 occurred on 22 Feb 2016. Enrolment in the study was ongoing in both the DLBCL Cohort (to enrol more subjects with FL3B) and the MCL Cohort. The study will be considered completed when all subjects in each cohort have been followed for safety, disease progression, and survival for 2 years after their last dose of JCAR017.

The study was conducted at 14 study sites, all of which were in the United States.

Study BCM-001

The first subject signed an ICF for Study BCM-001 on 05 Jun 2018. The first leukapheresis for this study occurred on 18 Jun 2018, and the first infusion of JCAR017 occurred on 31 Jul 2018. The study was conducted at 12 study sites in 8 countries: Austria, Belgium, Finland, France, Italy, Japan, Spain, and Switzerland.

- **Conduct of the study**

Study 017001

As of the data cut-off date of 12 Aug 2019, 6 protocol amendments were filed during the conduct of the study. A summary of the main changes made in each amendment is provided below:

Amendment 1 (24 Sep 2015)

Provided additional information for additional JCAR017 cycles in subjects who achieve a response following JCAR017 therapy (the option for additional cycles was removed with Amendment 6).

Amendment 2 (14 Mar 2016)

A second group of subjects could be enrolled and treated at a higher dose of JCAR017 (100×10^6 CAR+ T cells); the planned maximum sample size was increased from 70 to 90 subjects.

Amendment 3 (29 Jun 2016)

Allowed for a third, higher JCAR017 dose level (150×10^6 CAR+ T cells); allowed for expansion groups to be opened; made efficacy a primary endpoint rather than secondary; updated the sample size of the study and other statistical methods as a result of the above changes; specified that efficacy evaluations were to be performed both by the Investigator and by a central IRC; clarified that subjects with PMBCL were allowed; changed inclusion criteria to disallow second-line transplant-ineligible subjects; clarified the timing of pre-treatment PET and CT scans.

Amendment 4 (05 Jan 2017)

Defined a more homogeneous PAS for efficacy analyses; specified that the study should continue enrolling subjects at the recommended regimen to reach a sample size of approximately 100 DLBCL Cohort subjects in the DC group to ensure at least 75 subjects in the PAS; clarified that all subjects in the DLBCL Cohort must have relapsed or refractory disease after at least 2 lines of therapy or after autologous HSCT and clarified definition of DLBCL subjects with regard to then current WHO guidelines; allowed subjects with secondary CNS involvement and excluded subjects with CNS-only disease; clarified that subjects with transformed iNHL were allowed.

Amendment 5 (14 Aug 2017)

Allowed for more than 1 dose confirmation group; excluded further enrolment of subjects with ECOG performance status of 2 at screening; updated PAS to exclude FL3B and DLBCL transformed from indolent histologies, as well as those with ECOG performance status of 2 or prior allo-HSCT.

Amendment 6 (13 Apr 2018)

Removed the possibility of additional cycles for subjects who responded to JCAR017 but did not achieve CR; added flexibility to enrolment numbers to ensure adequate enrolment for the PAS.

Protocol deviations

Among all enrolled subjects (which includes both DLBCL and MCL Cohorts), there were a total of 14 major protocol deviations, in particular: 7 subjects did not have confirmatory PET scans to demonstrate PET-positive disease following anticancer therapy for disease control received after screening; 1 subject had not received 2 prior treatments for the qualifying diagnosis of tFL (the subject had received 2 prior treatments for low-grade lymphoma); 1 subject was enrolled with ECOG performance status of 2 at screening; 1 subject developed CNS involvement by NHL between leukapheresis and JCAR017 (subsequently, the protocol was amended to allow subjects with secondary CNS lymphoma on study); 1 subject had the MUGA scan used to determine eligibility of adequate organ function done 1 year out of window.

Study BCM-001

As of the data cut-off date of 13 Sep 2019, 2 protocol amendments were filed during the conduct of the study. A summary of the main changes made in each amendment is provided below:

Amendment 1 (08 Jan 2018)

Transformed indolent B-NHL was restricted to tFL; definition of TNE subjects was revised; inclusion criterion for subjects with secondary DLBCL CNS involvement was revised.

Amendment 2 (28 Dec 2018)

Restricted enrolment to subjects with ECOG PS 0 to1, except for TNE subjects; exclusion criteria were added for subjects with vascular tumour invasion, DVT or PE within 3 months, and subjects with DVT/PE requiring therapeutic levels of anticoagulation. Subjects had to be clinically stable prior to JCAR017 infusion, including absence of active infection, absence of requirement for supplemental oxygen to sustain adequate oxygenation, uncontrolled cardiac arrhythmias, or hypotension requiring vasopressor support. Selection of subjects with primary or secondary CNS involvement was clarified: subjects were to be enrolled if the potential benefit outweighs the risk for the subject, as considered by the Investigator.

Amendment 3 (21 Nov 2019)

Additional details were provided for Cohorts 4 and 5. Cohort 6 (Richter's syndrome) was removed. Cohort 7 was added to explore the benefit/risk profile of JCAR017 outpatient treatment in Europe. Removed the DVT/PE/anticoagulation and vascular tumour invasion exclusion criteria as well as statements regarding stable disease/anticoagulation to be added to the LDC and Criteria for JCAR017 Treatment sections.

Protocol deviations

One subject in Cohort 1 in the Screened set had an important protocol deviation; this subject was retrospectively deemed not eligible after a biopsy at the time of disease relapse highlighted the presence of composite Hodgkin lymphoma/FL further confirmed to already be present at the time of study entry after a re-read of the baseline biopsy.

- **Baseline data**

Study 017001 and BCM-001 Cohort 1

The main demographic and disease characteristics at baseline and prior treatments of subjects treated in Study 017001, DLBCL Cohort, and Study BCM-001, Cohort 1 (JCAR017-treated Analysis Sets) are summarised in Table below:

Table 7. Baseline Characteristics of Subjects Treated in Study 017001, DLBCL Cohort, and Study BCM-001, Cohort 1 (JCAR017-treated Analysis Sets)

Parameter		Study BCM-001 Cohort 1		Study 017001 DLBCL Cohort
		As of 13 Sep 2019 (N = 27)	As of 19 Jun 2020 (N = 36)	As of 19 Jun 2020 (N = 270)
Age (years)	Median (min, max)	59.0 (40, 72)	61.5 (26, 72)	63.0 (18, 86)
Age group, n (%)	< 65 years	19 (70.4)	22 (61.1)	158 (58.5)
	≥ 65 years	8 (29.6)	14 (38.9)	112 (41.5)
Sex, n (%)	Male	18 (66.7)	25 (69.4)	174 (64.4)
	Female	9 (33.3)	11 (30.6)	96 (35.6)
ECOG PS at screening, n (%)	0	15 (55.6)	19 (52.8)	111 (41.1)
	1	11 (40.7)	16 (44.4)	155 (57.4)
	2	1 (3.7)	1 (2.8)	4 (1.5)

Parameter		Study BCM-001 Cohort 1		Study 017001 DLBCL Cohort
		As of 13 Sep 2019 (N = 27)	As of 19 Jun 2020 (N = 36)	As of 19 Jun 2020 (N = 270)
Histological subtype, n (%)	DLBCL NOS	22 (81.5)	31 (86.1)	137 (50.7)
	tiNHL[a]	NA	NA	18 (6.7)
	tFL[a]	6 (22.2)	7 (19.4)	60 (22.2)
	HGL	4 (14.8)	4 (11.1)	36 (13.3)
	FL Grade 3B	1 (3.7)	1 (2.8)	4 (1.5)
	PMBCL	0	0	15 (5.6)
Cell of origin, n (%)	GCB	17 (63.0)	22 (61.1)	119 (44.1)
	ABC, non-GCB	7 (25.9)	10 (27.8)	76 (28.1)
	Unknown	2 (7.4)	3 (8.3)	56 (20.7)
	NA	1 (3.7)	1 (2.8)	0
Number of previous lines of systemic therapies	Median (min, max)	3 (0, 5)	2 (0, 5)	3 (1, 8)
Number of previous lines of systemic therapy, n (%)	0	1 (3.7)	1 (2.8)	0
	1	0	0	9 (3.3)
	2	10 (37.0)	18 (50.0)	122 (45.2)
	3	9 (33.3)	8 (22.2)	68 (25.2)
	4	5 (18.5)	7 (19.4)	43 (15.9)
	≥ 5	2 (7.4)	2 (5.6)	28 (10.4)
Relapsed or refractory status to therapy, n (%)	Relapsed	7 (25.9)	8 (22.2)	56 (20.7)
	Refractory	20 (74.1)	28 (77.8)	214 (79.3)
Prior HSCT, n (%)	Yes	11 (40.7)	12 (33.3)	94 (34.8)
	Allogenic	0	0	9 (3.3)
	Autologous	11 (40.7)	12 (33.3)	90 (33.3)
	No	16 (59.3)	24 (66.7)	176 (65.2)
Use of anticancer therapy for disease control, n (%)	Yes	21 (77.8)	27 (75.0)	159 (58.9)
	No	6 (22.2)	9 (25.0)	111 (41.1)
LDH at pre-LDC visit, n (%)	< 500 U/L	19 (70.4)	28 (77.8)	212 (78.5)
	≥ 500 U/L	8 (29.6)	8 (22.2)	58 (21.5)

Parameter		Study BCM-001 Cohort 1		Study 017001 DLBCL Cohort
		As of 13 Sep 2019 (N = 27)	As of 19 Jun 2020 (N = 36)	As of 19 Jun 2020 (N = 270)
SPD by IRC, at pre-LDC visit, n (%)	< 50 cm²	17 (63.0)	25 (69.4)	185 (71.7)
	≥ 50 cm²	7 (25.9)	9 (25.0)	73 (28.3)
	Missing	3 (11.1)	2 (5.6)	0
CRP prior to JCAR017, n (%)	< 20 mg/L	16 (59.3)	22 (61.1)	118 (43.9)
	≥ 20 mg/L	11 (40.7)	14 (38.9)	151 (56.1)
IPI score, n (%)	Low risk	7 (25.9)	8 (22.2)	NA
	Low-intermediate risk	4 (14.8)	10 (27.8)	NA
	High-intermediate risk	9 (33.3)	11 (30.6)	NA
	High risk	7 (25.9)	7 (19.4)	NA

ABC = activated B-cell; CRP = C-reactive protein; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; GCB = germinal center B-cell; HGL = high grade lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology; HSCT = hematopoietic stem cell transplant; IPI = International Prognostic Index; IRC = independent review committee; JCAR017 = lisocabtagene maraleucel (liso-cel); LDC = lymphodepleting chemotherapy; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; NA = not applicable; NA = not applicable; NOS = not otherwise specified; PS = performance status; SPD = sum of product of perpendicular diameters; tFL = transformed follicular lymphoma; tiNHL = diffuse large B-cell lymphoma transformed from indolent non-Hodgkin lymphoma other than follicular lymphoma.

[a] Per World Health Organization classification, DLBCL NOS is defined as de novo DLBCL and DLBCL from transformation of indolent non-Hodgkin lymphoma. Study 017001 analyzed results in a more detailed fashion, by DLBCL NOS (de novo), tFL, and DLBCL transformed from indolent lymphomas, whereas Study BCM-001 included tFL in DLBCL NOS.

All leukapheresed set

Study 017-001

The DLBCL Leukapheresed Set had a median age of 62 years, with 141 of 344 subjects (41.0%) aged 65 or greater and 33 of 344 subjects (9.6%) aged 75 or greater. Subjects were predominantly male (222 of 344 subjects: 64.5%). At screening, most subjects in this group had an ECOG performance status of 1 or 0, with 8 of 344 subjects (2.3%) having an ECOG performance status of 2. Approximately one-half of subjects had DLBCL NOS (165 of 344 subjects; 48.0%) followed by DLBCL transformed from FL (83 of 344 subjects; 24.1%). Additionally, 8 of 344 subjects (2.3%) had CNS involvement by lymphoma at the time of infusion of JCAR017 or nonconforming product. The median time from diagnosis of the studied disease indication to first infusion of JCAR017 or nonconforming product was 19.2 months (range, 5 to 259 months). Most of the subjects (278 of 344; 80.8%) were refractory to their most recent prior treatment and 237 of 344 (68.9%) were chemorefractory. Fifty-eight of 344 subjects (16.9%) had a best prior response of PD or SD to any previous therapy, and 160 of 344 (46.5%) never achieved CR. Prior to LDC, 66 of 298 subjects (22.1%) had an LDH level ≥ 500 U/L and 82 of 281 subjects (29.2%) had SPD ≥ 50 cm2. The median number of prior systemic therapies was 3.0 (range, 1 to 12). One hundred fifteen of 344 subjects (33.4%) had received prior HSCT. Thirteen of 344 subjects (3.8%) received prior allogeneic stem cell transplant.

Of 298 patients who underwent leukapheresis for whom Breyanzi was manufactured in the dose range of 44-120 × 10^6 CAR+ viable T cells, 229 patients received Breyanzi and 69 patients did not. The baseline in such set is:

Table 8: Baseline demographic and disease-related characteristics

Characteristic	All leukapheresed (N=298)	Breyanzi-treated (N=229)
Median age, years (range)	62.0 (18, 82)	62.0 (18, 82)
≥ 65 years, n (%)	116 (38.9)	89 (38.9)
≥ 75 years, n (%)	25(8.4)	19(8.3)
Sex, n (%) Male Female	 197 (66.1) 101 (33.9)	 153 (66.8) 76 (33.2)
Prior HSCT, n (%) Autologous HSCT Allogeneic HSCT	106 (35.6) 100 (33.6) 11 (3.7)	87 (38.0) 84 (36.7) 8 (3.5)
ECOG performance status ECOG 0-1, n (%) ECOG 2, n (%)	 290 (97.3) 8 (2.7)	 225 (98.3) 4 (1.7)
Disease histology subtype, n (%)		
DLBCL, NOS	142 (47.7)	117 (51.1)
DLBCL transformed from indolent lymphoma	87 (29.2)	60 (26.2)
High-grade B cell lymphoma[a]	48 (16.1)	33 (14.4)
PMBCL	15 (5.0)	15 (6.6)
FL3B	6 (2.0)	4 (1.7)
Median number of prior therapies (range)	3 (1-12)	3 (1-8)
Chemorefractory[b], n (%)	212 (71.1)	160 (69.9)
Refractory[c], n (%)	246 (82.6)	186 (81.2)
Relapsed[d], n (%)	52 (17.4)	43 (18.8)
Secondary CNS lymphoma at time of Breyanzi infusion, n (%)	7 (2.3)	6 (2.6)
Never achieved CR from prior therapies, n (%)	141 (47.3)	103 (45.0)

[a] MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology.

[b] Chemorefractory is defined as experiencing stable disease (SD) or progressive disease (PD) to last chemo-containing regimen or relapsed < 12 months after autologous stem cell transplantation.

[c] The status was refractory if a patient achieved less than a complete response (CR) to last prior therapy.

[d] The status was relapsed if a patient achieved CR to last prior therapy.

Study BCM-001

In Cohort 1 (N = 45), subjects had a median age of 64.0 years (range: 26 to 73 years), with 25 (55.6%) subjects aged ≥ 40 to < 65 years and 19 (42.2%) subjects aged ≥ 65 to < 75 years. Subjects were predominantly white and male (82.2% and 66.7%, respectively). At screening, all but 1 subject (ECOG PS 2) had an ECOG PS of 1 or 0; 36 (80.0%) subjects had DLBCL NOS, of which 8 (17.8%) subjects had tFL, 7 (15.6%) subjects had HGBL (DHL/THL), and 1 (2.2%) subject had FL3B. Twelve (26.7%) subjects were high-intermediate risk per IPI while 9 (20.0%) subjects were high risk. The majority of subjects (24 [53.3%] subjects) were Ann Arbor Stage IV; 12 (26.7%) subjects were Stage II, 6 (13.3%) subjects were Stage I, and 3 (6.7%) subjects were Stage III.

- **Numbers analysed**

Study 017001 and BCM-001

Analysis sets are summarised in Tables below:

Study 017001 (data cut-off 12 Apr 2019)

Table 9 : Analysis Population, DLBCL Cohort

	DL2S N (%)	DL1S N (%)	DL1D N (%)	DL3S N (%)	Total N (%)
Screened Set					344
Eligible Set					338
Leukapheresed (ITT) Set[a]	225	63	7	47	342
JCAR017-Treated Analysis Set (DLBCL Treated Set)	176 (78.2)	45 (71.4)	6 (85.7)	41 (87.2)	268 (78.4)
JCAR017-Treated Efficacy Analysis Set (DLBCL Efficacy Set)	168 (74.7)	40 (63.5)	6 (85.7)	41 (87.2)	255 (74.6)
Primary Analysis Set (PAS; DL2S only)	133 (59.1)	NA	NA	NA	133 (38.9)
DLT-evaluable Analysis Set[b]	48 (21.3)	44 (69.8)	6 (85.7)	41 (87.2)	139 (40.6)
Efficacy-evaluable Analysis Set[b]	51 (22.7)	44 (69.8)	6 (85.7)	41 (87.2)	142 (41.5)
Per Protocol Analysis Set (subset of PAS)	131 (38.3)	NA	NA	NA	131 (38.3)
Per Protocol DLBCL Analysis Set (subset of DLBCL Treated Set)	169 (75.1)	42 (66.7)	6 (85.7)	41 (87.2)	258 (75.4)
qPCR Pharmacokinetic Analysis Set	176 (78.2)	44 (69.8)	6 (85.7)	41 (87.2)	267 (78.1)
PRO/QoL QLQ-C30 Evaluable Set	137 (60.9)	5 (7.9)	0	39 (83.0)	181 (52.9)

DL2S = Dose Level 2, Single Dose, DL1S = Dose Level 1, Single Dose, DL1D = Dose Level 1, 2 Dose, DL3S = Dose Level 3, Single Dose; DLBCL = diffuse large B-cell lymphoma; DE = dose expansion; DF = dose finding; DLT = dose-limiting toxicity; ITT = intent-to treat; mCRM = modified continual reassessment method; NA = not applicable; PAS = Primary Analysis Set; PRO = patient-reported outcomes; QLQ-C30 = Quality of Life Questionnaire C30; QoL = quality of life; qPCR = quantitative polymerase chain reaction.

Note: The denominator is the number of subjects in the Leukapheresed Set.

[a] More subjects are included in the Leukapheresed Set than the Eligible Set due to subjects having enrolled in the study although they did not meet eligibility criteria. In some cases, the subjects were allowed on study after discussion with the Sponsor and in other cases the deviations were identified retrospectively. Details are discussed in Section 10.1.1.

[b] Only used for mCRM calculations in the DF and DE groups

Data as of the 12 Apr 2019 cutoff

Study BCM-001 (data cut-off 19 Jun 2020)

Table 10: Analysis Population

Analysis Populations	Number of Subjects (%)[a]		
	Cohort 1	Cohort 3	Overall
Screened Set[b]	53 (100.0)	16 (100.0)	69 (100.0)
Leukapheresed (ITT) Set[c]	45 (84.9)	14 (87.5)	59 (85.5)
Enrolled Set[d]	44 (83.0)	14 (87.5)	58 (84.1)
JCAR017-treated Set[e]	36 (67.9)	10 (62.5)	46 (66.7)
Efficacy Evaluable Set[f]	36 (67.9)	10 (62.5)	46 (66.7)
PK Analysis Set[g]	36 (67.9)	10 (62.5)	46 (66.7)
qPCR PK Analysis Set	36 (67.9)	10 (62.5)	46 (66.7)
Flow Cytometry PK Analysis Set	36 (67.9)	NA[h]	36 (52.2)
PRO Analysis Set[i]	34 (64.2)	10 (62.5)	44 (63.8)

ITT = intent-to-treat; NA = not applicable; PK = pharmacokinetic; PRO = patient-reported outcome; qPCR = quantitative polymerase chain reaction.
[a] Percentages are based on number of screened subjects in each cohort.
[b] All subjects who signed informed consent.
[c] All subjects who have undergone leukapheresis.
[d] All subjects who signed informed consent, who passed all eligibility criteria at screening, and underwent leukapheresis.
[e] All subjects who received JCAR017 in accordance with drug product release specifications.
[f] All subjects who received the JCAR017 cell product in accordance with drug product release specifications, and who had a baseline assessment and at least 1 post-JCAR017 infusion disease assessment.
[g] Subjects in the JCAR017-treated Set who had both baseline and on-study PK measurements in the JCAR017-treated Set. Also broken down by availability of specific PK types.
[h] The PK assessments by flow cytometry were not conducted for Cohort 3 (at Japanese sites).
[i] All subjects who completed their baseline PRO questionnaires and have at least 1 postbaseline measurement in the JCAR017-treated Set.
Note: One subject underwent leukapheresis but was retrospectively deemed not eligible due to composite Hodgkin lymphoma/follicular lymphoma and received nonconforming product. This subject is included in the Leukapheresed population but excluded from the Enrolled and JCAR017-treated Set.
Data cutoff date: 19 Jun 2020.

Outcomes and estimation

<u>Manufacturing time</u>

Table 11: Studies 017001 and BCM-001 Cohort 1: Manufacturing and turnaround times, <u>Leukapheresed Set</u>

	017001 DLBCL Cohort (N = 345)	BCM-001 Cohort 1 (N = 45)
Time From Leukapheresis to Liso-cel Product Availability (days)[a]		
N (lots)	112[b]	35[c]
Median	24.0	29.0
Q1, Q3	22.0, 28.0	26.0, 30.0
Minimum, maximum	17, 51	24, 38
Time From Leukapheresis to Liso-cel Infusion (days)[a]		
N (lots infused)	273	36
Median	37.0	43.0
Q1, Q3	33.0, 47.0	42.0, 45.5
Minimum, maximum	27, 224	36, 107
Manufacturing failure, n/N (%)[d]	39/342 (11.4)	4/45 (8.9)

DLBCL = diffuse large B-cell lymphoma; liso-cel = lisocabtagene maraleucel; Q = quartile.
[a] Data from nonconforming product are not included in the calculation.
[b] Product availability was only available from March 2018 (N = 112 lots) (CSR 017001 Section 10.2.2.2).
[c] The product availability dates for 1 liso-cel-treated subject had not been entered in the data set before the data cutoff of 19 Jun 2020.
[d] Manufacturing failure rate was defined as the number of subjects for whom liso-cel product (conforming at time of release) could not be manufactured divided by the number of subjects who had leukapheresis and manufacturing information available. Rejected lots (ie, lots for subjects who withdrew after manufacturing was initiated but for which release testing was never completed) are excluded from the calculation.
Data cutoff date = 19 Jun 2020.

Overall Response Rate (ORR) and Complete Response Rate (CRR)

Study 017001 (data cut-off 12 Apr 2019)

The primary analysis, based on an earlier data cut-off date of 12 Apr 2019, showed that study 017001 met its prespecified primary efficacy endpoint in the PAS by rejecting the null hypothesis of ORR (per IRC assessment) ≤ 40% (p <0.0001). It also met all key secondary efficacy endpoints including CR rate in the PAS, and ORR and CR rate in chemorefractory subjects in the PAS by rejecting the respective null hypotheses.

Analyses in other datasets

ORR per IRC assessment in the Leukapheresed Set for the DLBCL Cohort (ITT set) was 60.5% (95%CI 55.1 - 65.7), and CR rate was 43.6% (95%CI 38.3 - 49.0).

Table 12. Study 017001: Overall Response rate per IRC Assessment, DLBCL Efficacy Set and DLBCL Efficacy DL2S v4 Set

Parameter	DL2S N = 169	DL1S N = 40	DL1D N = 6	DL3S N = 41	Total N = 256	DL2S v4 N = 120
Best overall response[a], n (%)						
Complete response	88 (52.1)	24 (60.0)	3 (50.0)	21 (51.2)	136 (53.1)	63 (52.5)
Partial response	37 (21.9)	3 (7.5)	1 (16.7)	9 (22.0)	50 (19.5)	27 (22.5)
Stable disease	17 (10.1)	6 (15.0)	1 (16.7)	4 (9.8)	28 (10.9)	11 (9.2)
Non-progressive disease	2 (1.2)	1 (2.5)	0	1 (2.4)	4 (1.6)	1 (0.8)
Progressive disease	17 (10.1)	4 (10.0)	1 (16.7)	6 (14.6)	28 (10.9)	11 (9.2)
Not evaluable	8 (4.7)	2 (5.0)	0	0	10 (3.9)	7 (5.8)
Overall response rate, n (%)						
CR + PR	125 (74.0)	27 (67.5)	4 (66.7)	30 (73.2)	186 (72.7)	90 (75.0)
95% CI[b]	66.7-80.4	50.9-81.4	22.3-95.7	57.1-85.8	66.8-78.0	66.3-82.5
Complete response rate, n (%)						
CR	88 (52.1)	24 (60.0)	3 (50.0)	21 (51.2)	136 (53.1)	63 (52.5)
95% CI[b]	44.3-59.8	43.3-75.1	11.8-88.2	35.1-67.1	46.8-59.4	43.2-61.7

CI = confidence interval; CLOVER = Clinical Outcomes Across Manufacturing Process Versions; CR = complete response; CSR = clinical study report; DL1D = Dose Level 1, 2 Dose; DL1S = Dose Level 1, Single Dose; DL2S = Dose Level 2, Single Dose; DL3S = Dose Level 3, Single Dose; DLBCL = diffuse large B-cell lymphoma; IRC = Independent Review Committee; PR = partial response; v4 = version 4 (proposed commercial manufacturing process).

[a] Best overall response was the best disease response recorded from the time of the final JCAR017 infusion of the first cycle until disease progression, end of study, the start of another anticancer therapy, or hematopoietic stem-cell transplantation.

[b] Two-sided 95% exact Clopper-Pearson CIs.

Data cutoff date 12 Aug 2019.

In the DLBCL Efficacy Set, the median time to first CR or PR was 0.95 months (range: 0.7 to 8.9 months), and the median time to first CR was 0.95 months (range: 0.8 to 12.5 months). In the DLBCL Efficacy DL2S v4 Set, the median time to response to first CR or PR and also to first CR was the same as in the DLBCL Efficacy Set, although the range was narrower for time to first CR (range: 0.8 to 8.9 months).

The ORR by Investigator in the DLBCL Efficacy Set was similar to that using IRC assessment (73.0% [95%CI: 67.2 - 78.4]), as was the CR rate (52.0% [95%CI: 45.6 - 58.2]).

Concordance Between IRC and Investigator Assessments in the DLBCL Efficacy Set, defined as the number of responders from both IRC and investigator assessment plus the number of non-responders from both IRC and investigator assessment, divided by the number of subjects with response assessments from both IRC and investigator assessment, was 90.2%.

Study BCM-001

Data cutoff date 19 Jun 2020

The ORR per IRC assessment in the Leukapheresed Set (ITT population) in Cohort 1 was 55.6% (95%CI 49, 70.4), and a CR rate of 31.1% (95%CI 18.2 - 46.6).

Table 13. Sensitivity Analysis of Overall Response Rate Based on IRC Assessment (Efficacy Evaluable Set)

Parameter	Cohort 1 N = 36	Cohort 3 N = 10	Overall N = 46
Best Overall Response, n (%)			
Complete Response	12 (33.3)	5 (50.0)	17 (37.0)
Partial Response	10 (27.8)	2 (20.0)	12 (26.1)
Stable Disease	8 (22.2)	0	8 (17.4)
Progressive Disease	6 (16.7)	3 (30.0)	9 (19.6)
Overall Response Rate[a]			
n (%)	22 (61.1)	7 (70.0)	29 (63.0)
95% CI[b]	43.5 - 76.9	34.8 - 93.3	47.5 - 76.8
p-value for test of hypothesis[c]	0.008	0.055	0.001
Complete Response Rate[d]			
n (%)	12 (33.3)	5 (50.0)	17 (37.0)
95% CI[b]	18.6 - 51.0	18.7 - 81.3	23.2 - 52.5

CI = confidence interval; IRC = Independent Review Committee.
[a] Overall response rate (for Cohorts 1 and 3) is defined as the proportion of subjects who achieved an objective response of partial response or better according to Lugano criteria (Cheson, 2014).
[b] Two-sided 95% CI based on exact Clopper-Pearson method.
[c] Overall response rate > 40% against the null hypothesis that the overall response rate ≤ 40%. Significance level is 1-sided alpha = 0.025.
[d] Complete response rate is defined as the proportion of subjects who achieved a best overall response of complete response.
One case was reported as nonprogressive disease per IRC because the positron emission tomography scan was not performed and IRC assessment per computed tomography was stable disease.
Data cutoff date: 19 Jun 2020.

The ORR per investigator assessment in Cohort 1 was 66.7% (95%CI 49, 81.4), and the CR rate was 36.1% (95%CI 20.8 - 53.8). Concordance Between IRC and Investigator Assessments, defined as the number of responders from both IRC and investigator assessment plus the number of non-responders from both IRC and investigator assessment, divided by the number of subjects with responses from both IRC and investigator assessment, was 96.3%.

Duration of Response (DOR), Progression-free Survival and Event-free Survival

Study 017001 (data cut-off 12 Aug 2019)

- DOR

The median DOR follow-up for responders per IRC assessment (n=186) in the DLBCL Efficacy Set was 16.4 months. At all timepoints, the most common reasons for censoring of responders were ongoing or completed the study. Among non-responders (n=70), all but 5 had progressed, died, or withdrawn from the study. In the DLBCL Efficacy DL2S v4 Set, for responders per IRC assessment (n=90), the median DOR follow-up was shorter (9.1 months).

In the DLBCL Efficacy Set, the median DOR by IRC was 16.8 months (95%CI 7.9-NR, see Table below).

Table 14. Study 017001: Duration of Responses per IRC Assessment for Responders, DLBCL Efficacy Set and DLBCL Efficacy DL2S v4 Set

Parameter	DL2S N = 169	DL1S N = 40	DL1D N = 6	DL3S N = 41	Total N = 256	DL2S v4 N = 120
Subjects achieved CR or PR, n	125	27	4	30	186	90
Progression or death, n (%) [a]	62 (49.6)	12 (44.4)	1 (25.0)	15 (50.0)	90 (48.4)	46 (51.1)
Progression	49 (39.2)	11 (40.7)	1 (25.0)	14 (46.7)	75 (40.3)	37 (41.1)
Death	13 (10.4)	1 (3.7)	0	1 (3.3)	15 (8.1)	9 (10.0)
Censored, n (%) [a]	63 (50.4)	15 (55.6)	3 (75.0)	15 (50.0)	96 (51.6)	44 (48.9)
Ongoing	52 (41.6)	0	0	15 (50.0)	67 (36.0)	43 (47.8)
Completed the study	8 (6.4)	14 (51.9)	3 (75.0)	0	25 (13.4)	0
Discontinued the study	2 (1.6)	1 (3.7)	0	0	3 (1.6)	1 (1.1)
Received JCAR017 retreatment	1 (0.8)	0	0	0	1 (0.5)	0
Duration of response (months)						
Median, 95% CI [b]	13.3, 6.0-NR	NR, 3.7-NR	NR, 0.9-NR	7.3, 2.4-NR	16.8, 7.9-NR	9.1, 4.1-NR
Q1, Q3	2.1, NR	2.0, NR	NR, NR	2.2, NR	2.1, NR	2.1, NR
Min, Max	0.0, 23.5	0.0, 27.4	0.9, 23.0	0.0+, 11.3+	0.0+, 27.4	0.0, 19.9+

Parameter	DL2S N = 169	DL1S N = 40	DL1D N = 6	DL3S N = 41	Total N = 256	DL2S v4 N = 120
Probability of continued response post-initial response, (%)						
6 months	58.7	61.5	75.0	52.6	58.6	56.1
95% CI [b]	49.3-66.9	40.3-77.1	12.8-96.1	32.4-69.3	51.0-65.5	45.0-65.8
≥ 12 months	51.4	57.4	75.0	NR	51.5	48.4
95% CI [b]	42.0-60.0	36.4-73.8	12.8-96.1	NR-NR	43.7-58.7	37.3-58.6
≥ 18 months	47.7	57.4	75.0	NR	49.2	40.3
95% CI [b]	37.6-57.1	36.4-73.8	12.8-96.1	NR-NR	41.1-56.7	26.5-53.7
≥ 24 months	NR	53.3	NR	NR	43.6	NR
95% CI [b]	NR-NR	32.6-70.3	NR-NR	NR-NR	34.4-52.5	NR-NR
Follow-up, months						
Median, 95% CI [c]	14.5, 11.4-16.8	23.3, 22.8-23.5	23.0, 23.0-23.0	8.1, 7.1-10.6	16.4, 11.4-17.1	11.5, 11.1-16.4
Min, Max	0.0, 23.5	0.0, 27.4	0.9, 23.0	0.0+, 11.3+	0.0+, 27.4	0.0, 19.9+

CI = confidence interval; CR = complete response; DL1D = Dose Level 1, 2 Dose; DL1S = Dose Level 1, Single Dose; DL2S = Dose Level 2, Single Dose; DL3S = Dose Level 3, Single Dose; DLBCL = diffuse large B-cell lymphoma; EMA = European Medicines Agency; IRC = Independent Review Committee; Max = maximum; Min = minimum; NR = not reached; PR = partial response; Q1 = first quartile; Q3 = third quartile; v4 = version 4 (proposed commercial manufacturing process).

[a] Denominator is number of subjects who achieved CR or PR.

[b] Kaplan-Meier method was used to obtain 2-sided 95% CIs.

[c] Reverse Kaplan-Meier method was used to obtain the median follow-up and its 95% CIs.

Note: EMA censoring rules were applied.

+ At least 1 subject is still ongoing in this group.

Data cutoff date 12 Aug 2019.

Analysis of DOR by IRC using FDA censoring rules showed results consistent with the analysis using EMA censoring rules.

Median DOR by Investigator assessment using EMA censoring rules in the DLBCL Efficacy Set and DLBCL Efficacy DL2S v4 Set was shorter (9.2 months [95%CI 5.1 - NR] and 10.6 months [95%CI 5.3 - NR], respectively) when compared with median DOR based on IRC assessment using EMA censoring rules. This, however, was consistent with analysis of DOR in the DLBCL Efficacy Set based on investigator assessment using FDA censoring rules, where the median DOR was 10.4 months (95%CI: 5.1 - NR).

Analysis of DOR by BOR by Investigator in the DLBCL Efficacy Set and DLBCL Efficacy DL2S v4 Set using EMA censoring rules also yielded results that were similar compared to those based on IRC assessment using EMA censoring rules.

Median DOR per IRC assessment (using EMA censoring rules) in the Leukapheresed Set for the DLBCL Cohort (ITT set) was 13.3 months (95%CI 6.6 - 21.1), with a median DOR follow-up of 16.7 months. After initial response, the probability of continued response at 6 and 12 months was 58.1% (95%CI 50.9 - 64.6) and 50.2% (95%CI 43.0 - 57.0), respectively.

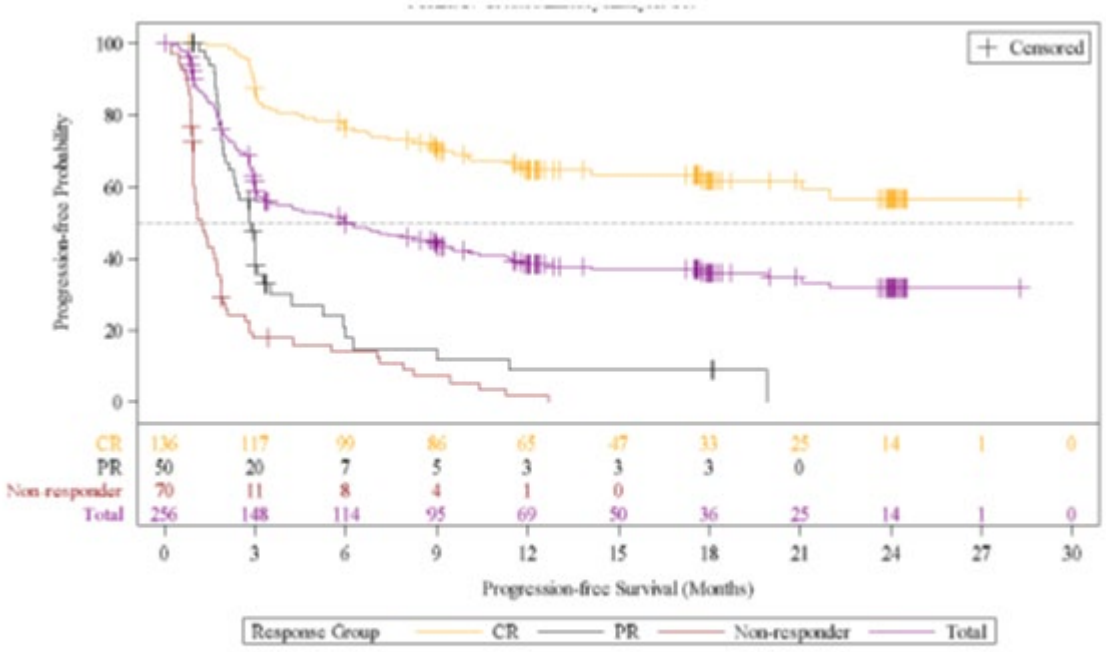
- PFS

In the DLBCL Efficacy Set, subjects had a median PFS by IRC of 6.0 months (95%CI: 3.3 - 9.0), with a median PFS follow-up of 17.5 months. The estimated PFS rate at 6 and 12 months was 50.0% (95%CI: 43.6 - 56.1) and 38.4% (95%CI: 32.1- 44.6), respectively.

In the DLBCL Efficacy DL2S v4 Set, the median PFS was similar (5.9 months [95%CI: 3.0 - 10.0]), but the median PFS follow-up was shorter (12.3 months); the estimated PFS rates at 6 and 12 months were also similar.

PFS per IRC assessment by BOR is summarised in figure below.

Figure 9. Study 017001: Progression-Free Survival per IRC Assessment by Best Overall Response, DLBCL Efficacy Set



CR = complete response; DLBCL = diffuse large B-cell lymphoma; EMA = European Medicines Agency; IRC = Independent Review Committee; PR = partial response

Notes: Median follow-up time was 17.6 months for CR and 18.1 months for PR (Table 18).
EMA censoring rules were applied.

Data cutoff date 12 Aug 2019.

Analysis of PFS in the DLBCL Efficacy Set and DLBCL Efficacy DL2S v4 Set based on IRC assessment using FDA censoring rules showed results consistent with the analysis using EMA censoring rules.

Median PFS by investigator assessment using EMA censoring rules in the DLBCL Efficacy Set and DLBCL Efficacy DL2S v4 Set was shorter (3.9 months and 3.5 months, respectively) when compared with IRC assessment using EMA censoring rules, as were the estimated PFS rates at 6 months (42.5% and 44.1%, respectively) and 12 months (34.8% and 36.9%, respectively). Median PFS based on investigator assessment using FDA censoring rules in the DLBCL Efficacy Set was also shorter (4.1 months) compared with IRC assessment using EMA censoring rules, as were estimated PFS rates at 6 months (43.4%) and 12 months (36.3%). Analysis of PFS by BOR in the DLBCL Efficacy Set and DLBCL Efficacy DL2S v4 Set based on investigator assessment using EMA censoring rules also yielded results that were similar to those based on IRC assessment using EMA censoring rules.

Median PFS by IRC (using EMA censoring rules) in the Leukapheresed Set for the DLBCL Cohort (ITT set) was 4.8 months (95%CI 4.3 - 6.6), with a median PFS follow-up of 19.0 months. The PFS rate at 6 and 12 months was 45.9% (95%CI 40.4 - 51.3) and 35.1% (95%CI 29.8 - 40.4).

The median PFS ratio, defined as the ratio of PFS on the most recent line of therapy prior to JCAR017 to the PFS on JCAR017 by Investigator assessment was 0.65 in the DLBCL Efficacy Set and 0.66 in the DLBCL Efficacy DL2S using EMA censoring rules. The PFS ratio using FDA censoring rules for the DLBCL Efficacy Set was consistent with that using EMA censoring rules.

Study BCM-001 (data cut-off 19 Jun 2020)

- DOR

Table 15. Duration of Response Based on IRC Assessment Using EMA Censoring Criteria (JCAR017-treated Set

Parameter	Cohort 1 N = 36	Cohort 3 N = 10	Overall N = 46
Time to Event, n (%)			
Number of Subjects with Event	14 (38.9)	4 (40.0)	18 (39.1)
Progressive Disease	13 (36.1)	4 (40.0)	17 (37.0)
Death	1 (2.8)	0	1 (2.2)
Censored	8 (22.2)	3 (30.0)	11 (23.9)
No Documented Progressive Disease and No Death	8 (22.2)	3 (30.0)	11 (23.9)
Duration of Response (Months)			
Median (95% CI)[a]	3.50 (2.20, NE)	9.07 (2.10, NE)	4.30 (2.23, 9.23)
Q1, Q3[a]	2.20, NE	2.14, NE	2.20, NE
Min, Max	1.08, 16.95	2.10, 12.06	1.08, 16.95
Continued Response Rate, % (SE)			
1 Month	100.0 (0.00)	100.0 (0.00)	100.0 (0.00)
3 Months	54.5 (10.62)	71.4 (17.07)	58.6 (9.15)
6 Months	40.9 (10.48)	71.4 (17.07)	48.3 (9.28)
9 Months	40.9 (10.48)	57.1 (18.70)	43.4 (9.52)
12 Months	27.3 (13.15)	38.1 (19.93)	29.0 (10.50)
18 Months	NR (NR)	NR (NR)	NR (NR)
24 Months	NR (NR)	NR (NR)	NR (NR)

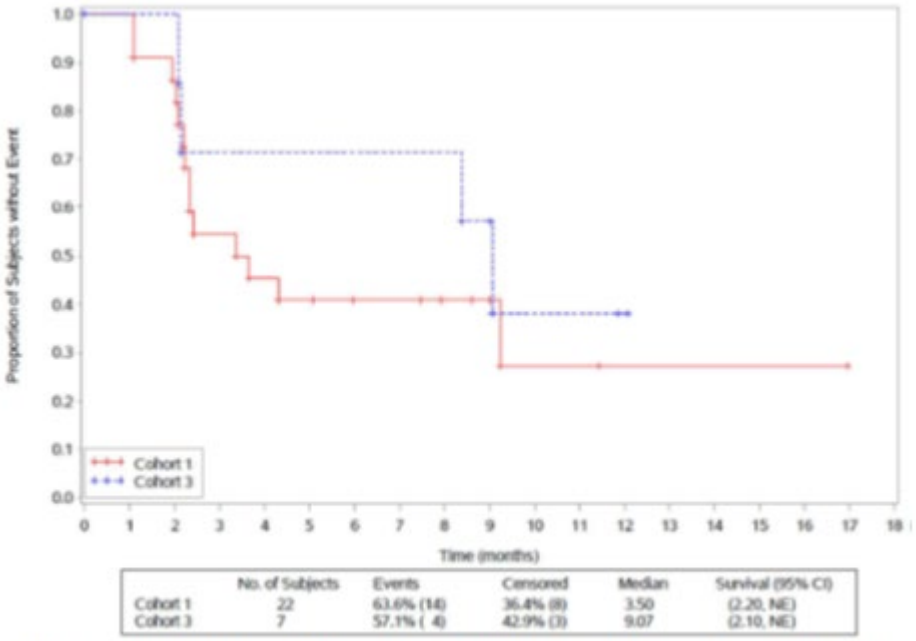
CI = confidence interval; EMA = European Medicines Agency; IRC = Independent Review Committee; Max = maximum; Min = minimum; NE = not evaluable; NR = not reached; Q1 = quartile 1; Q3 = quartile 3; SE = standard error.

[a] Median, Q1, Q3 are estimated from Kaplan-Meier product-limit estimates.

Note: Duration of response is defined as the interval from the first documentation of response to progressive disease or death from any cause, whichever occurs first.

Data cutoff date: 19 Jun 2020.

Figure 10, Kaplan-Meier Plot of Duration of Response Based on IRC Assessment Using EMA Criteria (JCAR017-treated Set)



	No. of Subjects	Events	Censored	Median	Survival (95% CI)
Cohort 1	22	63.6% (14)	36.4% (8)	3.50	(2.20, NE)
Cohort 3	7	57.1% (4)	42.9% (3)	9.07	(2.10, NE)

CI = confidence interval; EMA = European Medicines Agency; IRC = Independent Review Committee; NE = not evaluable.
Data cutoff date: 19 Jun 2020.

In Cohort 1 (N = 36), the KM estimate for the median DOR was 3.98 months (95% CI: 2.20 to NE; range: 0.03 to 16.95 months). The continued response rate at 1 month was 100.0%, at 3 months was 60.0% (SE ± 10.95), at 6 and 9 months was 45.0% (SE ± 11.12), and at 12 months was 30.0% (SE ± 14.32).

Analysis of DOR based on investigator assessment using EMA censoring rules in the JCAR017-treated Set yielded similar results. The median DOR was 4.47 months (95%CI 2.14, 9.07), with a median follow-up of 9.03 months.

Median DOR per IRC assessment using EMA censoring rules in the Leukapheresed Set was similar: 5.98 months (95%CI 2.23, 9.07).

- PFS

The median PFS per IRC Assessment using EMA censoring rules in Cohort 1 was 3.25 months (95%CI 2.89 – 5.36), with a median PFS follow-up of 8.13 months (see Table and Figure below).

Table 16. Progression-free Survival Based on IRC Assessment Using EMA Criteria (JCAR017-treated Set)

Parameter	Cohort 1 N = 36	Cohort 3 N = 10	Overall N = 46
Time to Event, n (%)			
Number of Subjects with Event	26 (72.2)	7 (70.0)	33 (71.7)
Progressive Disease	23 (63.9)	7 (70.0)	30 (65.2)
Death	3 (8.3)	0	3 (6.5)
Censored	10 (27.8)	3 (30.0)	13 (28.3)
No Documented PD and No Death	10 (27.8)	3 (30.0)	13 (28.3)
Progression-free Survival (Months)			
Median (95% CI)[a]	3.25 (2.89, 5.36)	6.34 (0.62, NE)	3.25 (2.99, 5.39)
Q1, Q3[a]	2.00, 10.15	1.05, NE	2.00, 10.02
Min, Max	0.23, 17.97	0.62, 12.98	0.23, 17.97
Progression-free Survival Rate, % (SE)			
1 Month	88.9 (5.24)	80.0 (12.65)	87.0 (4.97)
3 Months	56.8 (8.45)	70.0 (14.49)	60.0 (7.34)
6 Months	29.9 (7.89)	50.0 (15.81)	34.6 (7.19)
9 Months	26.6 (7.68)	50.0 (15.81)	32.1 (7.09)
12 Months	17.7 (8.87)	26.7 (15.01)	19.3 (7.29)
18 Months	NR (NR)	NR (NR)	NR (NR)
24 Months	NR (NR)	NR (NR)	NR (NR)

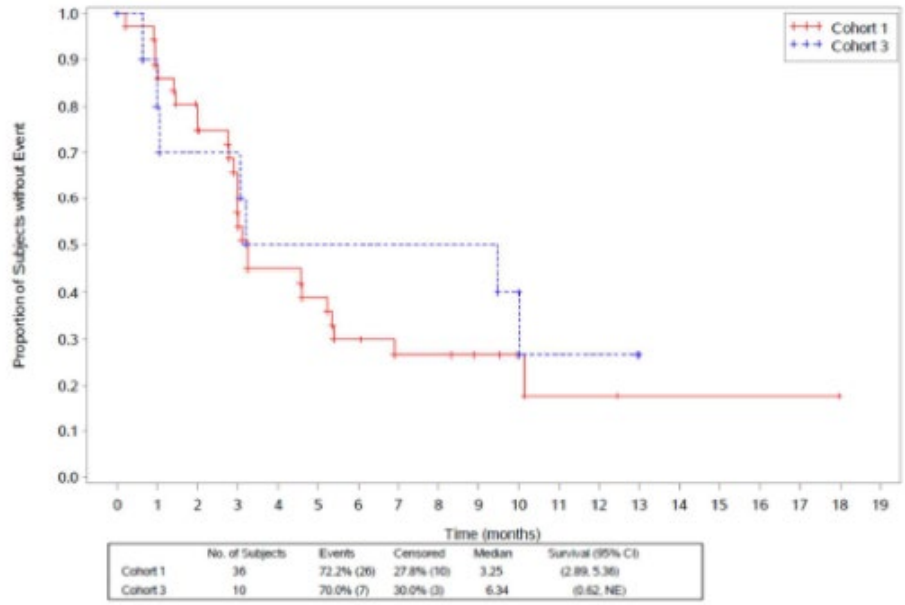
CI = confidence interval; EMA = European Medicines Agency; IRC = Independent Review Committee; Max = maximum; Min = minimum; NE = not evaluable; NR = not reached; PD = progressive disease; Q1 = quartile 1; Q3 = quartile 3; SE = standard error.

[a] Median, Q1, Q3 are estimated from Kaplan-Meier product-limit estimates.

Note: Progression-free survival is defined as the interval from the date of JCAR017 infusion to progressive disease or death due to any cause, whichever occurs first.

Data cutoff date: 19 Jun 2020.

Figure 11. Kaplan-Meier Plot of Progression-free Survival Based on IRC Assessemnt Using EMA Critiria (JCAR017-treated Set)



CI = confidence interval; EMA = European Medicines Agency; IRC = Independent Review Committee; NE = not evaluable.
Data cutoff date: 19 Jun 2020.

The median PFS by Investigator in Cohort 1 using the EMA censoring rules was shorter at 2.99 months (95%CI 2.76, 5.22).

Median PFS per IRC assessment using EMA censoring rules in the Leukapheresed Set (ITT) in Cohort 1 was 4. 53 months (95%CI 4.17 - 5.95).

-EFS

The median time to event for EFS per IRC Assessment in Cohort 1 was 3.07 months (95%CI 2.60, 6.90; see Table and Figure below).

Table 17. Event-free Survival Based on IRC Assessment Using EMA Criteria

Parameter	Cohort 1 N = 36	Cohort 3 N = 10	Overall N = 46
Time to Event, n (%)			
Number of Subjects with Event	28 (77.8)	7 (70.0)	35 (76.1)
Progressive Disease	21 (58.3)	7 (70.0)	28 (60.9)
Received a New Anticancer Therapy	5 (13.9)	0	5 (10.9)
Death	2 (5.6)	0	2 (4.3)
Censored	8 (22.2)	3 (30.0)	11 (23.9)
No Documented PD, No Death, and No New Anticancer Therapy	8 (22.2)	3 (30.0)	11 (23.9)

Parameter	Cohort 1 N = 36	Cohort 3 N = 10	Overall N = 46
Event-free Survival (Months)			
Median (95% CI)[a]	3.07 (2.60, 4.60)	6.34 (0.62, NE)	3.16 (2.76, 5.22)
Q1, Q3[a]	2.00, 6.90	1.05, NE	2.00, 10.02
Min, Max	0.23, 17.97	0.62, 12.98	0.23, 17.97
Event-free Survival Rate, % (SE)			
1 Month	88.9 (5.24)	80.0 (12.65)	87.0 (4.97)
3 Months	52.8 (8.32)	70.0 (14.49)	56.5 (7.31)
6 Months	27.8 (7.47)	50.0 (15.81)	32.6 (6.91)
9 Months	24.7 (7.25)	50.0 (15.81)	30.3 (6.80)
12 Months	16.5 (8.28)	26.7 (15.01)	18.2 (6.91)
18 Months	NR (NR)	NR (NR)	NR (NR)
24 Months	NR (NR)	NR (NR)	NR (NR)

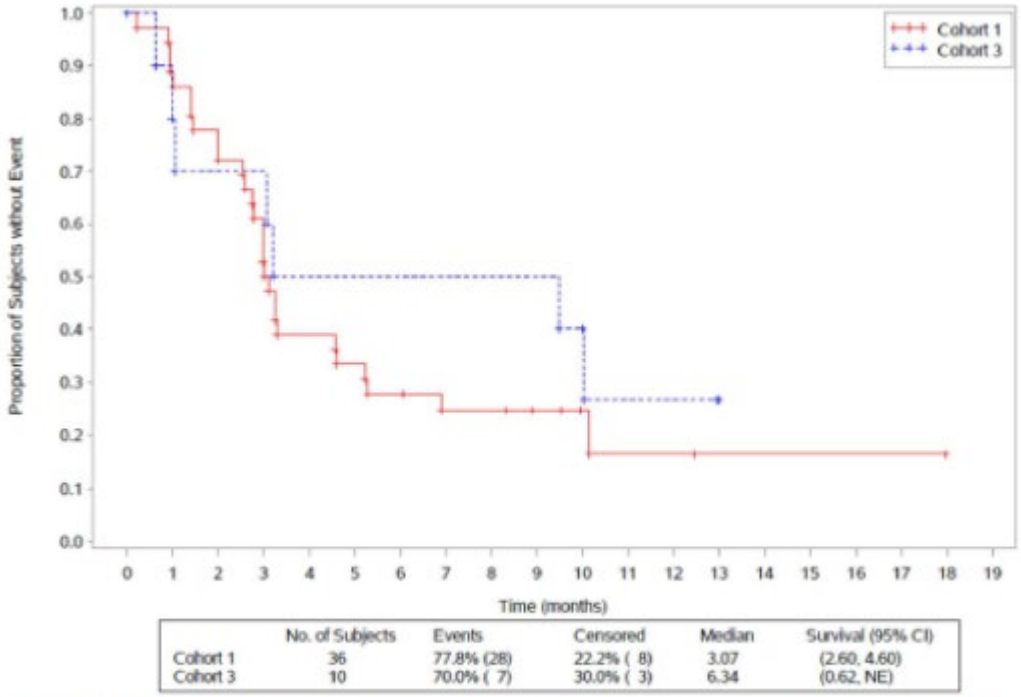
CI = confidence interval; EMA = European Medicines Agency; IRC = Independent Review Committee; Max = maximum; Min = minimum; NE = not evaluable; NR = not reached; Q1 = quartile 1; Q3 = quartile 3; SE = standard error.

[a] Median, Q1, Q3 are estimated from Kaplan-Meier product-limit estimates.

Note: Event-free survival is defined as the interval from the date of JCAR017 infusion to the earliest of the following events: death from any cause, progressive disease, or starting a new anticancer therapy.

Data cutoff date: 19 Jun 2020.

Figure 12. Kaplan-Meier of Event-free Survival based on IRC Assessment Using EMA criteria (JCAR017-treated Set)



	No. of Subjects	Events	Censored	Median	Survival (95% CI)
Cohort 1	36	77.8% (28)	22.2% (8)	3.07	(2.60, 4.60)
Cohort 3	10	70.0% (7)	30.0% (3)	6.34	(0.62, NE)

CI = confidence interval; EMA = European Medicines Agency; IRC = Independent Review Committee; NE = not evaluable.
Data cutoff date: 19 Jun 2020.

Investigator-assessed median EFS using EMA criteria in Cohort 1 was similar: 2.99 months (95%CI 2.60, 5.22).

The IRC-assessed median EFS using EMA criteria in Cohort 1 (Leukapheresed set) was 4.47 months (95%CI 3.94, 4.86).

Overall survival (OS)

Study 017001 (data cut-off date 12 Aug 2019)

In the DLBCL Efficacy Set, median OS was 21.1 months, with a median survival follow-up of 17.5 months (see Table below).

Table 18. Study 017001: Overall Survival, DLBCL Efficacy Set and DLBCL Efficacy DL2S v4 Set

Parameter	DL2S N = 169	DL1S N = 40	DL1D N = 6	DL3S N = 41	Total N = 256	DL2S v4 N = 120
Alive, n (%)	87 (51.5)	21 (52.5)	3 (50.0)	29 (70.7)	140 (54.7)	65 (54.2)
Death, n (%)	82 (48.5)	19 (47.5)	3 (50.0)	12 (29.3)	116 (45.3)	55 (45.8)
OS (months)						
Median, 95% CI [a]	19.9, 11.3-NR	NR, 6.8-NR	NR, 1.6-NR	NR, 10.3-NR	21.1, 13.3-NR	17.1, 10.0-NR
Q1, Q3	5.5, NR	5.1, NR	7.1, NR	8.2, 10.3	5.9, NR	5.4, NR
Min, Max	0.2, 33.9+	0.6, 42.0+	1.6, 36.3+	1.2+, 14.5+	0.2, 42.0+	0.2, 20.9+
Probability of OS, %						
≥ 6 months	72.6	72.1	83.3	84.7	74.7	69.8
95% CI [a]	65.2-78.7	55.3-83.5	27.3-97.5	69.0, 92.8	68.9, 79.6	60.6-77.2
≥ 12 months	56.8	59.0	50.0	51.3	57.9	55.9
95% CI [a]	49.0-64.0	42.0-72.6	11.1-80.4	22.0-74.5	51.3-63.8	46.4-64.3
≥ 18 months	50.7	56.3	50.0	NR	52.9	49.5
95% CI [a]	42.3-58.5	39.4-70.2	11.1-80.4	NR-NR	46.0-59.4	38.7-59.5
≥ 24 months	37.7	51.0	50.0	NR	44.9	NR
95% CI [a]	25.3-50.0	34.4-65.4	11.1-80.4	NR-NR	36.5-52.9	NR-NR
Follow-up (months)						
Median 95% CI [b]	17.5, 13.4-17.8	24.5, 24.1-34.5	31.6, 31.0-36.3	9.2, 8.8-9.7	17.5, 12.9-17.8	12.4, 12.1-14.3
Min, Max	0.2, 33.9+	0.6, 42.0+	1.6, 36.3+	1.2+, 14.5+	0.2, 42.0+	0.2, 20.9+

CI = confidence interval; CLOVER = Clinical Outcomes Across Manufacturing Process Versions; CSR = clinical study report; DL1D = Dose Level 1, 2 Dose; DL1S = Dose Level 1, Single Dose; DL2S = Dose Level 2, Single Dose; DL3S = Dose Level 3, Single Dose; DLBCL = diffuse large B-cell lymphoma; Max = maximum; Min = minimum; NR = not reached; OS = overall survival; Q1 = first quartile; Q3 = third quartile; v4 = version 4 (proposed commercial manufacturing process).

[a] Kaplan-Meier method was used to obtain 2-sided 95% CIs.

[b] Reverse Kaplan-Meier method was used to obtain the median follow-up and its 95% CIs.

Note: OS was calculated from the day of the first JCAR017 infusion. The OS analysis included all available survival information, including long-term follow-up data from Study GC-LTFU-001. No censoring was done in the case of hematopoietic stem-cell transplantation.

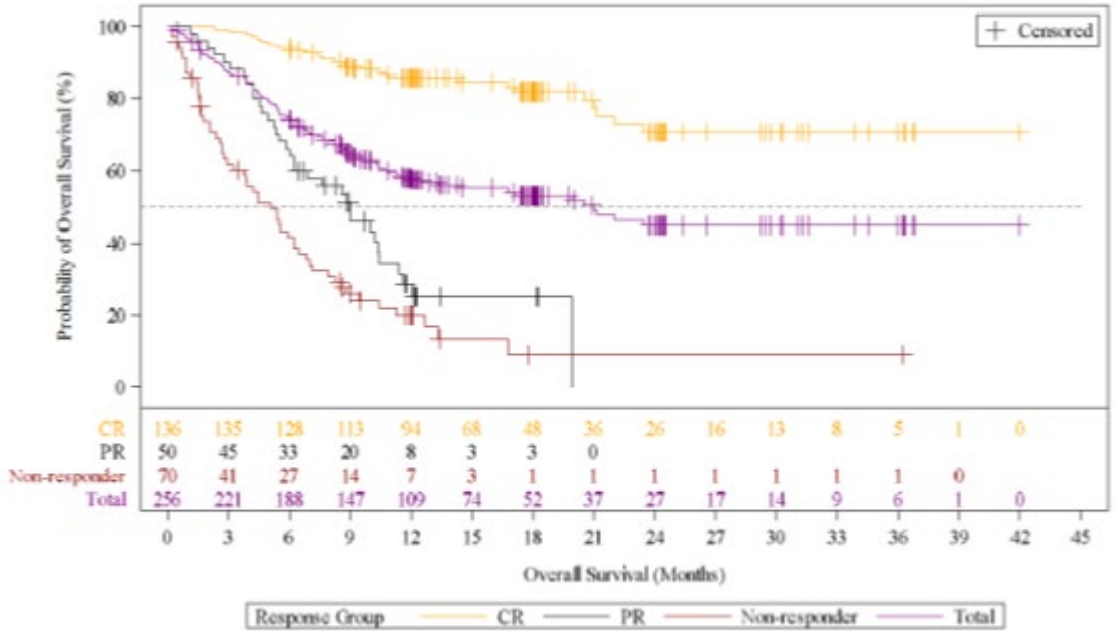
+ At least 1 subject is still alive in this group.

Data cutoff date 12 Aug 2019.

In the DLBCL Efficacy DL2S v4 Set, subjects had a shorter median OS of 17.1 months, with a shorter median survival follow-up (12.4 months).

Among subjects achieving a BOR of CR in the DLBCL Efficacy Set, the median OS was NR (95%CI NR - NR), whereas among subjects achieving PR, the median OS was 9.0 months (95%CI 6.0 - 10.4), with a plateau in the OS curve for subjects with CR (see Figure below).

Figure 13. Study 017001: Overall Survival by Best Overall Response, DLBCL Efficacy Set



CR = complete response; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; PR = partial response.
Note: Median follow-up time was 17.7 months for CR and 12.1 months for PR (Table 20).
Data cutoff date 12 Aug 2019

Results from the analysis of OS by BOR in the DLBCL Efficacy DL2S v4 Set were in line with those in the DLBCL Efficacy Set, although the median OS in subjects achieving PR was shorter at 6.0 months (95%CI 4.6 - 10.0).

Median OS was in the leukapheresed set 14.0 months (95%CI 11.1 - 21.1), with a median OS follow-up of 18.8 months. The estimated survival rates at 6 and 12 months were 70.2% (95%CI 65.0 - 74.8) and 54.0% (95%CI 48.5 - 59.2), respectively. The probability of survival at 12 months was similar to that in the DLBCL Efficacy Set, which was 57.9% (95%CI 51.3 - 63.8).

Study BCM-001 (data cutoff 19 Jun 2020)

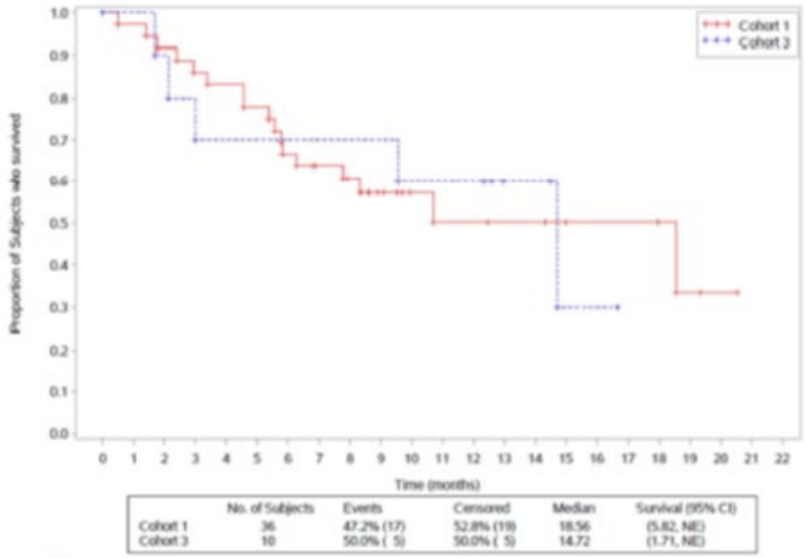
The median OS in Cohort 1 was 18.56 months (95%CI 5.82, NE), with a median follow-up for OS of 9.53 months (see Table and Figure below).

Table 19. Overall Survival (JCAR017-treated Set)

Parameter	Cohort 1 N = 36	Cohort 3 N = 10	Overall N = 46
Time to Event, n (%)			
Number of Deaths	17 (47.2)	5 (50.0)	22 (47.8)
Cause of Death	17 (47.2)	5 (50.0)	22 (47.8)
Multiple Organ Failure	0	3 (30.0)	3 (6.5)
Progressive Disease	15 (41.7)	1 (10.0)	16 (34.8)
Respiratory Failure	1 (2.8)	0	1 (2.2)
Sepsis *Candida albicans*	1 (2.8)	0	1 (2.2)
Unknown	0	1 (10.0)	1 (2.2)
Number Censored	19 (52.8)	5 (50.0)	24 (52.2)
Overall Survival (Months)			
Median (95% CI)[a]	18.56 (5.82 - NE)	14.72 (1.71 - NE)	14.72 (6.28 - NE)
Q1, Q3[a]	5.48, NE	3.02, NE	5.36, NE
Min, Max	0.5, 20.5	1.7, 16.7	0.5, 20.5
Overall Survival Rate, % (SE)			
1 Month	97.2 (2.74)	100.0 (0.00)	97.8 (2.15)
3 Months	86.1 (5.76)	80.0 (12.65)	84.8 (5.30)
6 Months	66.7 (7.86)	70.0 (14.49)	67.4 (6.91)
9 Months	57.3 (8.42)	70.0 (14.49)	60.3 (7.31)
12 Months	50.2 (9.96)	60.0 (15.49)	52.7 (8.14)
18 Months	50.2 (9.96)	NR (NR)	45.2 (9.86)
24 Months	NR (NR)	NR (NR)	NR (NR)
Follow-up (Months)			
Median[a]	9.53	13.72	12.35
95% CI[a]	8.57 - 14.32	12.35 - 16.66	8.90 - 14.46
Min, Max	0.49, 20.53	1.71, 16.66	0.49, 20.53

CI = confidence interval; Max = maximum; Min = minimum; NE = not evaluable; NR = not reported; Q1 = quartile 1; Q3 = quartile 3; SE = standard error.
[a] Median, Q1, Q3 are estimated from Kaplan-Meier product-limit estimates.
Note: Overall survival is defined as the interval from the date of JCAR017 infusion to the date of death due to any reason.
Data cutoff date: 19 Jun 2020.

Figure 14. Kaplan-Meier Plot of Overall Survival (KCAR017-treated Set)



CI = confidence interval; NE = not evaluable.
Data cutoff date: 19 Jun 2020.

Median OS in Cohort 1 in the Leukapheresed Set was 12.06 months (95%CI 7.29 - NE), with a shorter median survival follow-up of 11.01 months. The survival rate at 1 month was 100.0%, at 3 months was 93.3% (SE ± 3.72), at 6 months was 75.6% (SE ± 6.41), at 9 months was 57.8% (SE ± 7.36), at 12 months was 52.3% (SE ± 7.62), and at 18 months was 46.5% (SE ± 8.71).

Study 017001 updated analysis (data cut-off 19 Jun 2020)

In the updated efficacy analysis in Study 017001 with approximately 10 additional months of follow-up data (median follow-up for OS in Leukapheresed Set increased from 18.8 months to 25.4 months), efficacy outcomes in the ITT and JCAR017-treated sets considering subjects who received JCAR017 at DL2S and DL2Sv4 are summarised in Tables and Figures below:

Table 20. Study 017001 (DLBCL Cohort) – Summary of Efficacy Results per IRC Assessment, Leukapheresed Set and Subjects Receiving Nonconforming Product, Subjects Assigned to DL2S

Parameter	Leukapheresed Set		Subjects Receiving Nonconforming Product
	DL2S all versions (N = 228)	DL2Sv4 (N = 164)	DL2S all versions (N = 16)
Overall response rate, n (%)			
Complete + Partial Response	139 (61.0)	102 (62.2)	8 (50.0)
95% CI [a]	54.3-67.3	NA	24.7-75.3
Complete response rate, n (%)			
Complete Response	95 (41.7)	70 (42.7)	4 (25.0)
95% CI [a]	35.2-48.4	NA	7.3-52.4
Duration of response[b] (months)			
Median	13.3	8.7	7.5
95% CI [c]	6.0-NR	4.4-23.1	2.1-NR
Q1, Q3	2.1, 26.1	2.1, 26.1	3.4, NR
Min, Max	0.0, 26.3	0.0, 26.3	2.1, 23.6
Progression-free survival[b] (months)			
Median	5.0	4.5	3.9
95% CI[c]	4.3-7.3	4.1-7.1	1.1-9.2
Q1, Q3	2.8, 28.1	2.8, 25.1	1.8, 9.2
Min, Max	0.0, 28.6	0.0, 28.6	0.3, 24.5
Overall survival (months)			
Median	13.2	12.4	14.8
95% CI[c]	9.8-22.6	9.2-28.6	4.6-29.9[d]
Q1, Q3	4.3, 46.6	4.6, NR	4.6, NR[d]
Min, Max	0.3, 46.6	0.3, 32.0+	0.1, 42.8+[d]

CI = confidence interval; DL2S = Dose Level 2, Single Dose; DL2Sv4 = Dose Level 2, Single Dose, manufacturing process version 4; EMA = European Medicines Agency; IRC = Independent Review Committee; Max = maximum; Min = minimum; NR = not reached; OS = overall survival; Q = quartile.

[a] 2-sided 95% exact Clopper-Pearson CIs.

[b] Using EMA censoring rules

[c] Kaplan-Meier (KM) method was used to obtain 2-sided 95% CIs.

[d] OS data for subjects assigned to DL2S were not available; data in the table represent the summary of OS for all 25 subjects who received nonconforming product.

Data cutoff date: 19 Jun 2020

Table 21. Study 017001 (DLBCL Cohort) – Overall Response Rate per IRC Assessment, JCAR017-Treated Efficacy Analysis Set

Parameter	Dose Level 2 (all versions)		Dose Level 2 (version 4)	
	12 Aug 2019 (N = 169)	19 Jun 2020 (N = 170)	12 Aug 2019 (N = 120)	19 Jun 2020 (N = 121)
Overall response rate, n (%)				
Complete + partial response	125 (74.0)	127 (74.7)	90 (75.0)	92 (76.0)
95% CI [a]	66.7-80.4	67.5-81.0	66.3-82.5	67.4-83.3
Complete response rate, n (%)				
Complete response	88 (52.1)	89 (52.4)	63 (52.5)	65 (53.7)
95% CI [a]	44.3-59.8	44.6-60.1	43.2-61.7	44.4-62.8
Duration of response[b] (months)				
Median	13.3	19.0	9.1	11.1
95% CI[c]	6.0-NR	6.0-NR	4.1-NR	4.4-NR
Q1, Q3	2.1, NR	2.1, 26.1	2.1, NR	2.1, 26.1
Min, Max	0.0, 23.5	0.0, 26.3	0.0, 19.9+	1.1, 26.3

Parameter	Dose Level 2 (all versions)		Dose Level 2 (version 4)	
	12 Aug 2019 (N = 169)	19 Jun 2020 (N = 170)	12 Aug 2019 (N = 120)	19 Jun 2020 (N = 121)
Progression-free survival[b] (months)				
Median	6.7	6.8	5.9	6.0
95% CI[c]	3.1-10.4	3.2-11.3	3.0-10.0	3.0-11.4
Q1, Q3	2.0, NR	2.0, 27.3	2.0, NR	2.0, 27.3
Min, Max	0.0+, 24.4	0.2, 27.3	0.0+, 20.9+	0.2, 27.3
Overall survival (months)				
Median	19.9	21.4	17.1	27.3
95% CI[c]	11.3-NR	11.4-45.2	10.0-NR	10.0-NR
Q1, Q3	5.5, NR	5.5, 45.2	5.4, NR	5.5, NR
Min, Max	0.2, 33.9+	0.2, 45.2	0.2, 20.9+	0.2, 30.3+

CI = confidence interval; CR = complete response; DL2S = Dose Level 2, Single Dose; DL2Sv4 = Dose Level 2, Single Dose, manufacturing process version 4; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EMA = European Medicines Agency; IRC = Independent Review Committee; Max = maximum; Min = minimum; NR = not reached; ORR = overall response rate; PFS = progression-free survival; Q = quartile

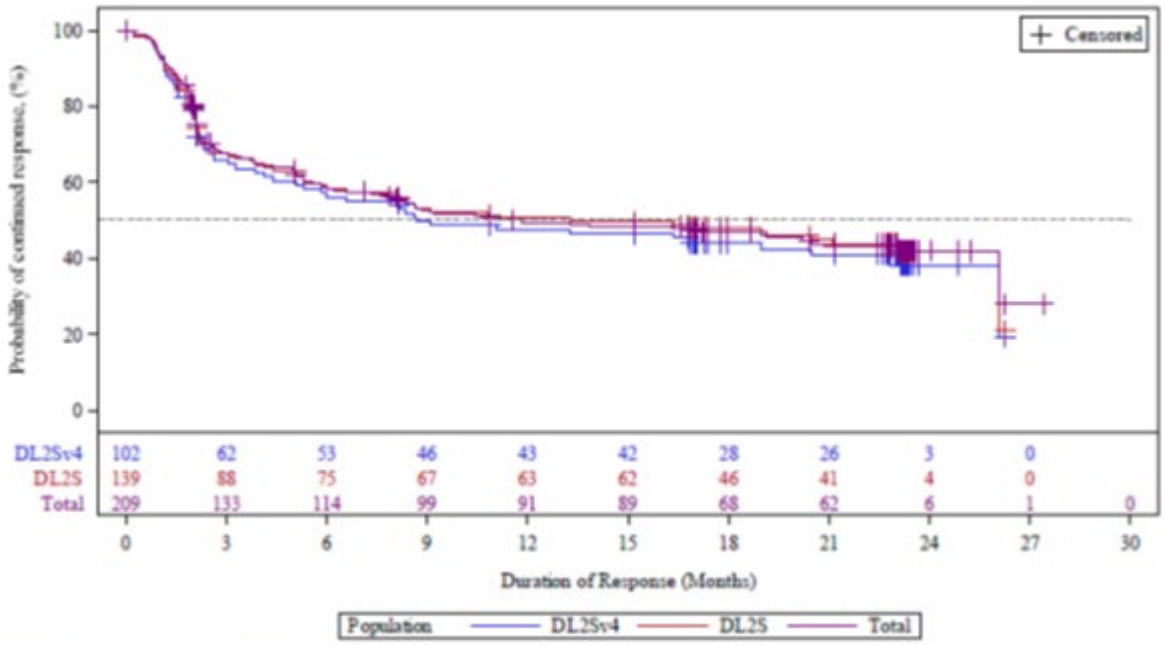
[a] 2-sided 95% exact Clopper-Pearson CIs.

[b] Using EMA censoring rules

[c] Kaplan-Meier (KM) method was used to obtain 2-sided 95% CIs.

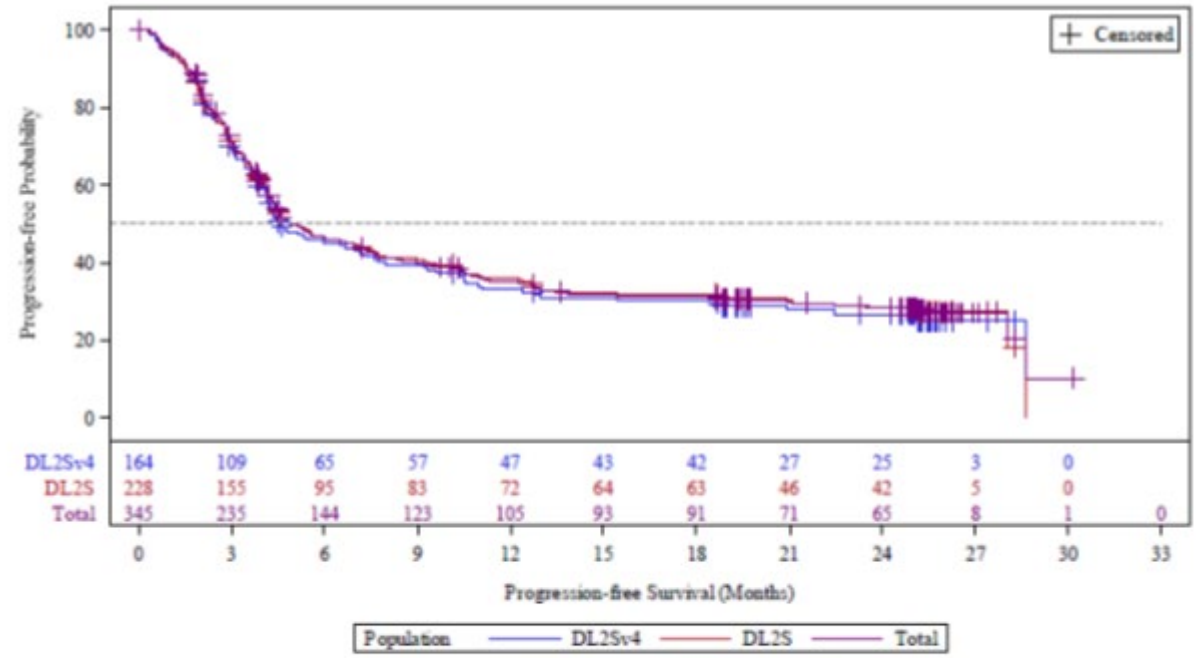
Data cutoff date: 19 Jun 2020

Figure 15. Study 017001 (DLBCL Cohort) – Duration of Response per IRC Assessment using EMA Censoring Rules, Leukapheresed Set



DL2S = Dose Level 2, Single Dose; DL2Sv4 = Dose Level 2, Single Dose, manufacturing process version 4; EMA = European Medicines Agency; IRC = Independent Review Committee.
Data cutoff date: 19 Jun 2020

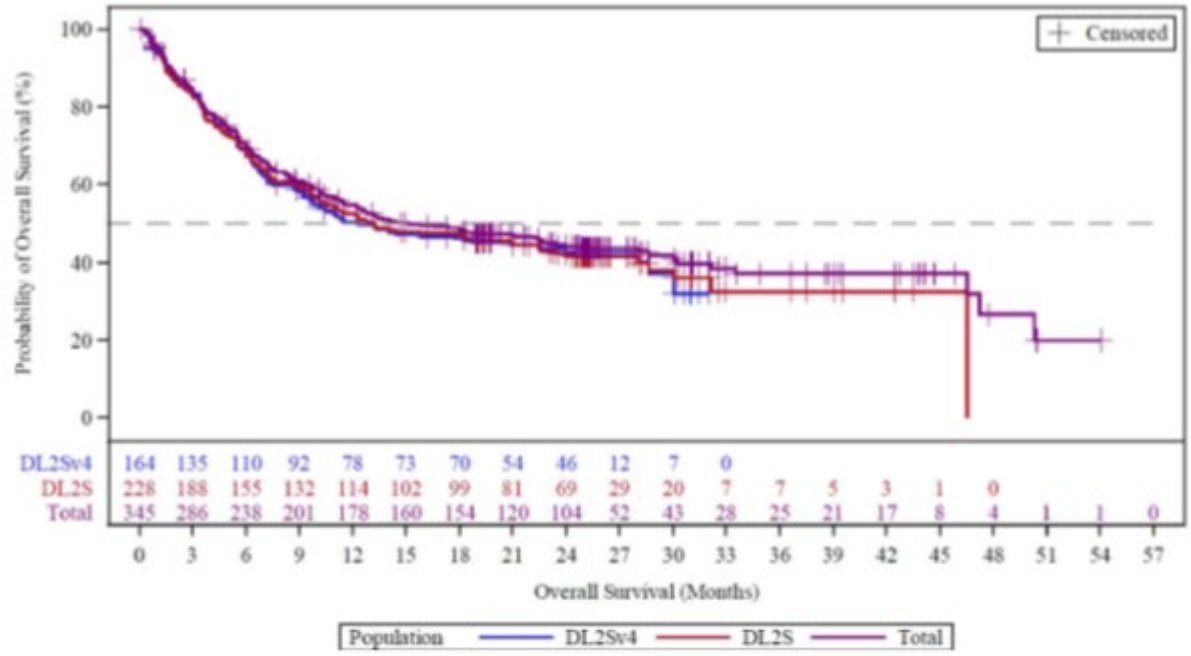
Figure 16. Study 017001 (DLBCL Cohort) – Progression-Free Survival per IRC Assessment using EMA Censoring Rules, Leukapheresed Set



DL2S = Dose Level 2, Single Dose; DL2Sv4 = Dose Level 2, Single Dose, manufacturing process version 4; EMA = European Medicines Agency; IRC = Independent Review Committee.
Data cutoff date: 19 Jun 2020

At the time of the updated data cut (19 Jun 2020), results in the JCAR017 efficacy analysis set for patients who received JCAR017 at DL2S were summarised in Table below.

Figure 17. Study 017001 (DLBCL Cohort) – Overall Survival, Leukapheresed Set



DL2S = Dose Level 2, Single Dose; DL2Sv4 = Dose Level 2, Single Dose, manufacturing process version 4.
Data cutoff date: 19 Jun 2020

Table 22. Study 017001 (DLBCL cohort) – Overall Response rate per IRC Assessemnt. JCAR017-Treated Efficacy Analysis Set

Parameter	Dose Level 2 (all versions)		Dose Level 2 (version 4)	
	12 Aug 2019 (N = 169)	19 Jun 2020 (N = 170)	12 Aug 2019 (N = 120)	19 Jun 2020 (N = 121)
Overall response rate, n (%)				
Complete + partial response	125 (74.0)	127 (74.7)	90 (75.0)	92 (76.0)
95% CI [a]	66.7-80.4	67.5-81.0	66.3-82.5	67.4-83.3
Complete response rate, n (%)				
Complete response	88 (52.1)	89 (52.4)	63 (52.5)	65 (53.7)
95% CI [a]	44.3-59.8	44.6-60.1	43.2-61.7	44.4-62.8
Duration of response[b] (months)				
Median	13.3	19.0	9.1	11.1
95% CI[c]	6.0-NR	6.0-NR	4.1-NR	4.4-NR
Q1, Q3	2.1, NR	2.1, 26.1	2.1, NR	2.1, 26.1
Min, Max	0.0, 23.5	0.0, 26.3	0.0, 19.9*	1.1, 26.3

Parameter	Dose Level 2 (all versions)		Dose Level 2 (version 4)	
	12 Aug 2019 (N = 169)	19 Jun 2020 (N = 170)	12 Aug 2019 (N = 120)	19 Jun 2020 (N = 121)
Progression-free survival[b] (months)				
Median	6.7	6.8	5.9	6.0
95% CI[c]	3.1-10.4	3.2-11.3	3.0-10.0	3.0-11.4
Q1, Q3	2.0, NR	2.0, 27.3	2.0, NR	2.0, 27.3
Min, Max	0.0*, 24.4	0.2, 27.3	0.0*, 20.9*	0.2, 27.3
Overall survival (months)				
Median	19.9	21.4	17.1	27.3
95% CI[c]	11.3-NR	11.4-45.2	10.0-NR	10.0-NR
Q1, Q3	5.5, NR	5.5, 45.2	5.4, NR	5.5, NR
Min, Max	0.2, 33.9*	0.2, 45.2	0.2, 20.9*	0.2, 30.3*

CI = confidence interval; CR = complete response; DL2S = Dose Level 2, Single Dose; DL2Sv4 = Dose Level 2, Single Dose, manufacturing process version 4; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EMA = European Medicines Agency; IRC = Independent Review Committee; Max = maximum; Min = minimum; NR = not reached; ORR = overall response rate; PFS = progression-free survival; Q = quartile

[a] 2-sided 95% exact Clopper-Pearson CIs.

[b] Using EMA censoring rules

[c] Kaplan-Meier (KM) method was used to obtain 2-sided 95% CIs.

Data cutoff date: 19 Jun 2020

Study 017001 updated analysis (data cut-off 04 Jan 2021)

Of 298 patients who underwent leukapheresis for whom Breyanzi was manufactured in the dose range of 44 120 × 106 CAR+ viable T cells, 229 patients received Breyanzi and 69 patients did not. The number of patients who were evaluable for efficacy was 216 (Efficacy set).

Efficacy was assessed on the basis of the primary endpoint, overall response rate (ORR), and secondary endpoints which included complete response (CR) rate, duration of response (DOR) as determined by an independent review committee (Table 23 and Figure 18). The median on-study follow-up time was 19.9 months (range 0.2 to 45.2 months).

Table 23. 017001 (TRANSCEND) study: Response rate, duration of response (IRC assessment)

	All leukapheresed (N=298)	**Efficacy set (N=216)**
Overall response rate[a], n (%) [95% CI]	179 (60.1) [54.3, 65.7]	157 (72.7) [66.2, 78.5]
Complete response, n (%) [95% CI]	128 (43.0) [37.3, 48.8]	115 (53.2) [46.4, 60.0]
Partial response, n (%) [95% CI]	51 (17.1) [13.0, 21.9]	42 (19.4) [14.4, 25.4]

	All leukapheresed (N=298)	Efficacy set (N=216)
Duration of response (DOR)[a,b] (months)	n=179	n=157
Median	16.8	20.2
[95% CI][c]	[8.0, NR]	[8.2, NR]
Range	0.0, 27.4	0.0, 27.4
DOR if best response is CR[a,b] (months)	n=128	n=115
Median	26.1	26.1
[95% CI][c]	[23.1, NR]	[23.1, NR]
Range	0.0, 27.4	0.0, 27.4

CI=confidence interval; CR=complete response; IRC=Independent Review Committee; KM=Kaplan-Meier; NR=not reached

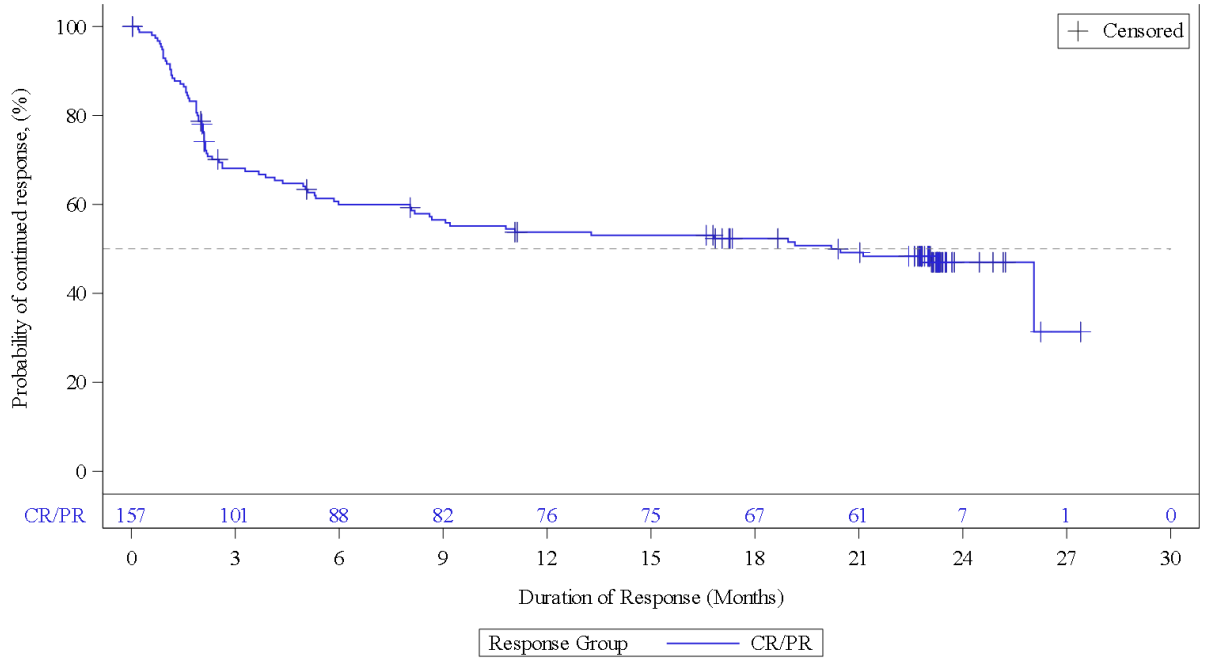
[a] Per the Lugano 2014 criteria, as assessed by IRC.

[b] Deaths after initiation of anti-cancer treatment were considered as events.

[c] KM method was used to obtain 2-sided 95% CIs.

[+] Ongoing.

Figure 18. Duration of response for responders per IRC assessment, TRANSCEND (017001) Efficacy set



CR = complete response; PR = partial response.

Deaths after initiation of anti-cancer treatment were considered as events

The median time to response (CR or partial response [PR]) was 1.0 months (range: 0.7 to 8.9 months). The median time to CR was 1.0 months (range: 0.8 to 12.5 months). Response durations were longer in patients who achieved a CR, as compared to patients with a best response of PR.

Six patients with secondary CNS lymphoma were treated and evaluable for efficacy in the

017001 (TRANSCEND) study. Three of these six patients achieved a CR; 2 of 3 patients had durable remissions of 23 months that remained ongoing at study completion. The safety profile of these patients with secondary CNS lymphoma was consistent with that observed in the overall population.

In the Efficacy set, the ORR results within PMBCL and FL3B were 79% (11/14 patients) and 100% (4/4 patients) respectively. CR rates were 50% for PMBCL and 100% for FL3B. The safety profile was consistent across these subtypes.

Study BCM-001 updated analysis (data cutoff 04 Jan 2021)

For Study BCM-001 Cohort 1, the efficacy outcomes at the data cutoff date of 04 Jan 2021 with longer median follow-up times (mFU for survival ~16 months in the ITT set) were consistent with those observed at the data cutoff date of 19 Jun 2020, (see table below):

Table 24. Study BCM-001 Cohort 1 Efficacy Results per IRC Assessment in the JCAR017-Treated Set and Leukapheresed (ITT) Set

Parameter	Study BCM-001, Cohort 1			
	19 Jun 2020 Data Cut		04 Jan 2021 Data Cut	
	Leukapheresed Set N=45	JCAR017-treated Set N=36	Leukapheresed Set N=45	JCAR017-treated Set N=36
ORR[a], n (%) [95% CI][b]	25 (55.6) [40.0 - 70.4]	22 (61.1) [43.5 - 76.9]	25 (55.6) [40.0 - 70.4]	22 (61.1) [43.5, 76.9]
CR Rate[c], n (%) [95% CI][b]	14 (31.1) [18.2 - 46.6]	12 (33.3) [18.6 - 51.0]	14 (31.1) [18.2 - 46.6]	12 (33.3) [18.6, 51.0]
DOR[d] (Months)				
Median (95% CI)[e]	3.35 (2.23, NR)	3.50 (2.20, NR)	3.35 (2.23, 11.27)	3.50 (2.20, 11.27)
Q1, Q3[f]	2.20, NR	2.20, NR	2.20, NR	2.20, NR
Min, Max	1.08, 16.95	1.08, 16.95	1.08, 22.97	1.08, 22.97
mFU[g] – DOR (95% CI)[h]	8.81 (5.09, 11.43)	8.61 (5.09, 11.43)	14.09 (11.04, 17.15)	11.37 (11.04, 17.02)
PFS[i] (Months)				
Median (95% CI)[h]	4.53 (4.17, 5.95)	3.25 (2.89, 5.36)	4.63 (4.17, 6.44)	3.25 (2.96, 5.39)
Q1, Q3[f]	3.45, 8.08	2.00, 10.15	3.45, 11.60	2.76, 12.12
Min, Max	1.61, 19.35	0.23, 17.97	1.61, 25.36	0.23, 23.98
mFU[g] – PFS (95% CI)[h]	10.91 (8.31, 14.52)	9.53 (6.90, 12.45)	16.39 (13.34, 20.11)	12.29 (11.96, 18.04)

Parameter	Study BCM-001, Cohort 1			
	19 Jun 2020 Data Cut		04 Jan 2021 Data Cut	
OS[i] (Months)				
Median (95% CI)[b]	12.06 (7.29, NR)	18.56 (5.82 - NR)	13.50 (7.29, 23.33)	14.98 (5.82, NR)
Q1, Q3[f]	6.05, NR	5.48, NR	6.05, NR	5.48, NR
Min, Max	1.9, 22.1	0.5, 20.5	1.9, 28.8	0.5, 27.3
mFU[g] for OS (95% CI)[h]	11.01 (9.99, 16.39)	9.53 (8.57 - 14.32)	16.56 (13.67, 20.93)	15.05 (12.22, 20.73)
Probability of OS, %				
≥ 6 months (SE)	75.6 (6.41)	66.7 (7.86)	75.6 (6.41)	66.7 (7.86)
≥ 12 months (SE)	52.3 (7.62)	50.2 (9.96)	53.2 (7.46)	55.3 (8.33)
≥ 18 months (SE)	46.5 (8.71)	50.2 (9.96)	44.0 (7.94)	46.4 (9.12)
≥ 24 months (SE)	NR (NR)	NR (NR)	28.3 (10.58)	25.8 (12.60)

BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; EMA = European Medicines Agency; IRC = independent review committee; ITT = intent-to-treat; Max = maximum; mFU = median follow-up; Min = Minimum; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response; SE = standard error

[a] ORR is defined as the proportion of subjects who achieved an objective response of PR or better according to Lugano Classification 2014

[b] 2-sided 95% confidence interval based on Clopper-Pearson method

[c] CRR is defined as the proportion of subjects who achieved a BOR of CR

[d] DOR is defined as the interval from the first documentation of response to progressive disease or death from any cause, whichever occurs first

[f] Median, Q1, Q3 are estimated from Kaplan-Meier product-limit estimates

[g] Median time to follow-up is calculated using the reverse Kaplan-Meier method

[h] PFS is defined as the interval from the date of JCAR017 infusion to progressive disease or death due to any cause, whichever occurs first

[i] OS is defined as the interval from the date of JCAR017 infusion to the date of death due to any reason

Note: EMA censoring rules were applied.

Health-related Quality of Life

Study 017001

Among the 269 DLBCL Treated Set subjects in Study 017001, 181 subjects (67%) were evaluable for the EORTC QLQ-C30, herein defined as the PRO (EORTC QLQ-C30) Evaluable Population, and 186 (69%) were evaluable for the EQ-5D-5L, herein defined as the PRO (EQ-5D-5L) Evaluable Population.

The analysis of mean changes from baseline in the EORTC QLQ-C30 analysis showed that patients experienced improvement in global health status starting from Month 2 post-infusion, and in fatigue (starting from Month 9 post-infusion). Other HRQoL domain scores remained stable up until Month 18.

With respect to the EQ-5D-5L, at baseline, mean health index scores and EQ-VAS scores were 0.8 and 68.3, respectively. Compliance rates, based on the PRO (EQ-5D-5L) Evaluable Population, were 65.6% of those who were in follow-up at Month 9 and 65.8% of those who were in follow-up at Month 18. Mean EQ-5D-5L health utility index scores decreased 1 month after JCAR017 infusion, which was followed by fluctuations in scores between Months 2 and 3, and then an improvement from Month 6 through Month 18 compared with baseline. Mean EQ-VAS scores were higher from Month 1 through Month 18 compared with baseline.

Study BCM-001

Study subjects generally had comparable baseline scores in the primary domains of the EORTC QLQ-C30 compared to the age- and gender-adjusted general population, except for the fatigue domain in which the study subjects were borderline meaningfully worse. Results from group-level analyses indicated that these domains were generally maintained over time following treatment with JCAR017, with a trend of improvement over the first 60 to 90 days. For the FACT-LymS, the results were generally similar to the primary domains of the EORTC QLQ-C30, with a clinically meaningful improvement observed at Day 60. A trend of small and gradual worsening after Day 90 was observed. It should be considered that data

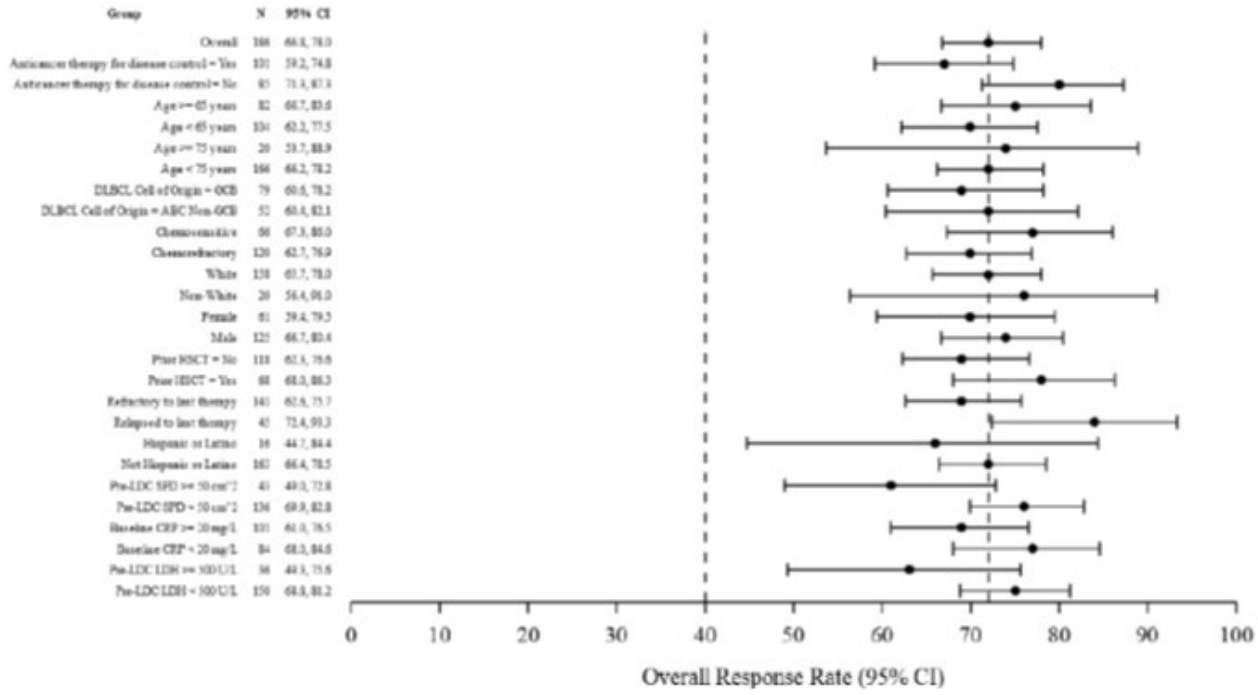
from subjects experiencing disease progression and/or AEs associated with subsequent anticancer treatments continued to be included in the analysis.

Ancillary analyses

Study 017001 Subgroup Analyses

Analyses were performed on the subgroups pre-specified in the Study 017001 SAP. Additionally, subgroup analyses for efficacy were performed by use of anticancer therapy for disease control after screening, pre-LDC SPD (<50 cm^2 vs ≥50 cm^2 [per IRC]), pre-LDC LDH (<500 U/L vs ≥ 500 U/L), CRP at baseline (< 20 mg/L versus ≥20 mg/L), pre-leukapheresis ALC (<0.3 × 10^9/L versus ≥0.3 × 10^9/L), and ECOG PS prior to LDC (0 or 1 vs 2). Results are summarised in figures and tables below:

Figure 19. Study 017001: Overall Response rate per IRC Assessment in Subgroups, DLBCL Efficacy Set



ABC = activated B-cell; CI = confidence interval; CRP = C-reactive protein; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; GCB = germinal center B-like; HSCT = hematopoietic stem-cell transplantation; IRC = Independent Review Committee; LDC = lymphodepleting chemotherapy; LDH = lactate dehydrogenase; ORR = overall/objective response rate; SPD = sum of the products of the perpendicular diameters.

Notes: N represents the number of subjects with response.

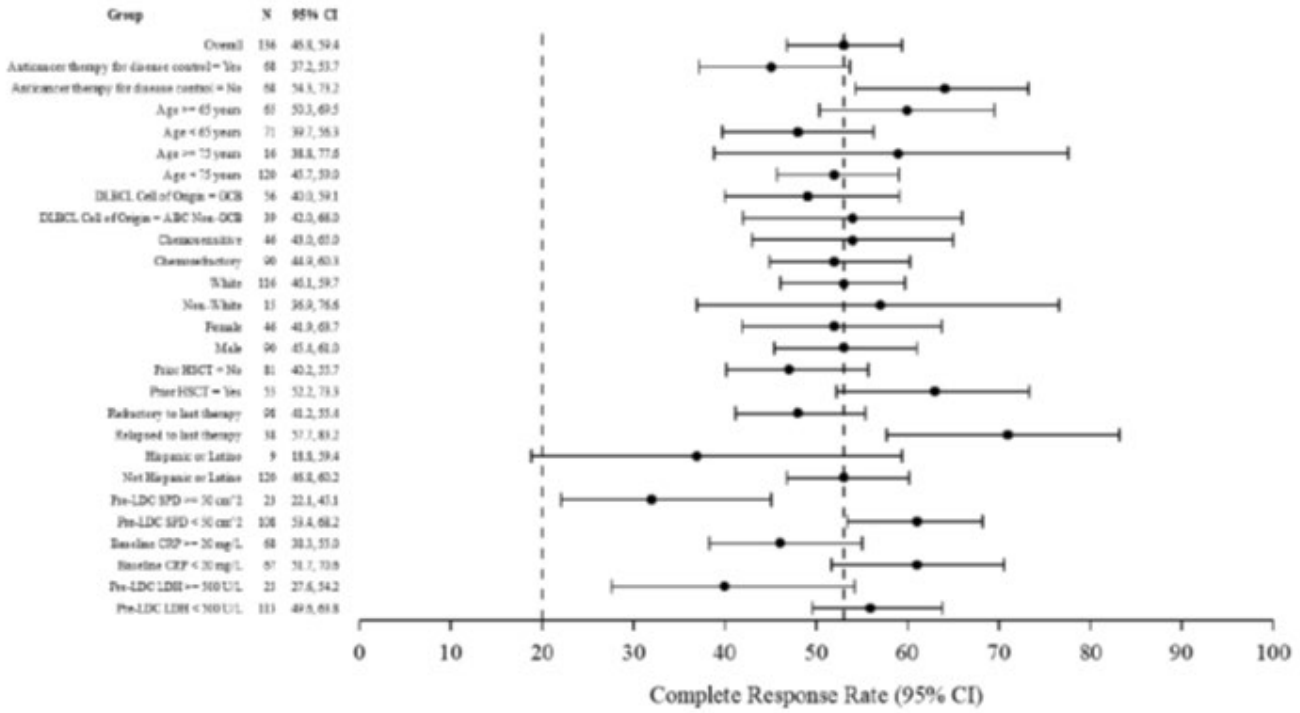
Non-White includes American Indian or Alaska Native, Asian, Black or African American, Multiple, and Not Reported (CSR 017001 Table 14.1.5.1.1.a).

Left-hand vertical line at 40% represents the null hypothesis for ORR (Section 1.1.1.11.1). Right-hand vertical line at 72.7% represents the ORR in the DLBCL Efficacy Set (Table 12).

Overall response rate and 2-sided 95% exact Clopper-Pearson confidence intervals are displayed.

Data cutoff date 12 Aug 2019.

Figure 20. Study 017001: Complete Response Rate per IRC Assessment in Subgroups, DLBCL Efficacy Set



ABC = activated B-cell; CR = complete response; CRP = C-reactive protein; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; GCB = germinal center B-like; HSCT = hematopoietic stem-cell transplantation; IRC = Independent Review Committee; LDC = lymphodepleting chemotherapy; LDH = lactate dehydrogenase; SPD = sum of the products of the perpendicular diameters.

Notes: N represents the number of subjects with CR.

Non-White includes American Indian or Alaska Native, Asian, Black or African American, Multiple, and Not Reported (CSR 017001 Table 14.1.5.1.1.a).

Left-hand vertical line at 20% represents the null hypothesis for CR rate (Section 1.1.1.11.2). Right-hand vertical line at 53.1% represents the overall/objective response rate in the DLBCL Efficacy Set (Table 12).

Complete response rate and 2-sided 95% exact Clopper-Pearson confidence intervals are displayed.

Data cutoff date 12 Aug 2019.

Table 25. Study 017001: Duration of Response by Demographic and Disease Characteristics – per IRC Assessment, DLBCL Efficacy Set (All Doses Combined)

Subgroup	N	N with PR/CR	Median DOR (Months) (95% CI)
Age			
< 65 years	148	104	19.2 (5.3-NR)
≥ 65 years	108	82	9.2 (5.1-NR)
< 75 years	229	166	13.3 (7.3-NR)
≥ 75 years	27	20	NR (1.8-NR)
Sex			
Male	169	125	9.1 (5.1-NR)
Female	87	61	19.2 (5.3-NR)
Cell of origin			
GCB	113	79	16.8 (5.8-NR)
Non-GCB	72	52	13.3 (2.2-NR)
SPD prior to LDC			
< 50 cm^2	177	136	21.1 (8.6-NR)
≥ 50 cm^2	70	43	5.3 (2.1-19.2)
LDH prior to LDC			
< 500 U/L	199	150	21.1 (9.2-NR)
≥ 500 U/L	57	36	4.1 (1.9-8.2)
Baseline CRP			
< 20 mg/L	109	84	NR (21.1-NR)
≥ 20 mg/L	146	101	5.3 (2.2-10.8)
Prior response status			
Refractory	203	141	10.8 (6.0-NR)
Relapsed	53	45	NR (5.0-NR)
Prior HSCT			
Yes	87	68	21.1 (5.0-NR)
No	169	118	11.1 (5.3-NR)
Prior chemoresponse status			
Chemorefractory	171	120	13.3 (5.3-NR)
Chemosensitive	85	66	19.2 (5.6-NR)
Use of anticancer therapy for disease control			
Yes	150	101	9.1 (5.3-NR)
No	106	85	21.1 (5.6-NR)

CI = confidence interval; CR = complete response; CRP = C-reactive protein; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EMA = European Medicines Agency; GCB = germinal center B-like; HSCT = hematopoietic stem-cell transplantation; IRC = Independent Review Committee; LDC = lymphodepleting chemotherapy; LDH = lactate dehydrogenase; NR = not reached; PR = partial response; SPD = sum of the products of the perpendicular diameters.
Note: EMA censoring rules were applied.
Data cutoff date 12 Aug 2019.

ECOG score prior to LDC

Nine of 256 subjects (3.5%) had an ECOG performance status of 2 prior to LDC. Results in this subgroup are summarised in the table below.

Table 26. Study 017001, ECOG Performance Status of 2: Efficacy Results by Subject Based on IRC Assessment, DLBCL Efficacy Set

BOR by IRC	Response Ongoing at Data Cutoff Date (Yes/No)	DOR (Months)	Alive at Data Cutoff Date (Yes/No)	Survival Time Post JCAR017 (Days)[a]
CR	No	2.0	No	205
CR	No	5.3	No	643
CR	No	1.1	No	332
CR	No	5.1	No	511
CR	No	0.7	No	127
PR	No	0.2	No	35
NE	NA	NA	No	21
PD	NA	NA	No	165
PD	NA	NA	No	50

BOR = best overall response; CR = complete response; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EMA = European Medicines Agency; IRC = Independent Review Committee; NA = not applicable; NE = non-evaluable; PD = progressive disease; PR = partial response.
[a] Day of death of last day subject is known to be alive is calculated in reference to the day of first JCAR017 infusion.
Note: EMA censoring rules were applied.

Secondary Central Nervous System Lymphoma at First Infusion

Across Studies 017001 and BCM-001, a total of 4 (57.1%) out of 7 efficacy-evaluable subjects with secondary CNS lymphoma prior to the first liso-cel infusion achieved a CR by IRC assessment. In Study 017001, CR was observed in 3 of the 6 (50.0%) subjects with secondary CNS lymphoma included in the DLBCL Efficacy Set. Updated efficacy data demonstrated durable remission at 23 months in 2 (33.3%) of these subjects. For these 2 subjects, CR remains ongoing as of the data cut-off date of 19 Jun 2020. In Study BCM-001, the 1 subject with secondary CNS lymphoma also achieved CR per IRC assessment (DOR: 9.1 months). This subject experienced disease progression but was alive at the data cut-off date.

Subjects with Prior Allogeneic Stem-cell Transplantation (HSCT)

Seven of 256 subjects (2.7%) who were treated on Study 017001 had undergone prior allo-HSCT. Results in this specific subgroup are summarised in the table below.

Table 27. Study 017001 – Summary of Efficacy per IRC Assessment in Subjects in the JCAR017-tretaed Efficacy Analysis Set with Prior Allo-HSCT

Treatment Group	BOR by IRC	Response Ongoing at Data Cutoff Date (Yes/No)	DOR (Months)[a]	PFS (Months)[a]	Alive at Data Cutoff Date (Yes/No)	Survival Time Post JCAR017 (Months)[b]
DL1S/v2	CR	Yes	0	0.8	No	45.6
DL2S/v4	CR	Yes	15.2	18.0	Yes	18.0
DL3S/v4	CR	Yes	16.6	17.5	Yes	24.0
DL2S/v4	PR	No	0.8	1.7	No	2.3
DL2S/v4	PR	No	1.0	1.7	No	10.0
DL2S/v3	SD	NA	NA	2.9	No	2.9
DL1S/v2	PD	NA	NA	5.4	No	5.4

Allo-HSCT = allogeneic hematopoietic stem-cell transplant; BOR = best overall response; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EMA = European Medicines Agency; HSCT = hematopoietic stem-cell transplant; IRC = Independent Review Committee; JCAR017 = lisocabtagene maraleucel (liso-cel); NA = not applicable; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

[a] EMA censoring rules were applied for DOR and PFS.

[b] Day of death of last day subject is known to be alive is calculated in reference to the day of first JCAR017 infusion.

Data cutoff date: 19 Jun 2020.

Results in Large B-cell Lymphoma Subtypes

With the updated 2016 WHO classification, DLBCL NOS is now defined as de novo DLBCL and DLBCL from transformation of indolent NHL. In addition, the former group of double/triple hit lymphomas is now categorised as its own group: high-grade B-cell lymphoma MYC and BCL2 and/or BCL6 rearrangements (Swerdlow, 2016).

Subgroup analyses of ORR, DOR, PFS, and OS per IRC assessment by LBCL subtypes are summarised in Tables and Figures below:

Table 28. Study 017001: Summary of Response Rates per IRC Assessment in Large B-Cell Lymphoma Subtypes, DLBCL Efficacy Set (All Doses Levels and Versions Combined)

Efficacy Endpoint	DLBCL (NOS, HGL, tFL, tNHL) N = 239	DLBCL Histology Subgroups				PMBCL N = 14	FL3B N = 3	Total N = 256
		DLBCL NOS N = 131	HGL N = 33	tFL N = 57	tNHL N = 18			
Overall Response Rate								
CR + PR, n (%)	173 (72.4)	89 (67.9)	25 (75.8)	48 (84.2)	11 (61.1)	11 (78.6)	2 (66.7)	186 (72.7)
95% CI [a]	66.3-78.0	59.2-75.8	57.7-88.9	72.1-92.5	35.7-82.7	49.2-95.3	9.4-99.2	66.8-78.0
Complete Response Rate								
CR, n (%)	127 (53.1)	64 (48.9)	20 (60.6)	36 (63.2)	7 (38.9)	7 (50.0)	2 (66.7)	136 (53.1)
95% CI [a]	46.6-59.6	40.0-57.7	42.1-77.1	49.3-75.6	17.3-64.3	23.0-77.0	9.4-99.2	46.8-59.4

CI = confidence interval; CR = complete response; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; FL3B = follicular lymphoma Grade 3B; HGL = high-grade lymphoma; IRC = Independent Review Committee; NOS = not otherwise specified; PMBCL = primary mediastinal B-cell lymphoma; PR = partial response; tFL = DLBCL transformed from follicular lymphoma; tNHL = DLBCL transformed from indolent non-Hodgkin lymphoma other than follicular lymphoma.

[a] Two-sided 95% exact Clopper-Pearson confidence intervals.

Note: Data cutoff date 12 Aug 2019.

Table 29. Study 017001: Summary of Overall Survival in Large B-cell Lymphoma Subtype, DLBCL Efficacy Set (All Dose Levels and Versions Combined)

Efficacy Endpoint	DLBCL (NOS, HGL, tFL, tiNHL) N = 239	DLBCL Histology Subgroups				PMBCL N = 14	FL3B N = 3	Total N = 256
		DLBCL NOS N = 131	HGL N = 33	tFL N = 57	tiNHL N = 18			
Alive, n (%)	126 (52.7)	62 (47.3)	19 (57.6)	39 (68.4)	6 (33.3)	11 (78.6)	3 (100)	116 (45.3)
Death, n (%)	113 (47.3)	69 (52.7)	14 (42.4)	18 (31.6)	12 (66.7)	3 (21.4)	0	140 (54.7)
OS (months)								
Median, 95% CI [a]	20.5, 11.4-NR	12.7, 9.0-21.1	NR, 6.5-NR	NR, 21.1-NR	6.5, 3.7-NR	NR, 12.1-NR	NR, NR-NR	21.1, 13.3-NR
Q1, Q3	5.6, NR	5.4, NR	5.0, NR	11.4, NR	3.7, 16.8	NR, NR	NR, NR	5.9, NR
Min, Max	0.2, 36.8+	0.2, 36.8+	0.2, 33.9+	0.6, 36.3+	0.9, 24.3+	5.3, 18.5+	0.5+, 42.0+	0.2, 42.0+
Probability of OS, %								
≥ 6 months	73.8	72.0	69.7	84.2	61.1	85.7	100	74.7
95% CI [a]	67.7-78.9	63.4-79.0	51.0-82.4	71.9-91.5	35.3-79.2	53.9-96.2	NR-NR	68.9, 79.6
≥ 12 months	55.8	50.7	56.3	72.2	38.9	85.7	100	57.9
95% CI [a]	49.0-62.0	41.5-59.2	37.4-71.5	58.0-82.3	17.5-60.0	53.9-96.2	NR-NR	51.3-63.8
≥ 18 months	51.4	45.4	56.3	69.2	19.4	75.0	100	52.9
95% CI [a]	44.3-58.0	35.8-54.4	37.4-71.5	54.2-80.1	1.7-52.0	39.4-91.5	NR-NR	46.0-59.4
≥ 24 months	43.4	34.9	56.3	58.6	19.4	NR	100	44.9
95% CI [a]	35.0-51.4	23.7-46.4	37.4-71.5	39.3-73.6	1.7-52.0	NR-NR	NR-NR	36.5-52.9
Follow-up (months)								
Median 95% CI [b]	17.6, 13.8-18.0	17.6, 12.6-17.9	18.0, 12.1-23.8	17.7, 12.1-18.3	12.2, 8.8-24.3	12.1, 11.7-12.4	8.8, 0.5-42.0	17.5, 12.9-17.8
Min, Max	0.2, 36.8+	0.2, 36.8+	0.2, 33.9+	0.6, 36.3+	0.9, 24.3+	5.3, 18.5+	0.5+, 42.0+	0.2, 42.0+

CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; FL3B = Grade 3B follicular lymphoma; HGL = high-grade lymphoma; HSCT = hematopoietic stem-cell transplantation; Max = maximum; Min = minimum; NOS = not otherwise specified; NR = not reached; OS = overall survival; PMBCL = primary mediastinal B-cell lymphoma; Q1 = first quartile; Q3 = third quartile; tFL = DLBCL transformed from follicular lymphoma; tiNHL = DLBCL transformed from indolent non-Hodgkin lymphoma other than follicular lymphoma.

[a] Kaplan-Meier (KM) method is used to obtain 2-sided 95% confidence intervals.

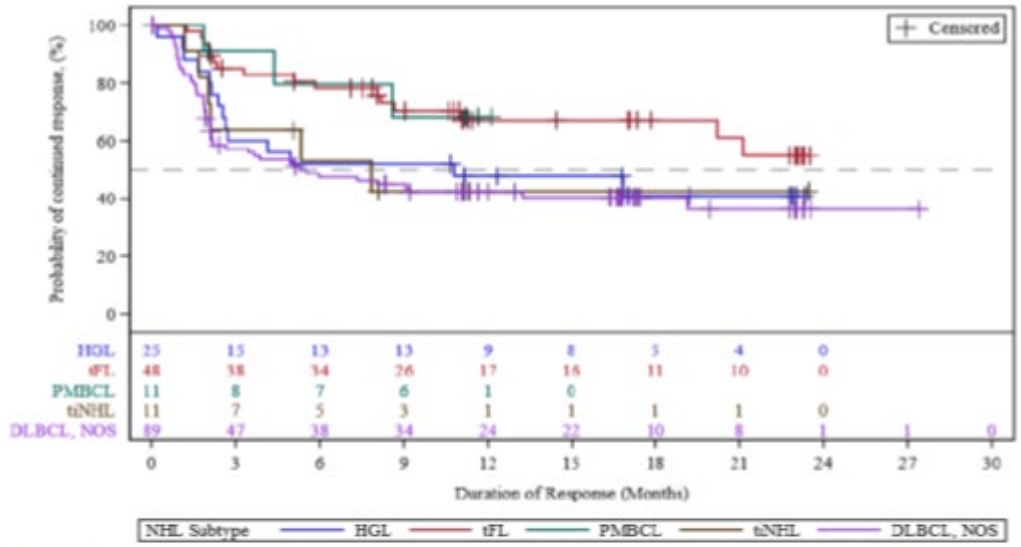
[b] Reverse KM method is used to obtain the median follow-up and its 95% confidence intervals.

Notes: The OS analysis includes all available survival information with long-term follow-up data from Study GC-LTFU-001. No censoring is done in the case of HSCT.

+ At least 1 subject is still alive in this group.

Data cutoff date 12 Aug 2019.

Figure 21. Study 017001: Duration of Response per IRC Assessemnt, DLBCL Efficacy Set – Subjects with DLBCL NOS, HGL, tFL, PMBCL, or tiNHL (all Dose Levels and Versions Combined)

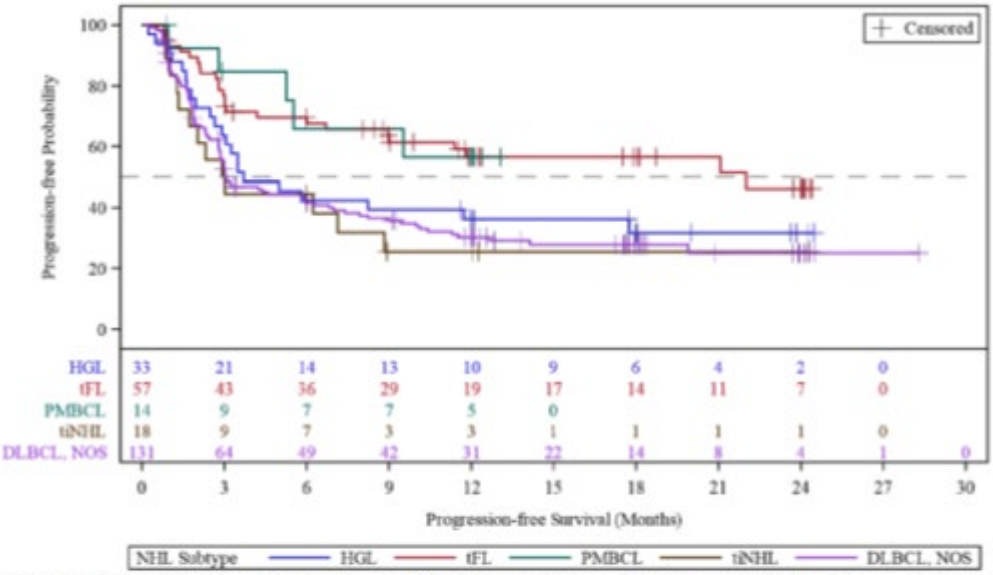


BCL2 and/or BCL6 = B-cell lymphoma gene 2 and/or 6; DLBCL = diffuse large B-cell lymphoma; EMA = European Medicines Agency; HGL = high-grade lymphoma; IRC = Independent Review Committee; MYC = myelocytomatosis oncogene; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal B-cell lymphoma; tFL = DLBCL transformed from follicular lymphoma; tiNHL = DLBCL transformed from indolent non-Hodgkin lymphoma other than follicular lymphoma.

Notes: Subjects with DLBCL transformed from indolent lymphomas with MYC and BCL2 and/or BCL6 rearrangements are not included as HGL.
EMA censoring rules were applied.

Data cutoff date 12 Aug 2019.

Figure 22. Study 017001: Progession-free Survival per IRC Assessemnt DLBCL Efficacy Set – Subjects with DLBCL NOS, HGL, tFL, PMBCL, or tiNHL (All doses Levels and versios Combined)



BCL2 and/or BCL6 = B-cell lymphoma gene 2 and/or 6; DLBCL = diffuse large B-cell lymphoma; EMA = European Medicines Agency; HGL = high-grade lymphoma; IRC = Independent Review Committee; MYC = myelocytomatosis oncogene; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal B-cell lymphoma; tFL = DLBCL transformed from follicular lymphoma; tiNHL = DLBCL transformed from indolent non-Hodgkin lymphoma other than follicular lymphoma.

Notes: Subjects with DLBCL transformed from indolent lymphomas with MYC and BCL2 and/or BCL6 rearrangements are not included as HGL.
EMA censoring rules were applied.

Data cutoff date 12 Aug 2019.

In the DLBCL Efficacy DL2S v4 Set, in subtypes with larger numbers of subjects, rates of response were consistent with those in the DLBCL Efficacy Set, with the exception of a lower CR rate in subjects with HGL (n=18, CR rate of 50%). Subgroup analyses of ORR, DOR, and PFS by large B-cell lymphoma subtypes, based on Investigator assessment were also consistent with the analyses based on IRC assessment.

Updated subgroup analyses were provided for tiNHL (data cut-off 19 Jun 2020 and 04 Jan 2021) and PMBCL(data cut-off 19 Jun 2020) and are summarised in Tables below.

Table 30. Study 017001: Efficacy Results per IRC Assessment in Selected NHL Subtypes and Total JCAR017-Treated DLBCL Efficacy Set

Efficacy Endpoint	tiNHL overall N = 18[b]	PMBCL N = 14	Total DLBCL Efficacy Set N = 257
Overall Response Rate (ORR)			
CR + PR, n (%)	10 (55.6)	11 (78.6)	187 (72.8)
95% CI [a]	30.8, 78.5	49.2, 95.3	66.9, 78.1
Complete Response Rate (CR rate)			
CR, n (%)	6 (33.3)	7 (50.0)	136 (52.9)
95% CI [a]	13.3, 59.0	23.0, 77.0	46.6, 59.2
Duration of Response[c] (DOR)			
Median (months)	5.3	NR	13.3
95% CI	1.2, NR	4.4, NR	8.0, NR
Progression-free Survival[c] (PFS)			
Median (months)	2.6	NR	6.0
95% CI	1.0, 7.1	5.3, NR	3.5, 9.0
Overall Survival (OS)			
Median (months)	6.5	NR	27.3
95% CI	3.7, 16.8	12.1, NR	16.2, 45.6

CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EMA = European Medicines Agency; IRC = Independent Review Committee; JCAR017 = lisocabtagene maraleucel; NHL = non-Hodgkin lymphoma; ORR = overall response rate; PMBCL = primary mediastinal B-cell lymphoma; PR = partial response; tiNHL = DLBCL transformed from indolent non-Hodgkin lymphoma other than follicular lymphoma; tMZL = transformed marginal zone lymphoma; tOther = DLBCL transformed from other indolent lymphomas, including Waldenström macroglobulinemia.

[a] Two-sided 95% exact Clopper-Pearson confidence intervals.

[b] Please see Figure 1, Figure 2, and Figure 3 for Swimmer's Plots of individual efficacy results in subjects with tiNHL (tMZL, tOther, and RS)

[c] IRC assessment with EMA censoring rules

Note: Data cutoff date 19 Jun 2020.

Table 31. Summary of Key Efficacy variable by Histologic Subtype – Study 017001

	JCAR017-treated Efficacy Set				JCAR017-treated Efficacy Set, DL1+DL2			
	tFL (N = 57)	tMZL (N = 10)	RS (N = 5)	tWM (N = 2)	tFL (N = 44)	tMZL (N = 7)	RS (N = 4)	tWM (N = 2)
ORR, n (%)	48 (84.2)	6 (60)	3 (60)	1 (50)	38 (86.4)	3 (43)	2 (50)	1 (50)
CRR, n (%)	35 (61.4)	5 (50)	1 (20)	0	27 (61.4)	2 (29)	1 (25)	0
DOR, mos.								
Median (95% CI)	NR (11.8-NR)	ND	ND	ND	NR (19.0-NR)	ND	ND	ND
Range	1.2, 25.2	1.7, 23.2	1.2, 2.1	5.3[b]	1.2, 25.2	1.7, 23.1	1.2, 2.0	5.3
PFS, mos.								
Median (95% CI)	21.4 (9.0, NR)	ND	ND	ND	NR (9.0-NR)	ND	ND	ND
Range	0.6, 26.0	2.3, 24.1	0.8, 3.0	0.4, 6.2	0.6, 26.0	2.3, 24.0	0.8, 7.1	0.4, 6.2
OS, mos.								
Median (95% CI)	NR (22.0-NR)	ND	ND	ND	NR (21.1-NR)	ND	ND	ND
Range	0.6, 50.2[a]	3.8, 30.4[a]	0.9, 16.2	6.2, 37[a]	0.6, 50.2[a]	3.8, 24.0[a]	0.9, 7.1	6.2, 37[a]

CI = confidence interval; CRR = complete response rate; DL = dose level; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; mos = months; ND = not done; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RS = Richter's syndrome (DLBCL transformed from chronic lymphocytic leukemia/small lymphocytic lymphoma; tFL = DLBCL transformed from follicular lymphoma; tMZL = DLBCL transformed from marginal zone lymphoma; tWM = DLBCL transformed from Waldenstrom macroglobulinemia.

[a] Ongoing at data cutoff.

[b] Only 1 subject had a response in the tWM group.

Data cutoff date = 04 Jan 2021.

Clinical outcomes across manufacturing process versions

Results are summarised in the table below.

APPENDIX A. SUMMARY OF CLINICAL RESULTS IN SUBJECTS TREATED WITH PRODUCT MANUFACTURED WITH PRECOMMERCIAL AND PROPOSED COMMERCIAL PROCESSES, DLBCL COHORT, DL1S+DL2S

Process Version:	**v2+v3**	**v4**			**Total**
Vector Manufacturing Site:	**v1.0**	**v1.0**	**v1.2**	**v1.0 + v1.2**	
Number Treated:	**N=93**	**N=110**	**N=16**	**N=126**	**N=219**
ORR, n/N (%)[a] 95% CI	62/89 (69.7) 59.0, 79.0	77/106 (72.6) 63.1, 80.9	13/14 (92.9) 66.1, 99.8	90/120 (75.0) 66.3, 82.5	152/209 (72.7) 66.2, 78.6
CR rate, n/N (%) 95% CI	49/89 (55.1) 44.1, 65.6	54/106 (50.9) 41.0, 60.8	9/14 (64.3) 35.1, 87.2	63/120 (52.5) 43.2, 61.7	112/209 (53.6) 46.6, 60.5
Median DOR, months[b], 95% CI	NR, 9.2-NR	13.3, 3.9-NR	NR, 1.6-NR	13.3, 4.1-NR	NR, 9.1-NR
Probability of cont response ≥ 6 months, % 95% CI[b]	65.8 52.1-76.4	58.4 45.9-69.0	59.8 28.5-81.0	58.7 47.3-68.5	61.6 53.0-69.1
Median PFS, months, 95% CI	9.0, 2.9-NR	6.8, 3.0-17.7	NR, 1.9-NR	9.0, 3.0-17.7	9.0, 3.3-NR
Probability of PFS ≥ 6 months, % 95% CI	52.5 41.1-62.7	50.0 39.1-59.9	71.4 40.6-88.2	53.0 42.9-62.2	52.8 45.3-59.8
Any CRS, n (%)[c]	36 (38.7)	40 (36.4)	8 (50.0)	48 (38.1)	84 (38.4)
Grade 3-4 CRS, n (%)	2 (2.2)	4 (3.6)	0	4 (3.2)	6 (2.7)
Any iiNT, n (%)	23 (24.7)	36 (32.7)	4 (25.0)	40 (31.7)	63 (28.8)
Grade 3-4 iiNT, n (%)[d]	11 (11.8)	12 (10.9)	0	12 (9.5)	23 (10.5)
Median transgene C_{max} (copies/µg) [a] Q1, Q3	35104.2 6784.8, 91291.4	23999.2 10877.7, 96340.7	16866.1 8698.3, 38416.1	23564.6 9806.3, 77218.8	23999.2 8629.5, 89126.4
Median transgene AUC_{0-28} (day* copies/µg) [a] Q1, Q3	226837.7 46642.4, 821275.0	243717.7 98710.9, 689751.7	134013.8 99730.6, 310392.1	203809.9 98710.9, 632107.8	215081.2 92676.8, 689751.7

AUC_{0-28} = area under the curve through 28 days after infusion; CI = confidence interval; C_{max} = maximum observed concentration; cont = continued; CR = complete response; CRS = cytokine release syndrome; DL1S = Dose Level 1, single dose; DL2S = Dose Level 2, single dose; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; iiNT = investigator-identified neurologic toxicity; ORR = objective response rate; PFS = progression-free survival; Q1 = first quartile; Q3 = third quartile

[a] Efficacy outcomes are presented for the DLBCL Efficacy Set; PK outcomes are presented for the DLBCL qPCR PK Set.

[b] In subjects achieving CR or PR.

[c] CRS is defined as MedDRA PT = Cytokine release syndrome and graded based on the Lee, 2014 grading criteria.

[d] NT is defined as investigator-identified central nervous system treatment-emergent adverse event related to JCAR017, graded based on NCI CTCAE v 4.03 criteria.

Data as of the 12 Aug 2019 cutoff.

Subjects with Absolute Lymphocyte Count (ALC) Below 0.3 × 10^9/L Prior to Leukapheresis

JCAR017 was successfully manufactured in 36 of the 45 (80%) subjects who had ALC <0.3 × 10^9/L prior leukapheresis and in 251 of the 278 (90%) subjects who had ALC ≥0.3 × 10^9/L prior leukapheresis. Among the 269 subjects in the DLBCL Treated Set, 28 subjects had ALC <0.3 × 10^9/L (including 1 subject with <0.1 × 10^9/L) and 227 subjects had ALC ≥0.3 × 10^9/L; 14 subjects had an unknown status for ALC prior to leukapheresis.

Demographics characteristics were similar between subjects with ALC below and above 0.3 × 10^9/L prior leukapheresis. ORR and CRR results are summarised in the table below:

Table 32. Study 017001, ALC Status Prior to Leukapheresis: Summary of Response rate per IRC Assessment, DLBCL Efficacy Set

Parameter	ALC Prior to Leukapheresis	
	< 0.3 × 10^9/L N = 27	≥ 0.3 × 10^9/L N = 215
Overall response rate, n (%)		
CR + PR	20 (74.1)	154 (71.6)
95% CI [a]	53.7, 88.9	65.1, 77.5
Complete response rate, n (%)		
CR	10 (37.0)	116 (54.0)
95% CI [a]	19.4, 57.6	47.0, 60.8

ALC = absolute lymphocyte count; CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; IRC = Independent Review Committee; PR = partial response.
[a] Two-sided 95% exact Clopper-Pearson CIs.
Data cutoff date: 12 Aug 2019.

Median DOR was 5.3 months (95%CI 1.6 - NR) in subjects with ALC <0.3 × 10^9/L and 20.2 months (95%CI 8.2 - NR) in subjects with ALC ≥0.3 × 10^9/L. Median PFS was 3.1 months (95%CI 1.8 - 11.4) and 6.7 months (95%CI 3.3 - 10.4), respectively, with 33.3% and 41.9% of subjects, respectively, free of progression at data cut-off date. The comparability of the results is limited due to the relatively small size of the ALC <0.3 × 10^9/L subset (n=27).

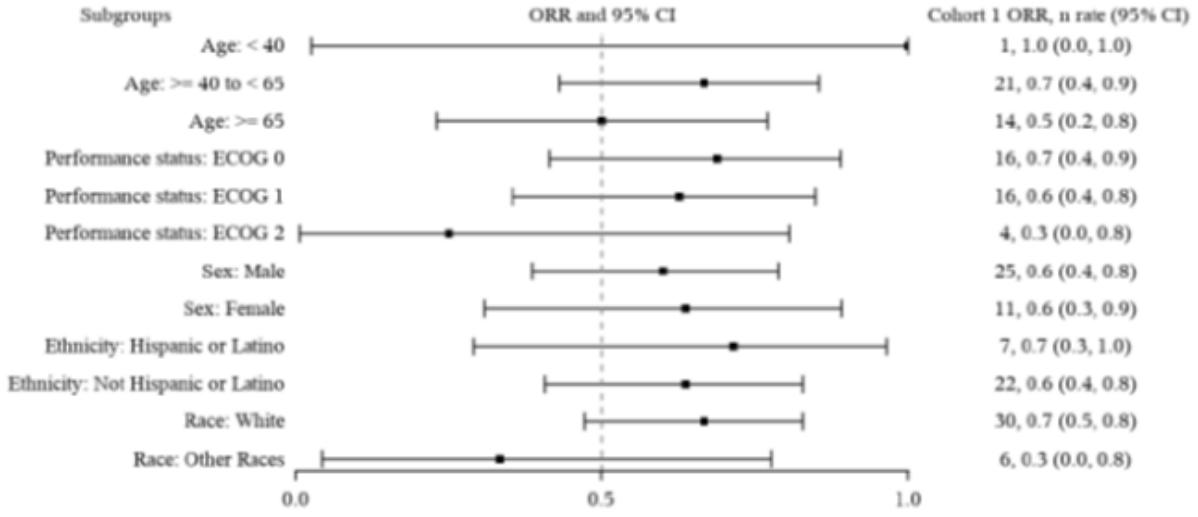
Retreatment subgroup

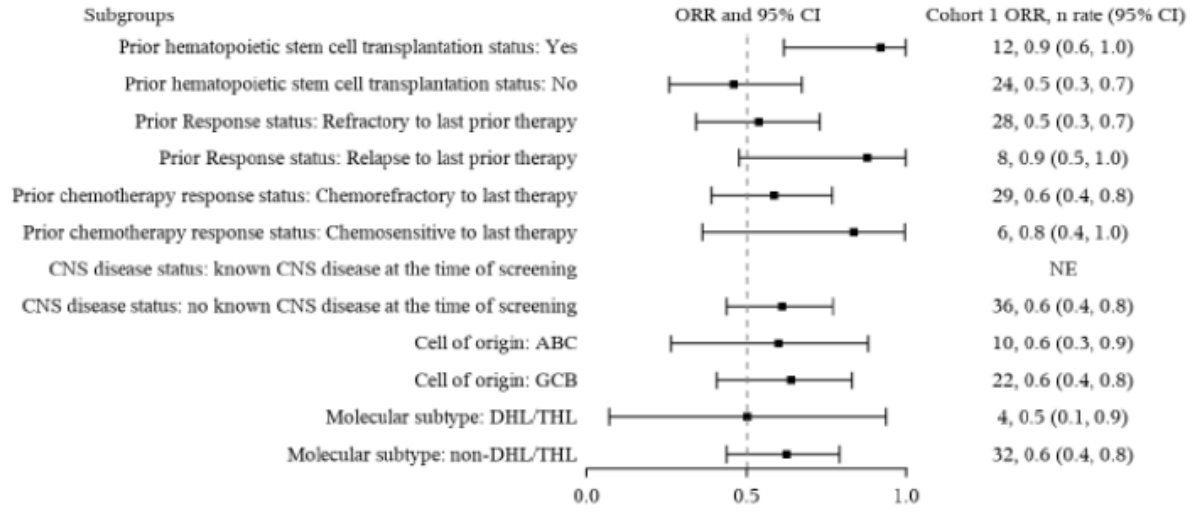
A total of 16 subjects in the DLBCL Treated Set received retreatment cycles with JCAR017 for PD following CR. The ORR per investigator assessment after retreatment cycles was 18.8% (95%CI 4.0 - 45.6), with a CR rate of 12.5% (95%CI 1.6 - 38.3).

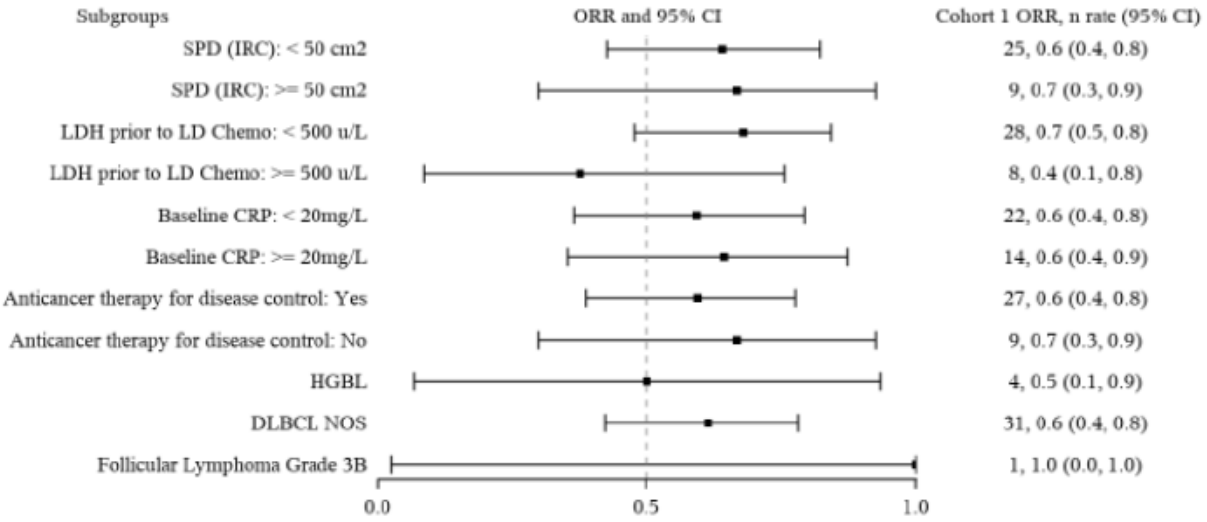
Study BCM-001 Subgroup Analyses

Due to the small sample size, no formal subgroup analyses were performed. Preliminary results for ORR by IRC in Cohort 1 are summarised in Figures below.

Figure 23. Forest plot of Overall Response Rate – IRC Assessment JCAR017-Treated Set







Summary of main efficacy results

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

Table 33. Summary of efficacy for trial 017001

Title: A Phase 1, multicenter, open-label study of JCAR017, CD19-targeted chimeric antigen receptor (CAR) T Cells, for relapsed and refractory B-cell non-Hodgkin lymphoma			
Study identifier	017001; NCT02631044, TRANSCEND NHL		
Design	Open-label, multicentre, multicohort, seamless design, Phase 1 study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		At least 2 years not applicable not applicable
Hypothesis	Exploratory: to determine the safety, antitumour activity, and pharmacokinetics of JCAR017		
Treatments groups	DLBCL Cohort Leukapheresed Set		All leukapheresed subjects in the DLBCL Cohort, including subjects who received JCAR017 or nonconforming product as well as subjects who discontinued prior to receiving JCAR017 or nonconforming product
	DLBCL Cohort Efficacy Analysis Set		Subjects in the DLBCL Cohort who received at least one dose of JCAR017 and who had PET-positive disease present before JCAR017 administration based on IRC assessment
	DLBCL Cohort Efficacy Analysis Set, DL2S, v4		All subjects in the DLBCL Efficacy Analysis Set who received JCAR017 cell product at DL2S (100×10^6 CAR+ T cells single-dose regimen) manufactured using the proposed commercial process v4
Endpoints and definitions	Primary endpoint	**ORR**	The proportion of subjects with a BOR of either CR or PR by IRC assessment based on the Lugano 2014 criteria
	Secondary endpoints	**CRR**	The proportion of subjects achieving a BOR of CR by IRC assessment based on the Lugano 2014 criteria
		DOR	Duration of response evaluated based on IRC assessments for subjects who achieved a CR or PR per the Lugano 2014 criteria and following the censoring rules per EMA guidelines
		PFS	The time from first infusion of JCAR017 to PD, per IRC assessment based on the Lugano 2014 criteria, or death

		OS	The time from treatment with JCAR017 to the date of death
Database lock	19 Jun 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Interim analysis		
Descriptive statistics and estimate variability	Treatment group	Leukapheresed (ITT) Set	Efficacy Analysis Set	Efficacy Analysis Set, DL2S, v4
	Number of subject	N=345	N=257	N=121
	ORR (%)	60.6%	72.8%	76.0%
	95%CI	(55.2, 65.8)	(66.9, 78.1)	(67.4, 83.3)
	CRR (%)	43.2%	52.9%	53.7%
	95%CI	(37.9, 48.6)	(46.6, 59.2)	(44.4, 62.8)
	Median DOR (months)	11.8	13.3	11.1
	95%CI	(7.3, 23.1)	(8.0, NR)	(4.4, NR)
	Median PFS (months)	4.9	6.8	6.0
	95%CI	(4.4, 7.0)	(3.3, 12.7)	(3.0, 11.4)
	Median OS (months)	15.2	27.3	27.3
	95%CI	(11.4, 23.4)	(16.2, 45.6)	(10.0, NR)
Notes	NA			

Table 34. Summary of efficacy for trial JCAR017-BCM-001

Title: A Phase 2, single-arm, multi-cohort, multi-centre trial to determine the efficacy and safety of JCAR017 in adult subjects with aggressive b-cell non-Hodgkin lymphoma		
Study identifier	JCAR017-BCM-001; NCT03484702, TRANSCEND WORLD	
Design	Open-label, multi-centre, multi-cohort, Phase 2 study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	At least 2 years not applicable not applicable

Hypothesis	Exploratory: to determine the efficacy and safety of JCAR017		
Treatments groups	Cohort 1 (EU) JCAR017-treated Set		All subjects who received JCAR017
	Cohort 1 (EU) Enrolled Set		All subjects who signed informed consent, passed all eligibility criteria, and underwent leukapheresis.
Endpoints and definitions	Primary endpoint	**ORR**	The proportion of subjects with a BOR of either CR or PR by IRC assessment based on the Lugano 2014 criteria
	Secondary endpoints	**CRR**	The proportion of subjects achieving a BOR of CR by IRC assessment based on the Lugano 2014 criteria
		DOR	Duration of response evaluated based on IRC assessments for subjects who achieved a CR or PR per the Lugano 2014 criteria and following the censoring rules per EMA guidelines
		EFS	The time from the date of JCAR017 infusion to the earliest of the following events: death from any cause, PD per IRC assessment based on the Lugano 2014 criteria, or starting a new anticancer therapy
		PFS	The time from first infusion of JCAR017 to PD, per IRC assessment based on the Lugano 2014 criteria, or death
		OS	The time from treatment with JCAR017 to the date of death
Database lock	04 Jan 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Interim analysis		
Descriptive statistics and estimate variability	Treatment group	Cohort 1 (EU) JCAR017-treated Set	Cohort 1 (EU) Enrolled Set
	Number of subject	N=36	N=45
	ORR (%)	61.1%	55.6%
	95%CI	(43.5, 76.9)	(40, 70.4)
	CRR (%)	33.3%	31.1%

	95%CI	(18.6, 51)	(18.2, 46.6)
	Median DOR (months)	3.50	3.35
	95%CI	(2.20, NR)	(2.23, 11.27)
	Median EFS (months)	3.07	4.40
	95%CI	(2.60, 4.60)	(3.45, 5.95)
	Median PFS (months)	3.25	4.63
	95%CI	(2.96, 5.39)	(4.17, 6.44)
	Median OS (months)	14.98	13.50
	95%CI	(5.48, NR)	(7.29, 23.33)
Notes	NA		

Clinical studies in special populations

N/A

In vitro biomarker test for patient selection for efficacy

N/A

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

Subjects with Follicular Lymphoma Grade 3B

Overall, 8 subjects in Studies 017001 (n=4), BCM-001 (n=2) and BCM-002 (n=2) had FL3B. Clinical data were provided for the 6 subjects in Studies 017001 and BCM-001 with a data cutoff of 19 Jun 2020.

For the 6 subjects diagnosed with FL3B by the investigators in Studies 017001 and BCM-001, additional histopathological data were obtained from the investigational sites that supported the diagnosis of FL3B as per WHO classification system in 4 subjects (Swerdlow, 2008; Swerdlow, 2017). For the remaining 2 subjects, the diagnosis was based on pathologist's conclusions and investigator's clinical assessment.

The 4 subjects with FL3B in Study 017001 were 45 to 71 years of age with 3 subjects female and 1 subject male, and all subjects were white. One subject had prior HSCT, and no subjects received anticancer treatment for disease control. Median on-study follow-up time was 14.8 months (range 8.9 to 24.0). The best response to any prior therapy was CR for 3 subjects and PR for 1 subject. Prior to lymphodepleting chemotherapy (LDC), no subjects had lactate dehydrogenase (LDH) ≥ 500 U/L and 1 subject had sum of perpendicular diameters (SPD) ≥ 50 cm^2. The 2 subjects from Study BCM-001 were 48 years (female, white, Cohort 1) and 72 years of age (male, Asian, Cohort 3). Prior to LDC, neither of these subjects had LDH ≥ 500 U/L or ≥ 50 cm^2. All 6 subjects with FL3B in both Studies 017001 and BCM-001 were refractory to prior treatment, including 2 subjects receiving auto-haematopoietic stem cell transplant (HSCT). Subjects were European Cooperative Oncology Group performance score (ECOG) 0 at screening.

Updated efficacy data in subjects with FL3B (data cutoff 04 Jan 2021) are summarised in the table below.

Table. 35. Studies 017001 and BCM-001, Subjects with FL3B: Efficacy Results by Subject Based on IRC Assessment, DLBCL Efficacy Set and JCAR017 Treated Set

		Data Cutoff Date			
		19 Jun 2020	04 Jan 2021		
	Best Overall Response	Duration of Response (months)	Response Ongoing at Data Cutoff Date	Duration of Response (months)	Alive at Data Cutoff Date
Study 017001					
00X-XXXX	CR	17.3	Yes	17.3	Yes
00X-XXXX	CR	23.0	Yes	23.0[a]	Yes
00X-XXXX	CR	8.1	Yes	11.1[a]	Yes
00X-XXXX	CR	1.7	Yes	11.1[a]	Yes
Study BCM-001					
00X-XXXX	CR	16.95	Yes	22.97	Yes
00X-XXXX	CR	9.03	Yes	17.08	Yes

CR = complete response; DLBCL = diffuse large B-cell lymphoma; EMA = European Medicines Agency; FL3B = follicular lymphoma Grade 3B; IRC = Independent Review Committee; JCAR017 = lisocabtagene maraleucel.
Note: EMA censoring rules were applied.
[a] Subjects completed Study 017001. Duration of response shown was censored at the time of Study 017001 completion. Subjects enrolled in the long-term follow-up Study GC-LTFU-001 with confirmation of ongoing survival at last check before 04 Jan 2021 cutoff.

Bridging Analysis Between Study 017001 and Study BCM-001

Preliminary analyses suggested numerical differences in efficacy outcomes between studies 017001 and BCM-001 (see table below).

Table 36. Liso-cel Efficacy in Study 017001, DLBCL Cohort and Study BCM-001 Cohort 1

	Study BCM-001 Cohort 1[a]		Study 017001 DLBCL Cohort[b]
	As of 13 Sep 2019	As of 19 Jun 2020	As of 19 Jun 2020
Parameter	JCAR017-treated Set (N = 27)	JCAR017-treated Set (N = 36)	JCAR017 Treated Efficacy Analysis set (N = 257)
Overall response rate[c], n (%)	13 (48.1)	22 (61.1)	187 (72.8)
95% CI	28.7, 68.1	43.5, 76.9	66.9, 78.1
Complete response rate[c], n (%)	7 (25.9)	12 (33.3)	136 (52.9)
95% CI	11.1, 46.3	18.6, 51.0	46.6, 59.2
Median DOR[c] (95% CI), months	2.53 (1.08, 9.23)	3.50 (2.20, NR)	13.3 (8.0, NR)
Median duration of CR[c] (95% CI), months	9.23 (2.33, 9.23)	9.23 (2.43, NR)	26.1 (20.2, NR)
Median PFS[c] (95% CI), months	2.99 (2.00, 5.22)	3.25 (2.89, 5.36)	6.0 (3.5, 9.0)
Median OS (95% CI), months	8.34 (3.38, NR)	18.56 (5.82, NR)	27.3 (16.2, 45.6)
≥ 6-month OS, %	57.5	66.7	74.9
≥ 12-month OS, %	28.8	50.2	58.8

CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response; DL = dose level; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; IRC = independent review committee; JCAR017 = lisocabtagene maraleucel (liso-cel); NR = not reached; OS = overall survival; PFS = progression-free survival.
[a] Study BCM-001: dose of 100 × 10^6 CAR+ T cells and product version 4 (v4).
[b] Study 017001: 45 subjects received DL1S (50 × 10^6 CAR+ T cells as single dose), 6 subjects received DL1D (50 × 10^6 CAR+ T cells as 2-dose), 178 subjects received DL2S (100 × 10^6 CAR+ T cells as single dose), 41 subjects received DL3S (150 × 10^6 CAR+ T cells as single dose). Product versions v2, v3, v4.
[c] Based on IRC assessment using European Medicines Agency censoring rules.

Analysis of PK and product characteristics between Study 017001 and Study BCM-001 demonstrated drug product analytical comparability and similar PK expansion profiles across studies. To appraise the

clinical relevance of this numerical difference in response rates between Study 017001 and Study BCM-001 Cohort 1, an exploratory bridging analysis of response data from the studies was conducted.

Methods

The primary objective of this analysis was to compare the efficacy, defined as ORR and CR rate at Month 1 and Month 3 of JCAR017-treated subjects in Study BCM-001 (Cohort 1) and Study 017001 (DLBCL Cohort) (Bridging Analysis Sets), adjusting for differences in key clinical factors. The secondary endpoints were DOR and PFS.

Eligibility criteria in Study BCM-001 (Cohort 1) were similar to those in Study 017001. Since study BCM-001 did not enrol subjects with tiNHL and PMBCL, these subsets were excluded from the Bridging Analysis Set, which eventually included all subjects who had received the JCAR017 cell product (manufactured using process v.4), in accordance with DP release specifications at a single dose of 100 x 10^6 CAR+ T cells, and had at least 1 month follow-up after their first infusion.

The variables included in the logistic model were selected as they identified study subjects with high tumour burden (SPD and LDH), high inflammatory state (CRP) or a higher risk for a poor treatment outcome (increased age, higher ECOG PS, more prior lines of treatment). The pre-lymphodepleting chemotherapy (LDC) visit was chosen as the timepoint for LDH, SPD, CRP, and ECOG PS measures. If pre-LDC measures were not available, measures before Study Day 1 (baseline) or at screening were used as the second and third choice, respectively.

As requested by the CHMP, additional sensitivity analyses were performed as follows:

- Model 1 adjusted for IPI components at screening such as number of extranodal sites ≥ 2, Ann Arbor disease stage > 2, age > 60 years, LDH > ULN, ECOG PS (0, 1, or 2), as well as bulky disease (longest target lesion ≥ 10 cm), relapsed to the last therapy, number of prior lines of therapy, and use of anticancer therapy for disease control

- Model 2 adjusted for IPI score > 2, bulky disease at screening, relapsed to the last therapy, number of prior lines of therapy, and use of anticancer therapy for disease control

Logistic regression models, including the study indicator and the factors listed above as covariates, were fitted to ORR and CR rate outcomes at 1 and 3 months separately. One month and 3 months were chosen to control for length of follow-up, so there is no systematic bias introduced with longer timepoints where responses would have more chance to evolve. To mitigate the issue of small sample size of the BCM-001 data, a Bayesian approach was used in addition to the classical logistic regression approach. The Bayesian approach was implemented with R-package Markov Chain Monte Carlo (MCMC) package (Martin, 2019) using a proper diffused prior with 0.0003 precision. For the Bayesian approach, the posterior distribution, posterior mean, median and 95% credible interval of rate differences (BCM-001 versus 017001 Bridging Analysis Sets) were reported. Trace plots for each parameter in each model were checked. For the classical logistic regression approach, the rate difference estimates and 95% confidence intervals (CIs) were calculated by Gcomputation as implemented in R-package Regression Standardization (Sjolander, 2019). Standard logistic model outputs were also presented.

Results

Of the 40 subjects who received 100 x 10^6 CAR+ T cells drug product in Study BCM 001, 4 subjects who received nonconforming product were excluded from the D120 Bridging Analysis Set. Thus, 36 subjects from Cohort 1 of Study BCM-001 were included in the D120 Bridging Analysis Set.

In Study 017001, 150 of the 257 subjects in the DLBCL Efficacy Set were excluded from the D120 Bridging Analysis Set, including 87 subjects treated with dose regimens other than DL2S, 49 subjects

who received liso-cel manufactured with a process other than v4, 12 subjects with PMBCL, and 2 subjects with tiNHL. Thus, 107 subjects from Study 017001 were included in the D120 Bridging Analysis Set.

The bridging analysis was performed using the data cutoff date of 19 Jun 2020 (corresponding to the BCM-001 Cohort 1 primary analysis). Baseline characteristics were similar across studies, except for the use of anticancer therapy for disease control that was more frequent in Study BCM-001 compared to Study 017001 (75.0% versus 47.7%).

Additional baseline disease characteristics, which were included in the adjustment Model 1 and Model 2: subjects from Study BCM-001 had a higher tumour burden compared to subjects from Study 017001 with a higher proportion of subjects with ≥ 2 extranodal sites (41.7% versus 27.1%), a higher proportion of subjects with bulky disease (longest target diameter ≥10 cm; 16.7% versus 8.4%), a higher proportion of subjects with LDH >ULN (75.0% versus 53.3%), and a higher proportion of subjects with IPI >2 (50.0% versus 38.3%).

Unadjusted response rates (ORR and CR rate) based on IRC assessment at Months 1 and 3 are presented in the table below for the primary and D120 Bridging Analyses.

Table 37. Unadjusted Overall and Complete Response Rate in Studies BCM-001 and 017001 by Indepenedent Review Committee (Primary and Day 120 Bridging Analysis) (Bridging Analysis Set)

	Primary Analysis		Day 120 Analysis	
	Study 017001 (N = 105)[b]	Study BCM-001 (N = 24)	Study 017001 (N = 107)[b]	Study BCM-001 (N = 36)
Overall response rate (CR + PR)[a]				
Month 1				
n/n*	72/105	13/24	74/107	20/36
ORR, %	68.6	54.2	69.2	55.6
95% CI	58.78, 77.28	32.82, 74.45	59.50, 77.73	38.10, 72.06
Month 3				
n/n*	36/105	4/18	38/107	12/36
ORR, %	34.3	22.2	35.5	33.3
95% CI	25.30, 44.19	6.41, 47.64	26.50, 45.35	18.56, 50.97
Complete response rate[a]				
Month 1				
n/n*	45/105	7/24	47/107	8/36
CR rate, %	42.9	29.2	43.9	22.2
95% CI	33.24, 52.89	12.62, 51.09	34.34, 53.85	10.12, 39.15
Month 3				
n/n*	29/105	4/18	31/107	11/36
CR rate, %	27.6	22.2	29.0	30.6
95% CI	19.34, 37.20	6.41, 47.64	20.61, 38.54	16.35, 48.11

CI = confidence interval; CR = complete response; D120 = day 120; n = number of responders; n* = number of subjects who had 1 or 3 months follow-up; ORR = overall response rate; PR = partial response; tiNHL = diffuse large B-cell lymphoma transformed from indolent non-Hodgkin lymphoma other than follicular lymphoma.

[a] Calculated as the number of responders (n) divided by the number of subjects who had 1- or 3-month follow-up from the liso-cel infusion (n*).

[b] In the primary and D120 analyses of Study 017001, 2 subjects with tiNHL were excluded from the Bridging Analysis Set.

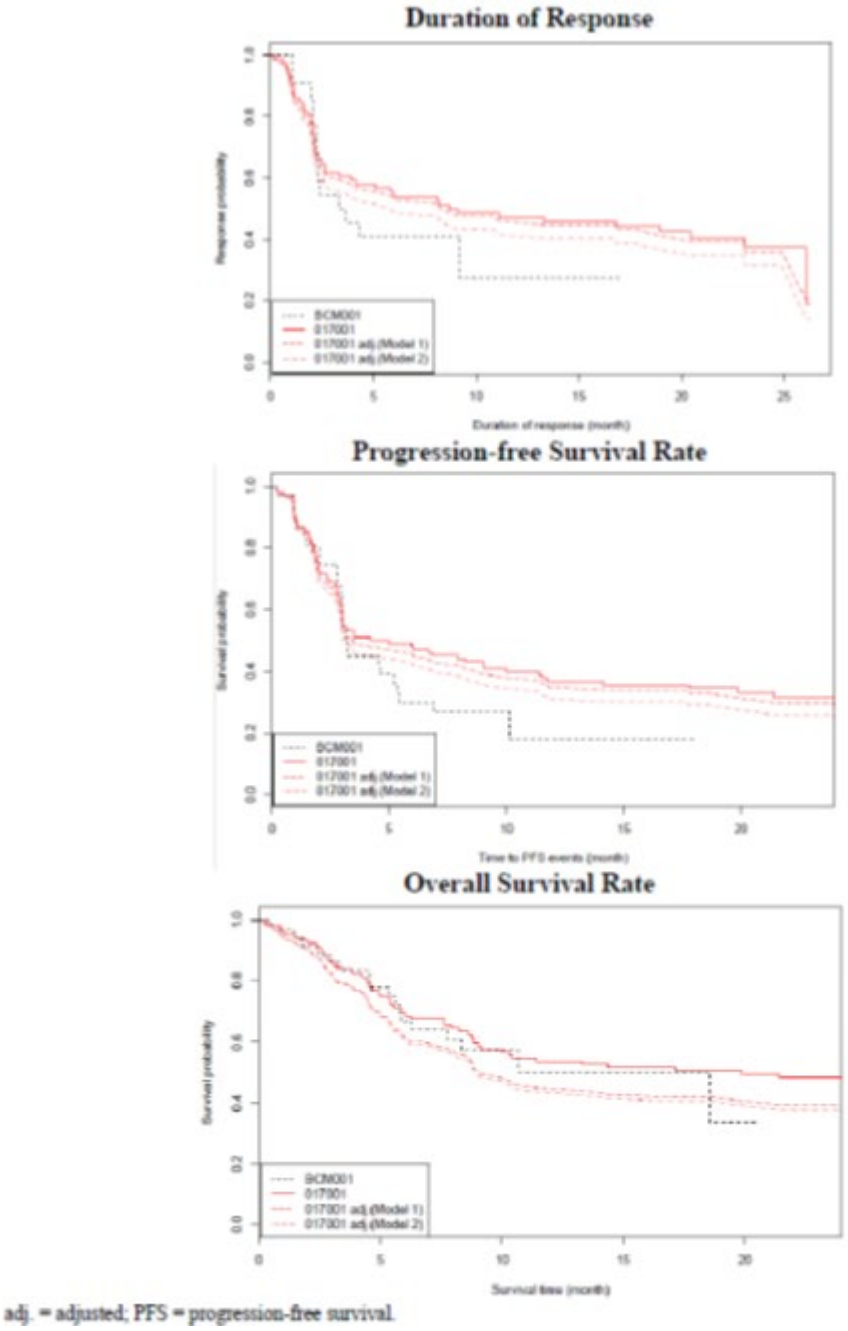
After adjustment for the baseline factors with the Original Adjustment Model, the peak of distribution shifted to 0 for ORR and CR rate at Month 1. At Month 3, the peak of distribution is close to 0 both before and after the adjustment, demonstrating that the response rates were already similar between studies without adjustment. Adjustment for baseline factors improved comparability at Month 1; Month 3 responses were similar even before adjustment.

Sensitivity analyses using Bayesian logistic models 1 and 2 also improved comparability in the CR rate at Month 1 between the 2 studies, while the adjustment effect on the ORR rate at Month 1 was minimal. The ORR and CR rate at Month 3 were similar between the 2 studies, even prior to adjustment.

Time-to-event Efficacy Endpoints

The estimated DOR, PFS rate, and OS rate for the Bridging Analysis Set without adjustment and adjusted using Model 1 and Model 2 are provided in Figure below.

Figure 24. Unadjusted and Adjusted Kaplan-Meier Curves for Duration of Response, Progression-Free Survival Rate and Overall Survival Rate (Bridging Analysis Set, Day 120 Analysis)



adj. = adjusted; PFS = progression-free survival.

Duration of Response

The Kaplan Meier (KM) estimate for median DOR in the Bridging Analysis Set was 8.67 months (95% CI: 3.88, NR) for Study 017001 and 3.50 months (95% CI:2.33, NR) for Study BCM-001. Overall, adjustment using Models 1 and 2 minimally improved the comparability of the DOR rate between the 2 studies. In the Intent-to-treat (ITT) Analysis Set, adjustment using these models minimally improved the comparability of the DOR rate between the 2 studies.

Progression-free Survival

The KM estimate for median PFS in the Bridging Analysis Set was 4.99 months (95% CI: 3.02, 11.4) for Study 017001 and 3.25 months (95% CI: 2.99, 6.9) for Study BCM-001. Adjustment using these models slightly improved comparability of the PFS rate between the 2 studies. Overall, adjustment effect was minimal, similar to what was observed in the DOR analyses. In the ITT Analysis Set, adjustment using these models slightly improved the comparability of PFS rate between the 2 studies.

Overall Survival

The KM estimate for median OS in the Bridging Analysis Set was 19.88 months (95% CI: 9.0, NR) for Study 017001 and 18.56 months (95% CI: 6.28, NR) for Study BCM-001. The estimates of OS rates at all the specified timepoints were already similar between the 2 studies with overlapping CIs prior to the adjustment. In the ITT Analysis Set, the estimates of OS rates at all the specified timepoints were already similar between the 2 studies with overlapping CIs prior to the adjustment.

Supportive study(ies)

Systematic Literature Review of Clinical Evidence on the Treatment of 3L+ Relapsed or Refractory (R/R) B-Cell non-Hodgkin Lymphoma (NHL)

Methods

The SLR was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported in alignment with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) guidelines (Higgins JPT, 2011, Moher, 2009).

The database search was restricted to the publication years 01 Jan 2003 through 02 Dec 2019 since the first trial for rituximab, the SOC in newly diagnosed large B-cell lymphomas, was published in 2002. The last updated was conducted on 02 Dec 2019.

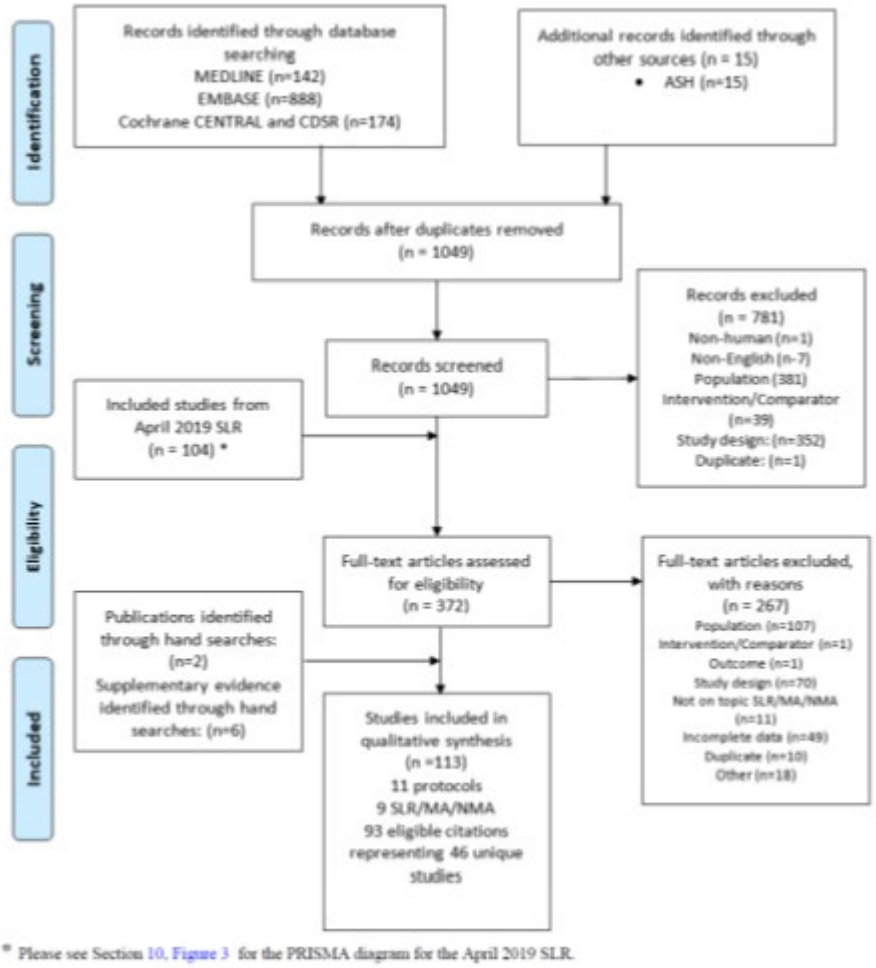
Potentially eligible studies were screened by two independent reviewers. Allowed interventions/comparators included single-agent or multiagent chemotherapy, chemoimmunotherapy, single-agent or multiagent immunotherapy, CAR T-cell therapies, allo-HSCT, auto-HSCT, best supportive care, placebo and no comparator. Studies had to have ≥25 patients by treatment arm (or ≥50 patients per study). Studies had to be conducted in one or more of the following countries: Belgium, the Netherlands, Switzerland, Denmark, Finland, Norway, Sweden, Germany, France, Italy, Spain, the UK, the US, Japan, Australia, and Canada.

Quality assessment checklists for either trials or observational studies were completed for each study using checklists recommended by NICE (2009). All publications were assessed, except for conference proceedings, due to insufficient methodological data to assess study quality.

Results

Study search and selection results are summarised in the figure below:

Figure 25. PRISMA Flow Diagram



* Please see Section 10, Figure 3 for the PRISMA diagram for the April 2019 SLR.

A total of 4 RCTs, 19 Phase 1 or 2 single-arm trials, and 22 observational studies (3 prospective, 19 retrospective) were identified in the literature search. Forty-two studies (93%) included patients with DLBCL, while three studies (7%) only included patients with PMBCL (Armand, 2019, Herrera, 2019, Zinzani, 2017). No studies exclusively enrolled patients with FL3B.

Across studies that only enrolled patients with DLBCL, the median age ranged from 52 to 73 years. Twelve studies included patients with PMBCL and/or FL3B in addition to DLBCL. The percentage of patients with PMBCL in this SLR ranged from 1% to 13% of the study population. FL3B was reported in only 3 studies and represented 1% to 9% of the study population. In the three studies that exclusively enrolled patients with PMBCL, median age ranged from 33 to 35.5 years and the proportion of female participants was higher than in studies that enrolled patients with DLBCL (54% to 57%) (Armand, 2019, Herrera, 2019, Zinzani, 2017).

Four studies included agents that have been approved in the EU for use in the 3L+ r/r DLBCL indication: axicabtagene ciloleucel (Locke, 2019), tisagenlecleucel (Schuster, 2019d), polatuzumab vedotin plus bendamustine and rituximab (Sehn, 2020), and pixantrone dimaleate (Pettengell, 2012, Pettengell, 2016). Of these trials, three only included patients with DLBCL, while ZUMA-1 (axicabtagene ciloleucel) also included patients with PMBCL (8% of study population). The median age of the study populations was slightly lower in the two studies that evaluated CAR T-cell therapies (56 to 58 years) than those evaluating pixantrone (60 years) or polatuzumab vedotin (67 years).

Overall response rate, CR, and partial response (PR) were reported in 36 (80%), 34 (76%), and 27 (60%) studies, respectively. Duration of response was reported in 20 (44%) studies. Overall survival

was reported by 35 (77%) studies and PFS was reported by 30 (67%) studies. Event-free survival was infrequently reported (5 studies, 11%).

Three major categories of interventions were identified: CAR T-cell therapies (n=8 studies), salvage therapy (n=32 studies), and HSCT (n=5 studies).

CAR T-cell therapies

Please, see the MAIC analysis below.

Salvage therapies

In patients with DLBCL of unreported subtypes, ORRs ranged from 4.9% to 59.5% (Brown, 2018, Morschhauser, 2019), CR rates ranged from 0% to 32.8% (Brown, 2018, Kahl, 2019), and DOR ranged from 4.6 months to 20.1 months (Jurczak, 2018, Witzig, 2011). The DOR of 20.1 months was observed in a study of patients with DLBCL who received MOR208 monotherapy (tafasitamab), an investigational product. This study included some patients being treated in the 2L setting (34%), with 69% of patients being refractory to a prior rituximab regimen. In one study of patients with DLBCL NOS (n=56), the ORR of patients treated with polatuzumab vedotin plus bendamustine and rituximab (n=29) was 35%, and the CR rate 31% (Sehn, 2018). Duration of response was not reported. In the single study that reported on patients with DLBCL transformed from indolent NHL (n=88), although ORR was not reported, 42% of patients achieved CR with R-GemOx (Cazelles, 2019). Duration of response was not reported. In patients with DLBCL of unreported subtypes, median OS ranged from 4.4 months (Van Den Neste, 2016) to 20.1 months (Morschhauser, 2019), median PFS ranged from 1.9 months (Palomba, 2019) to 5.6 months (Morschhauser, 2019), and median follow-up time ranged from 7.5 months (Kahl, 2019) to 51 months (Zaja, 2018). Patients receiving polatuzumab vedotin with bendamustine and rituximab (n=29) had a median OS and median PFS of 11.5 months and 6.0 months, respectively. (Sehn, 2018). Another study reported on patients with DLBCL transformed from indolent NHL (n=88) and patients with no previous indolent NHL (n=108) receiving R-GemOx: among patients with DLBCL transformed from previous indolent lymphoma, median OS was 21 months and median PFS was 3 months, compared to a median OS of 8 months and median PFS of 6 months in DLBCL patients without previous indolent NHL (Cazelles, 2019).

Two studies reported response outcomes in patients with PMBCL (Armand, 2019, Zinzani, 2019a). Treatment with nivolumab and brentuximab vedotin (n=30) was associated with an ORR of 73% and a CR rate of 37%, while median OS and PFS were not reached with a median follow-up time of 11.1 months (Zinzani, 2019a), and treatment with pembrolizumab (n=53) was associated with an ORR of 45% and a CR rate of 13%. Patients treated with pembrolizumab did not reach a median OS and had a median PFS of 5.5 months at a median follow-up of 12.5 months (Armand, 2019). Duration of response and median OS was not reached in either study.

No study presented results specific to patients with FL3B.

In patients with a median of two prior lines of therapy, ORRs and CR rates ranged from 3% to 73% (Ansell, 2019, Zinzani, 2019a) and 0% to 37% (Ansell, 2019, Zinzani, 2019a), respectively. Duration of response was 8.6 to 14.5 months (Coiffier, 2016, Zaja, 2018). Objective response rates reported in studies of patients with a median of three prior lines of therapy were slightly lower (ORR, 4.9% to 59.5%) Complete response rates and DOR in studies of patients with a median of three prior lines of therapy were 0% to 32.8% (Brown, 2018, Kahl, 2019) and 4.8 to 13.4 months (Kahl, 2019, Morschhauser, 2019), respectively. Survival outcomes did not differ with increasing median prior lines of therapy. The range of median OS across studies was similar in studies of patients with a median of three prior lines of therapy (4.6 months to 10.09 months) (Kahl, 2019, Pettengell, 2016) and in those of patients with a median of two prior lines of therapy (3.4 months to 12.4 months) (Eyre, 2016, Sehn, 2020). The longest survival rates were observed in patients who received pixantrone (16.1 months) (Pettengell, 2016) and

polatuzumab vedotin plus rituximab (20.1 months) (Morschhauser, 2019) after a median of three lines of therapy. Median PFS was also similar in studies of patients with a median 3 prior lines of therapy (1.41 months to 6.3 months) (Ansell, 2019, Pettengell, 2016) and those with a median 2 prior lines of therapy (2 months to 9.5 months) (Eyre, 2016, Sehn, 2020). The longest reported median PFS were observed in studies of therapies approved for DLBCL (polatuzumab vedotin plus bendamustine and rituximab: 6.7 months; pixantrone: 5.7 months) (Pettengell, 2012, Sehn, 2020).

Comparison with CAR T-treated Populations in Real-world Setting in Europe

To assess external validity of outcomes observed from Study 017001 and generalisability to the European target population, the applicant conducted a systematic literature review (SLR) to identify literature published on the treatment of CAR T- cell therapy in large B-cell lymphomas in the RW setting. The SLR searched MEDLINE and Embase via the Ovid platform up to 30 Nov 2020 and conference websites during 2018 to 2020 in accordance with methods recommended by the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions (Higgins, 2019). Results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher, 2009).

Overall, 17 of the 87 identified publications reported RW CAR T use in Europe-only populations. These included a cohort (N = 116) from France (Vercellino, 2020) and another cohort (N = 183) from the UK (Kuhnl, 2020) which currently represent the largest published RW CAR T-treated populations in Europe. The French cohort included all consecutive patients with R/R DLBCL treated in 5 French Lymphoma Study Association centres between June 2018 and January 2020, whereas the UK cohort included patients treated in the first 12 months of the national programme. A side-by-side comparison of the baseline demographic and disease characteristics of the UK and French RW cohorts versus Studies 017001 and BCM-001 is presented in the table below. The comparison is made based on the JCAR017-treated Set from both 017001 and BCM-001 studies to better align with the populations represented in the UK and French cohorts.

Table 38. Comparison of Baseline Demographics and Characteristics for the European Real-World Patients and Subjects Treated in Studies 017001 and BCM-001

Characteristic	French RW cohort (Vercellino, 2020)	UK RW cohort[a] (Kuhnl, 2020)	017001 DLBCL Treated Analysis Set	BCM-001 JCAR017-treated Set
Data cut	Not applicable	Not applicable	June 19, 2020	June 19, 2020
Sample size (N)	116	183	270	36
Age (years)				
Median (min, max)	NA	57 (18, 75)	63.0 (18, 86)	61.5 (26, 72)
Median (IQR)	60.74 (49.17, 67.61)	NA	63.0 (53.0, 70.0)	61.5 (52.5, 68.0)
Sex, n (%)				
Male	75 (65)	113 (62)	174 (64)	25 (69)
Female	41 (35)	70 (38)	96 (36)	11 (31)
ECOG PS at pre-lymphodepletion, n (%)				
0	50 (43)	159 (86.9)[b]	77 (28.5)	14 (38.9)
1	52 (45)		184 (68.1)	18 (50.0)
2	14 (12)	24 (13.1)	9 (3.3)	4 (11.1)
Bulky disease, n (%)				
No	101 (87)[d]	134 (73.2)[c]	238 (88.1)[d]	28 (77.8)
Yes	15 (13)[d]	49 (26.8)[c]	30 (11.1)[d]	6 (16.7)
Missing	0 (0)	0 (0)	2 (0.7)	2 (5.6)
Disease histology[e], n (%)				
DLBCL	93 (80)	132 (73)	191 (71)	28 (78)[f]
tFL	17 (15)	37 (20)	60 (22)	7 (19)
PMBCL	6 (5)	14 (8)	15 (6)	0 (0)
FL3B	0 (0)	0 (0)	4 (2)	1 (3)
Molecular subtype, n (%)				
Double/triple hit	NA	21 (11.4)	36 (13.3)	4 (11.1)

Characteristic	French RW cohort (Vercellino, 2020)		UK RW cohort[a] (Kuhnl, 2020)	017001 DLBCL Treated Analysis Set	BCM-001 JCAR017-treated Set
Prior lines of systemic therapy, n (%)					
Median (IQR)	Non-relapsed (n=61)	3 (2, 4)	NA	3.0 (2.0, 4.0)	2.0 (2.0, 3.5)
	Relapsed (n=55)	3 (2, 4)			
<3	NA		109 (60)	131 (48.5)	19 (52.8)
>=3	NA		74 (40)	139 (51.5)	17 (47.2)
< 4	82 (71)		NA	199 (73.7)	27 (75)
≥ 4	34 (29)		NA	71 (26.3)	9 (25)
IPI score at screening, n (%)					
0 or 1	Low: 36 (31.0)		47 (25.7)	86 (31.9)	Low: 8 (22.2)
2 or 3	Intermediate: 63 (54.3)		108 (59.0)	156 (57.8)	Intermediate: 21 (58.3)
4 or 5	High: 17 (14.7)		15 (8.2)	26 (9.6)	High: 7 (19.4)
Missing	0 (0)		13 (7.1)	2 (0.7)	0 (0)
Bridging therapy, n (%)					
No	15 (13)		29 (15.8)[#]	111 (41)	9 (25)
Yes	101 (87)		154 (84.2)[#]	159 (59)	27 (75)
Extranodal sites, n (%)					
< 2	83 (72)		132 (72)	195 (72.2)	21 (58.3)
≥ 2	33 (28)		49 (27)	73 (27.0)	15 (41.7)
Missing	0 (0)		2 (1)	2 (0.7)	0 (0)
Cell of origin, n (%)					
GCB	NA		88 (48)	119 (44)	22 (61)
Non-GCB	NA		59 (33)	76 (28)	10 (28)
Missing	NA		34 (19)	75 (28)	4 (11)

Characteristic	French RW cohort (Vercellino, 2020)	UK RW cohort[a] (Kuhnl, 2020)	017001 DLBCL Treated Analysis Set	BCM-001 JCAR017-treated Set
Refractory to last therapy, n (%)				
Relapsed (ie, was not refractory to last therapy)[h]	NA	45 (25)	56 (21)	8 (22.2)
Refractory	NA	138 (75)	214 (79)	28 (77.8)
Primary refractory, n (%)				
No	39 (34)	NA	60 (22.2)[i]	NA
Yes	77 (66)	NA	205 (75.9)[i]	
Unknown	0 (0)	NA	5 (1.9)[i]	
Prior auto-HSCT, n (%)				
No	83 (72)	158 (86)	180 (67)	24 (67)
Yes	33 (28)	25 (14)	90 (33)	12 (33)
Prior allo-HSCT, n (%)				
No	113 (97)	178 (97)	261 (97)	36 (100)
Yes	3 (3)	5 (3)	9 (3)	0 (0)
LDH at pre-lymphodepletion, n (%)				
Elevated: No	61 (53)	34 (19)	212 (78.5)	28 (78)
Elevated: Yes	55 (47)	124 (67)	58 (21.5)	8 (22)
Missing	NA	25 (14)	NA	NA
Time from apheresis to infusion, days				
Median (IQR) time from apheresis to infusion	NA	42 (35, 49)	36.5 (33, 47)	43.0 (42.0, 45.5)

allo-HSCT = allogeneic hematopoietic stem cell transplant; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FL3B = follicular lymphoma Grade 3B; GCB = germinal center B-cell; HGBL = high-grade B-cell lymphoma; HSCT = hematopoietic stem cell transplant; IPI = international prognostic index; IQR = interquartile range; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; NA = not available; PMBCL = primary mediastinal B-cell lymphoma; PS = performance status; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RW = real-world; tFL = transformed follicular lymphoma; UK = United Kingdom.

[a] Reported at time of approval unless specified otherwise.
[b] ECOG = 0 or 1 at pre-lymphodepletion was derived based on the data reported for the ECOG PS = 2 subgroup.
[c] Defined as ≥ 7.5cm.
[d] Defined as ≥ 10 cm.

[e] For the UK cohort, Kuhnl et al classified 122 patients as DLBCL and 10 patients as tMZL, tLPL, and tNLPHL. These categories were combined and reported in this table as DLBCL. These could also be grouped under tiNHL (transformed from other indolent lymphoma).
[f] For TRANSCEND-WORLD, DLBCL was recategorized to include DLBCL NOS and HGBL with MYC and BCL2 and or BCL6 rearrangements with DLBCL histology.
[g] Counts were not reported but were derived as the reported percentage multiplied by the study sample size.
[h] Definitions of refractory to last therapy differ between studies. For the UK cohort, refractory was defined as a progressive or stable disease as a best response to the last line of therapy. In TRANSCEND and TRANSCEND-WORLD, refractory was defined as partial response, progressive disease, or stable disease as the best response to last systemic or transplant therapy with curative intent.
[i] Data related to primary refractory from Study 017001 is derived based on the first prior systemic anti-cancer treatment received, then defined primary refractory status as: missing or unknown (when best response was blank or "unknown"), Yes/primary refractory (when best response was PD or SD), No/not primary refractory (when best response was CR or PR).

Efficacy and safety outcomes (not reported in the French cohort) from the RW cohorts and JCAR017 studies are presented for information only (see the table below). Findings should be viewed within the context of the different CAR T-cells administered, subjects available for evaluation during follow-up, cohort follow-up time, and methods of efficacy and safety assessment.

Table 39. Comparison of Efficacy and Safety Outcomes Reported in the European RW patients and Subjects Treated in Studies 017001 and BCM-001

Outcome	French RW cohort (Vercellino, 2020)	UK RW cohort (Kuhnl, 2020)	017001	BCM-001
Data cut	Not applicable	Not applicable	June 19, 2020	June 19, 2020
CAR T-cell	Kymriah, N = 49 Yescarta, N = 67	Kymriah, N = 44 Yescarta, N = 112	Liso-cel	Liso-cel
Efficacy Outcomes				
Sample size	116	156 (efficacy evaluable)	257 DLBCL-efficacy Set	36 JCAR017-treated Set
Study follow-up time, months (median)	8.2	9.9[a]	24.1[b]	9.53[b]
OS, months (median, 95% CI), leukapheresed patients[c]	NA	8.1 (7.0-10.0; N = 253)	15.2 (11.4-23.4; N = 345)	12.06 (7.29-NE; N = 45)
OS, months (median, 95% CI), infused patients[c]	NA	13.4 (9.7-NR)	27.3 (16.2-45.6)	18.56 (5.82-NR)
12-month OS rate, % (95% CI)	67 (57-79)	-	58.8 (52.5 -64.6)	50.2 (SE: 9.96)
Event-free survival, infused patients (months, 95% CI)	NA	3.2 (3.0, 4.6)	NA	3.07 (2.60, 4.60)[d]
Progression-free survival, months (median, 95% CI)	7.4 (3.0, not available)	-	6.0 (3.5, 9.0) per IRC, EMA	3.25 (2.89, 5.36) per IRC, EMA

Outcome	French RW cohort (Vercellino, 2020)	UK RW cohort (Kuhnl, 2020)	017001	BCM-001
Safety Outcomes				
Sample Size	NA	183	270 DLBCL Treated Set	36 JCAR017-treated Set
CRS, all grade, n (%)	NA	157 (86)	113 (42)	14 (39)
CRS, grade 3+, n (%)	NA	15 (8)	6 (2)	2 (6)
Neurotoxicity, all grade, n (%)	NA	63 (34) (ICANS)	80 (30) (iiNT)	8 (22) (iiNT)
Neurotoxicity, grade 3+, n (%)	NA	27 (15)	27 (10) (iiNT)	5 (14) (iiNT)
Tocilizumab use, n (%)	NA	115 (63)	52 (19)	7 (19)
Steroid use, n (%)	NA	65 (36)	56 (21)	9 (25)
ICU admission, n (%)	NA	59 (32)	34 (13)	4 (11)
Grade 3+ prolonged cytopenia				
Neutropenia at D28, n (%)	NA	75 (43)[f]	53 (20)[g] (Day 29, decreased neutrophil)	11 (31)[g] (Day 29, decreased neutrophil)
Thrombocytopenia at D28, n (%)	NA	69 (39)[f]	115 (43)[g] (Day 29, decreased platelet)	10 (28)[g] (Day 29, decreased platelet)

CAR = chimeric antigen receptor; CI = confidence interval; CRS = cytokine release syndrome; D = day; DLBCL = diffuse large B-cell lymphoma; ICANS = immune effector cell□associated neurotoxicity syndrome; ICU = intensive care unit; iiNT = investigator-identified neurotoxicity; OS = overall survival; NA = not available; NR = not reached; UK = United Kingdom.

[a] For infused patients.

[b] Median on-study follow-up time was reported, which is defined as (EOS date – first dose date + 1)/30.4375. If subjects were continuing on study, the data cutoff date was used to impute the EOS date for the purpose of the calculation.

[c] Response rates were reported by intervention rather than for the pooled cohort. Pooled rates were calculated as the weighted average of intervention-specific response rates.

[d] Definitions of the index (baseline) date for calculating OS are as follows. Kuhnl et al (2020) defined OS as time from approval to death or date of last contact. TRANSCEND and TRANSCEND-WORLD defined OS from date of infusion for the treated set and from date of leukapheresis for the enrolled set. Due to these differences, comparisons of overall survival between studies should be interpreted carefully.

[e] Based on investigator assessment using FDA censoring criteria.

[f] Not reported if assessed by laboratory values or by investigators as AEs.

[g] Assessed by laboratory values.

Indirect Treatment Comparison of CAR T-cell Therapies in Clinical Studies

In line with prior Committee for Medicinal Products for Human Use (CHMP) Scientific Advice (EMEA/H/SA/3617/1/2017/ADT/PR/III), the applicant performed a systematic literature review (SLR) that was included in the MAA (SLR Report). The SLR was conducted for the search period of 01 Jan 2003 to 02 Dec 2019 on the efficacy and safety of treatments for R/R LBCL in the 3L+ therapy. Study selection criteria were established a priori to inform the identification of relevant clinical studies. Of the 45 identified studies (including salvage chemotherapy and CAR T-cell therapies), two pivotal studies led to the approval of CAR T-cell therapies in the EU: the ZUMA-1 trial (Locke, 2019) for axi-cel and the JULIET trial (Schuster, 2019) for tisagenlecleucel. A summary of datasets used in this analysis is shown in the table below.

Table 40. Summary of datasets Used for Matching -adjusted Indirect Treatment Comparisons

Treatment	Trial Name	Data Cutoff[a]	Median Study Follow-up, months (range)	Analysis Set	N
Efficacy Outcomes					
Liso-cel	Study 017001	19 Jun 2020	NA	DLBCL Efficacy Set	257
Tisagenlecleucel – ORR, CR Rate	JULIET	08 Dec 2017	NA	Efficacy Analysis Set	93
Tisagenlecleucel – PFS, OS	JULIET	08 Dec 2017	14 (0.1-26)[b]	Safety Set/Full Analysis Set	111
Axi-cel	ZUMA-1	11 Aug 2018	27.1 (IQR 25.7-28.8)[c]	Phase 2 mITT Set	101
Safety Outcomes					
Liso-cel	Study 017001	19 Jun 2020	19.1 (0.2-45.2)[d]	DLBCL Treated Set	270
Tisagenlecleucel	JULIET	08 Dec 2017	14 (0.1-26)[b]	Safety Set/Full Analysis Set	111
Axi-cel	ZUMA-1	11 Aug 2018	27.4 (NA)[c]	Phase 1 + 2 Safety Analysis Set	108

axi-cel = axicabtagene ciloleucel; CR = complete response; DLBCL = diffuse large B-cell lymphoma; EOS = end of study; IQR = interquartile range; mITT = modified intent-to-treat; N = number; NA = not applicable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SmPC = Summary of Product Characteristics.

[a] Data cutoffs with most complete data availability were included.

[b] Median follow-up time was calculated from infusion to data cutoff (Schuster, 2019).

[c] The way in which median follow-up time was calculated was not reported (Locke, 2019; Yescarta SmPC).

[d] Median on-study follow-up time was reported, which is defined as (EOS date – first dose date + 1)/30.4375. If subjects were continuing on study, the data cutoff date was used to impute the EOS date for the purpose of the calculation (D120 017001 Table 14.3.1.1.6.a).

Clinical factors, most commonly baseline patient characteristics (eg, demographics, disease status) but also related to trial protocol (eg, eligibility criteria, receipt of bridging therapy), were identified through a targeted literature search of evidence on clinical factors prognostic of outcomes in 3L+ R/R LBCL, an inspection of factors reported in the Study 017001, ZUMA-1 and JULIET, as well as clinical expert input. A panel of 5 external clinical experts was established to further guide the identification and rank-order of clinical factors based on relative importance. Furthermore, statistical analyses using Study 017001 patient-level data were conducted to evaluate the strength of association of each clinical factor and each efficacy outcome and clinical factors were then ranked on this basis (ie, data-driven rank). Of the statistical methods considered, random forest regression (Breiman, 2001) was chosen as the method to obtain data-driven rankings, because it has been shown to demonstrate superior predictive power compared to the other methods considered and has a natural metric for variable ranking.

Results of Liso-cel versus Tisagenlecleucel are summarised in the table and figures below.

Table 41. Summary of MAIC Efficacy Results for the Comparison of Liso-cel to Tisagenlecleucel, Primary Analysis, Infused Patients

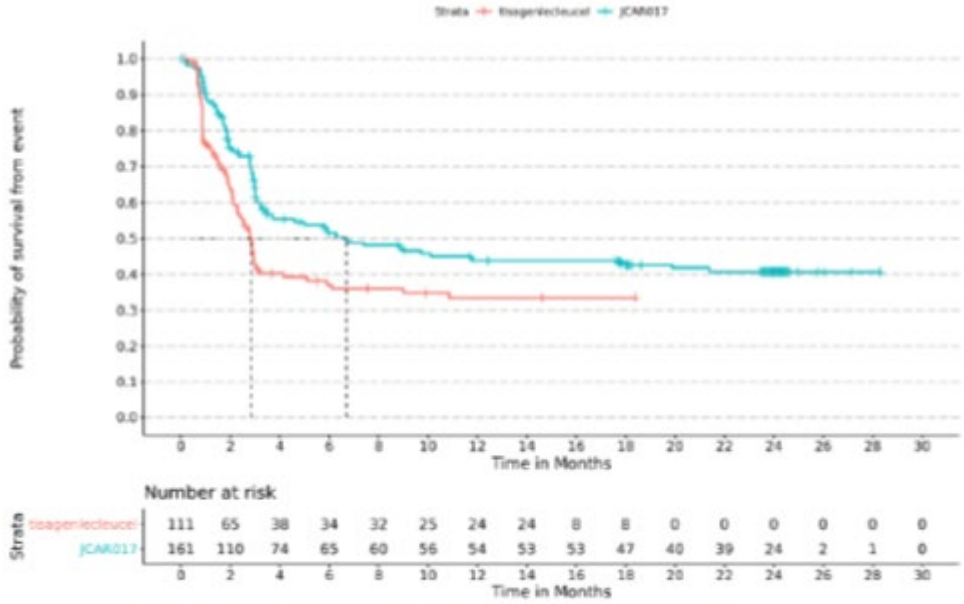
Parameter	Tisagenlecleucel (JULIET) Efficacy Analysis Set	Liso-cel (Study 017001) DLBCL Efficacy Set
Overall Response Rate		
N or ESS[a]	93	164.0
ORR, %	51.6	74.7
Odds Ratio (95% CI)		2.77 (1.63, 4.73)
P-value		< 0.001
Complete Response Rate		
N or ESS[a]	93	200.1
CR Rate, %	39.8	56.0
Odds Ratio (95% CI)		1.92 (1.17, 3.17)
P-value		0.010
Progression-free Survival		
N or ESS[a]	111	149.3
Median PFS (95% CI), Months	2.8 (2.3, 4.2)[b]	6.7 (3.5, NR)
Hazard Ratio (95% CI)		0.66 (0.47, 0.92)
P-value		0.013
Overall Survival		
N or ESS[a]	111	180.0
Median OS (95% CI), Months	11.7 (7.2, NR)[b]	28.9 (19.9, NR)
Hazard Ratio (95% CI)		0.66 (0.46, 0.93)
P-value		0.019

CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ESS = effective sample size; IPD = individual patient data; KM = Kaplan-Meier; liso-cel = lisocabtagene maraleucel; MAIC = matching-adjusted indirect comparison; N = sample size; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

[a] N for JULIET; ESS for Study 017001

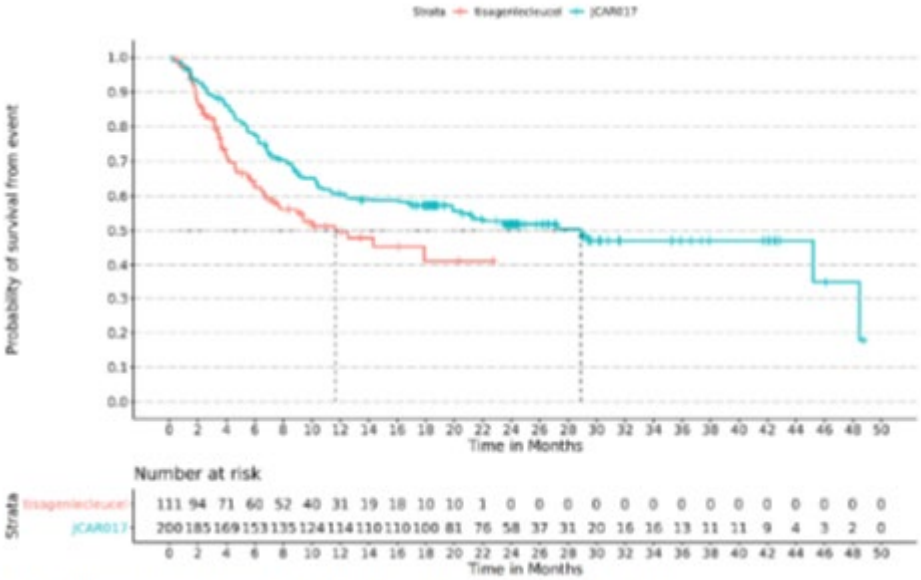
[b] The median was obtained from pseudo-IPD based on digitized KM curve.

Figure 26. Kaplan-Meier Curves of Progression-free Survival for Lios-cel and Tisagenlecleucel in Infused Patients, Matched and Adjusted Comparison (Primary Analysis; ESS=149.3)



ESS = effective sample size; JCAR017 = lisocabtagene maraleucel (liso-cel).

Figure 27. Kaplan-Meier Curves of Overall Survival fro Lios-cel and Tisagenlecleucel in Infused Patients. Matched and Adjusted Comparison (Primary Analysis ESS=180.0)



ESS = effective sample size; JCAR017 = lisocabtagene maraleucel (liso-cel).

Efficacy results from MAICs in the ITT Population were consistent with those in infused patients.

Adjusted TEAEs and AESIs in infused patients showed that the safety profiles between liso-cel and tisagenlecleucel were similar, with the exception of all-grade and Grade ≥ 3 CRS and Grade ≥ 3 prolonged cytopenia by laboratory assessment, the odds of which were statistically significantly lower for liso-cel (all-grade CRS: OR 0.52 [95% CI: 0.31, 0.87]; Grade ≥ 3 CRS: OR 0.10 [95% CI: 0.03, 0.31]; Grade ≥ 3 prolonged cytopenia by laboratory assessment: OR: 0.43 [95% CI: 0.26, 0.73]).

The results from MAICs of liso-cel versus axi-cel are summarised in the table and figures below.

Table 42. Summary of MAIC Efficacy Results for the Comparison of Liso-cel to Axi-cel, Primary Analysis, Infused patients

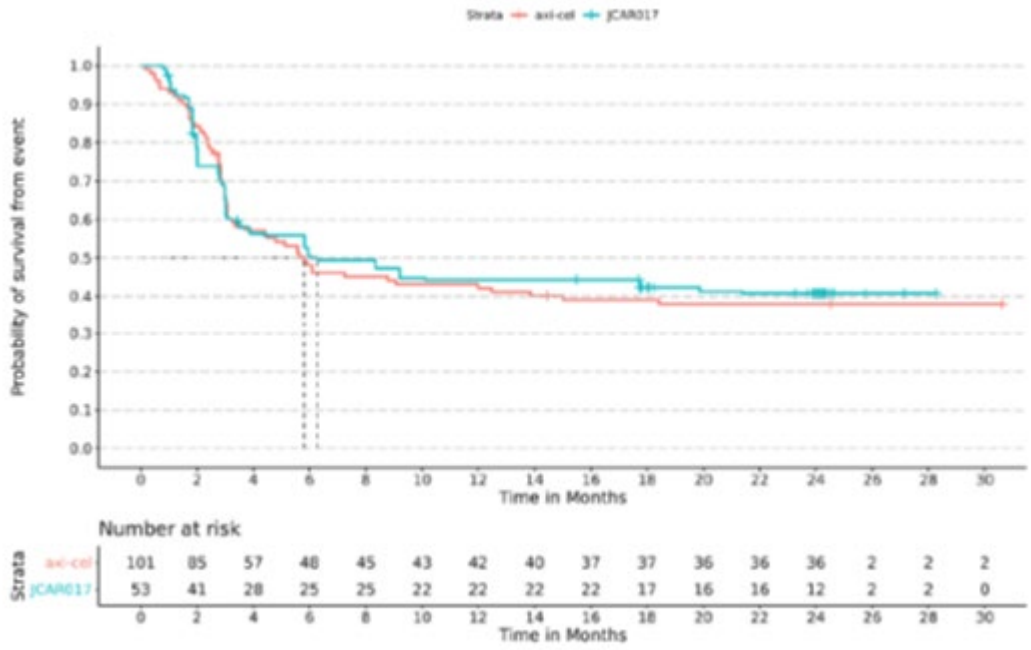
Parameter	Axi-cel (ZUMA-1)	Liso-cel (Study 017001)
Overall Response Rate		
N or ESS[a]	101	42.1
ORR, %	74.3	80.1
Odds Ratio (95% CI)		1.40 (0.56, 3.50)
P-value		0.473
Complete Response Rate		
N or ESS[a]	101	39.6
CR Rate, %	54.5	59.2
Odds Ratio (95% CI)		1.21 (0.56, 2.64)
P-value		0.627
Progression-free Survival		
N or ESS[a]	101	40.0
Median PFS (95% CI), Months	5.8 (3.4, 15.0)[b]	6.3 (3.0, NR)
Hazard Ratio (95% CI)		0.94 (0.57, 1.55)
P-value		0.818
Overall Survival		
N or ESS[a]	101	38.3
Median OS (95% CI), Months	NR (12.8, NR)[b]	48.5 (11.6, NR)
Hazard Ratio (95% CI)		0.78 (0.44, 1.42)
P-value		0.421

axi-cel = axicabtagene ciloleucel; CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ESS = effective sample size; IPD = individual patient data; KM = Kaplan-Meier; liso-cel = lisocabtagene maraleucel; MAIC = matching-adjusted indirect comparison; N = sample size; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

[a] N for ZUMA-1; ESS for Study 017001

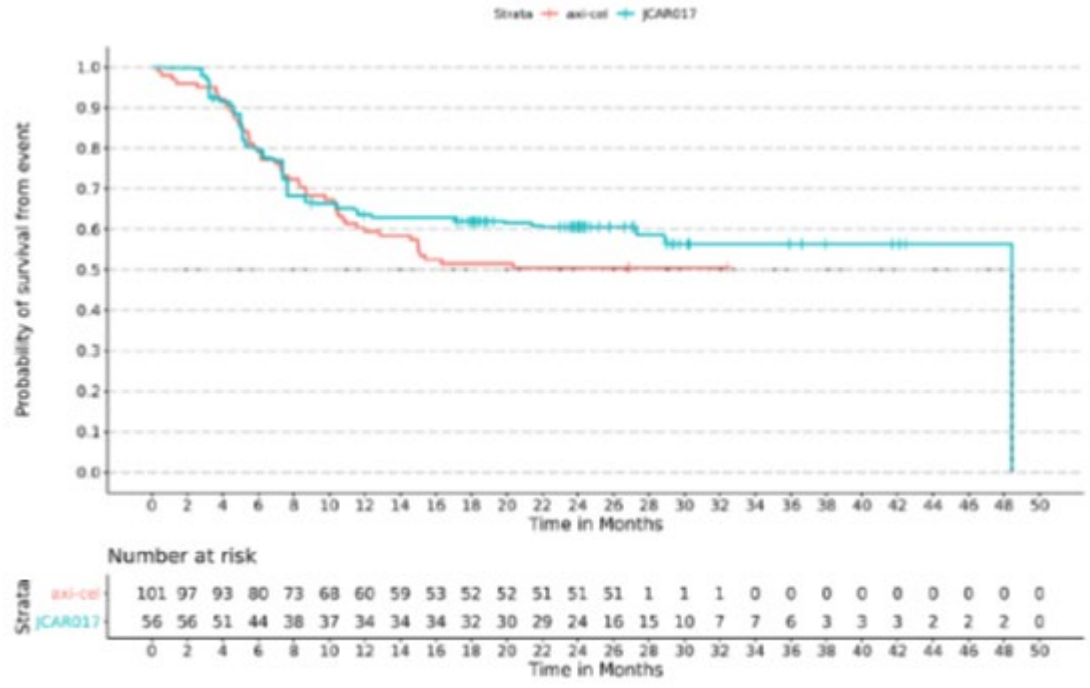
[b] The median was obtained from pseudo-IPD based on digitized KM curve.

Figure 28. Comparison Kaplan-Meier Curves of Progression-free Survival Between Liso-cel and Axi-cel for Infused Patients, Matched and Adjusted Comparison (Primary Analysis; ESS=40.0)



axi-cel = axicabtagene ciloleucel; ESS = effective sample size; JCAR017 = lisocabtagene maraleucel (liso-cel).

Figure 29. Comparison of Kaplan-Meier Curves of Overall Survival Between Liso-cel and Axi-cel fro Infused Patients. Matched and Adjusted Comparison (Primary Analayis; ESS=38.3)



axi-cel = axicabtagene ciloleucel; ESS = effective sample size; JCAR017 = lisocabtagene maraleucel (liso-cel).

As with infused patients, no significant difference in ORR was observed between liso-cel and axi-cel in the ITT Population.

In adjusted analyses of TEAEs and AESIs for liso-cel compared with axi-cel, liso-cel had statistically significantly lower odds of Grade ≥ 3 TEAEs, Grade 3 or 4 TEAEs, all-grade and Grade ≥ 3 CRS, all-grade

and Grade ≥ 3 study-defined NT, all-grade and Grade ≥ 3 NEs per ND/PD SOC, all-grade and Grade ≥ 3 study-defined NT of encephalopathy, all-grade and Grade ≥ 3 encephalopathy per ND/PD SOC, all-grade study-defined NT of aphasia, all-grade aphasia per ND/PD SOC, Grade ≥ 3 infections, all-grade hypogammaglobulinaemia, Grade ≥ 3 prolonged anaemia, neutropenia, and thrombocytopenia as AEs, and all-grade and Grade ≥ 3 febrile neutropenia. Additionally, the unmatched and unadjusted rates of Grade ≥ 3 aphasia per study protocol and per ND/PD SOC were lower with liso-cel than with axi-cel.

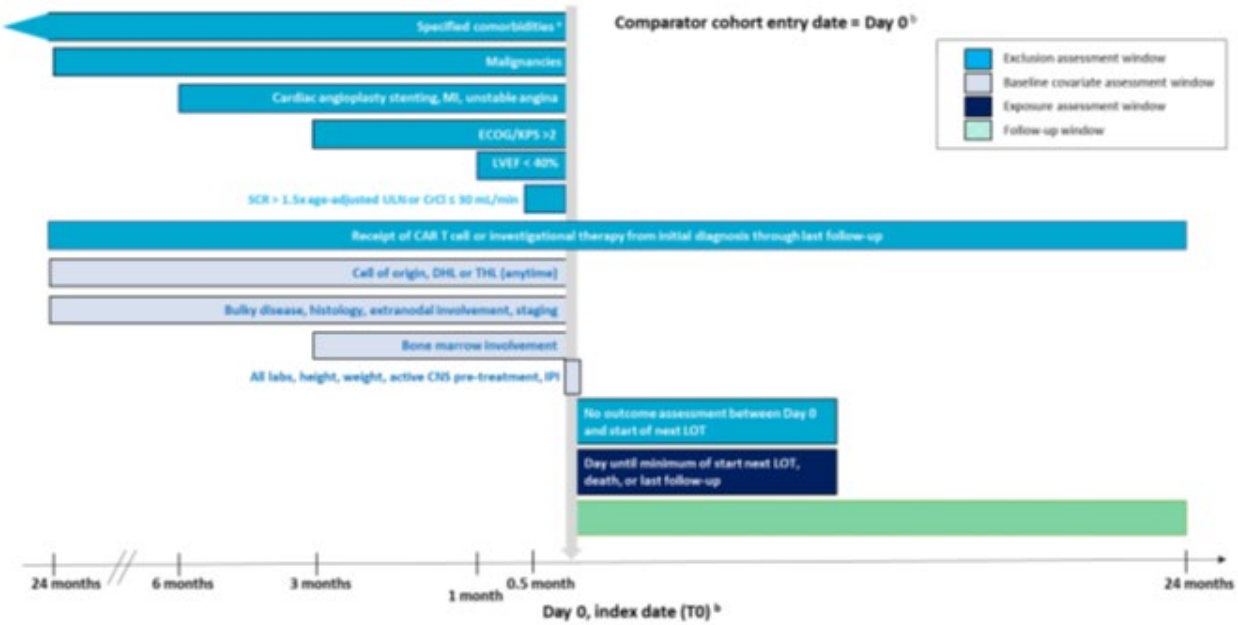
Study NDS-NHL-001 - A Global, Non-Interventional, Retrospective, Multi-Center Study To Generate Real-World Evidence Of Treatment Outcomes In Patients With R/R Large B-Cell Lymphoma (Third Line Of Therapy And Beyond)

Methods

Study NDS-NHL-001 was conducted to describe treatment patterns and evaluate clinical outcomes in patients diagnosed with R/R LBCL since 2003 or later who were being treated in RW clinical oncology settings. The study population consists of subjects who had received prior treatment with an anthracycline and rituximab (or another CD20-targeting agent), and who had started a subsequent line of therapy.

Study design is summarised in the figure below.

Figure 30. Study design, NDS-NHL-001



CAR = chimeric antigen receptor; CNS = central nervous system; CrCl = creatinine clearance (Cockcroft and Gault); DHL = double-hit lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = international prognostic index; KPS = Karnofsky Performance Scale; LOT = line of therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; R/R = relapsed or refractory; SAP = statistical analysis plan; SCR = serum creatinine; THL = triple-hit lymphoma; T0 = index date; ULN = upper limit of normal.

[a] See Appendix C of the SAP (Appendix 1) for the list of comorbidities and associated time windows.

[b] Day 0, Index date (T0): Start date of each patient's qualifying LOT after R/R to at least 2 LOTs and exposure anthracycline and to anti-CD20.

The acquired real-world data (RWD) were integrated and harmonised to conform to a standardised, common data model (CDM) for the analyses detailed herein. Patients from this study are hereafter referred to as RW patients.

JCAR017-treated subjects who were included in the DBLCL Cohort JCAR017-treated Efficacy Analysis Set (i.e., DLBCL Efficacy Set) from Study 017001 were used for comparisons with the RW patients.

A summary of the RW and Study 017001 analysis cohorts is provided in the table below.

Table 43. Updated Analysis Cohorts

Analysis Cohorts	Number of Subjects
Initial Comparator Cohort (ICC)	606
Qualifying Comparator Cohort (QCC)	381
Analytic Comparator Cohort (ACC)	381
Stratified Analytic Comparator Cohort (sACC)	257
JCAR017-treated Analysis Cohort (JTAC)[a]	257
JCAR017-treated Analysis Cohort who received only 2 prior LOTs (JTAC-2L)	118
Leukapheresed Cohort (LKC)[b]	345

DLBCL = diffuse large B-cell lymphoma; JCAR017 = lisocabtagene maraleucel (liso-cel); LOT = line of treatment.
[a] Includes JCAR017-treated subjects who were included in the DLBCL Cohort JCAR017-treated Efficacy Analysis Set (ie, DLBCL Efficacy Set) from Study 017001.
[b] Includes all subjects who had signed informed consent, who met all of the inclusion criteria and none of the exclusion criteria for Study 017001, and who underwent leukapheresis.

The index date for the RW patients in the primary analysis was analytically assigned as the date of initiation of the first qualifying LOT after previous exposure to an anthracycline and rituximab (or other CD20-targeting agent) and the completion of at least 2 prior LOTs (i.e. LOT3 or beyond). For subjects in Study 017001, the date of JCAR017 infusion was used as the index date. In the leukapheresed cohort and in the LDCC, the start dates of leukapheresis and LDC, respectively, were used as index dates.

For the RW patient FUP was calculated starting from the index date and ending with the completion of a maximum of 24 months of observation (to correspond with the maximum follow-up time in Study 017001), initiation of a subsequent LOT, HSCT, loss to follow-up (ie, date of last contact with the study site or date of last data in the study database), or death, whichever occurred first.

Progression-free survival was defined as time from index date to first documentation of PD, relapse death due to any cause, or end of the 24-month FUP, whichever occurs first. Duration of response was defined as duration of time from first investigator assessed best response (of PR or better) to documented PD, relapse, death from any cause, or end of FUP, whichever occurs first. PFS and DOR were not censored at start of new therapy after index date. Overall survival was defined as the time from the index date to death due to any cause or end of the 24-month FUP, whichever comes first. Patients who died were considered as having events occurring on the date of death. Patients who were alive were censored on the last-known-alive date, the data cut-off date (if applicable) or the end of maximum 24-month FUP, whichever was earlier. Censoring did not occur at the time of HSCT or at initiation of the next LOT. For Study 017001, data up to the cut-off date of 12 Aug 2019 are included in the RWE analysis.

As a conservative measure, the analysis allowed for as much as 15% overall missing data for covariates prognostic for the outcome (de Goeij, 2013; Dong, 2013; McNeish, 2017). The final PS model eventually included age, sex, months since diagnosis, number of prior LOTs per year since diagnosis to the index date, best response to any prior therapy, relapsed or refractory to last therapy, prior HSCT, chemorefractory or chemosensitive to last therapy, bulky disease and extranodal disease. In addition to these covariates, the PS model for patients with a first diagnosis of LBCL in 2010 or later also included disease histology and the PS model for patients with non-missing ECOG performance status also included disease histology, serum LDH, and active CNS involvement.

Stabilised inverse probability of treatment weights (IPTW) and matched-pair analysis were used as the primary analysis methods. To address the possible bias of RW cohorts towards longer survival outcomes by being indexed at an earlier line of therapy compared with the JTAC, two main sensitivity analyses were performed:

- Sensitivity analysis 1 (SA1) restricted the subjects in the JTAC to those with only 2 prior lines of therapy (JTAC-2L) and for whom JCAR017 infusion was third line.

- Sensitivity analysis 2 (SA2) matched RW patients to subjects in the JTAC with a similar categorical distribution of prior lines of therapy. This method generated the stratified Analytic Comparator Cohort (sACC).

The primary analysis was performed using the Generalised Linear Model and the Cox Proportional Hazards (CPH) model for time to first event, with adjustment for confounding factors using PS produced with stabilised IPTW for each balanced imputed dataset.

Blinded analysis was conducted for RW patients in the ACC. However, after analysts were unblinded to outcome data, it was found that 15 patients did not have investigator response assessments and 1 patient had inconsistencies in the start and end dates of the qualifying LOT and thus, should have been excluded from the analyses. After excluding these 16 patients from the ACC, the resulting ACC of 407 patients was used to generate PS and IPTWs.

Results

Comparison Between European and US Real-world Patients

In general, demographic and baseline disease characteristics were similar between European and US RW patients. Comparisons between cohorts for IPI score and disease stage are limited due to the extent of missing data, particularly for US RW patients. Of note, European RW patients were slightly younger than patients from the US (median age: 58.0 years versus 64.0 years, with 10.6% being ≥ 75 years of age versus 20.2%, respectively), and a lower percentage of European RW patients was male compared to US patients (54.3% versus 65.2%, respectively). A higher percentage of European RW patients were refractory to their last therapy compared with those from the US (94.7% versus 87.8%, respectively), with 29.8% of European RW patients having achieved a CR to any prior therapy compared with 36.2% of the US RW patients. Median LDH was higher in European RW patients compared to those from the US (447 U/L versus 280 U/L, respectively). A similar percentage of European and US RW patients had received prior HSCT (7.4% and 12.2%, respectively) and had bulky disease (18.1% versus 22.0%, respectively).

The unadjusted analysis suggested a numerically lower ORR in RW patients from Europe compared with RW patients from the US (33.0% [95% CI: 23.6, 43.4] versus 41.8% [95% CI: 36.0, 47.8], respectively. After median follow-up times of 7.5 months for European RW patients and 5.9 months for RW patients from the US, similar percentages of patients were alive (16.0% and 17.1%, respectively). The median unadjusted PFS was similar in RW patients from Europe and those from the US (3.1 months [95% CI: 2.2, 4.0] and 2.3 months [95% CI: 2.0, 2.6], respectively).

Median follow-up time for all surviving patients was longer for European RW patients compared with those from the US (24.0 months versus 18.3 months, respectively. At the end of the follow-up, 30.9% of the European RW patients were alive compared with 39.0% of RW patients from the US. The median unadjusted OS was 7.6 months (95% CI: 5.7, 11.7) for European RW patients and 8.0 months (95% CI: 6.2, 10.4) for RW patients from the US.

After balancing using stabilised IPTW, all selected baseline covariates were well balanced, and there were no statistically significant differences between European and US RW patients with respect to ORR, PFS or OS. These results suggest that European and US patients with 3L+ DLBCL treated in routine clinical practice have similar outcomes.

Comparison between RW patients and patients in study 017001

Generally, the demographics and baseline characteristics were comparable between the QCC and the JTAC (see table below).

Table 44: Study NDS-NHL-001: Covariate balance before and after balancing using stabilised IPTW of real-world and JCAR017-treated analysis cohorts

	Before Balancing			After Balancing		
Covariate	ACC (N = 407)	JTAC (N = 256)	Standardized Mean Difference (JTAC – ACC)	ACC (N = 407)	JTAC (N = 256)	Standardized Mean Difference (JTAC – ACC)
Age (mean), years	60.42	60.31	-0.0080	60.98	59.74	-0.0874
Sex (M = 1; F = 0)	0.63	0.66	0.0702	0.63	0.66	0.0650
Months Since Diagnosis to Index Date (mean)	21.39	31.29	0.3235	22.95	25.39	0.0895
Number of Prior LOTs per Year Since Diagnosis (mean)	2.00	2.23	0.1587	2.25	2.14	-0.0726
Best Response to Any Prior Therapy (PR/CR = 1, PD/SD = 0)	0.63	0.86	0.5512	0.73	0.75	0.0548
R/R to Last Therapy (Refractory = 1, Relapsed = 0)	0.89	0.79	-0.2663	0.86	0.84	-0.0522
Prior HSCT (Yes = 1, No = 0)	0.12	0.34	0.5476	0.19	0.21	0.0466
Chemorefractory or Chemosensitive Disease Type (Chemosensitive = 1, Relapse < 12 months after Auto-HSCT/ Last Chemo = 0)	0.28	0.33	0.1083	0.32	0.32	-0.0072
Bulky Disease[a] (Yes = 1, No = 0)	0.23	0.11	-0.3068	0.18	0.20	0.0635
Extranodal Disease (Yes = 1, No = 0)	0.57	0.53	-0.0905	0.55	0.58	0.0789

ACC = Analytic Comparator Cohort; auto-HSCT = autologous hematopoietic stem cell transplantation; CR = complete response; F = female; HSCT = hematopoietic stem cell transplantation; IPTW = inverse probability of treatment weights; JTAC = JCAR017-treated Analysis Cohort; LDH = lactate dehydrogenase; LOT = line of therapy; M = male; PD = progressive disease; PR = partial response; R/R = relapsed or refractory; RW = real-world; SD = stable disease.

[a] Bulky disease was defined as the presence of individual masses ≥ 10 cm in diameter.

Notes: Mean values were presented for continuous variables and percentages were presented for categorical variables. Multiple imputation procedures were performed to create 25 datasets. Estimates were then obtained using Rubin's rules to combine the individual estimates.

Standardized difference was obtained from JCAR017 minus RW and using stabilized weights when combining the mean and standard deviation.

If a covariate had more than 15% overall missing, the covariate was not used in the balancing.

A higher percentage of patients in the QCC were refractory to their last prior treatment (i.e., LOT2) compared with subjects in the JTAC (88.9% versus 75.0%, respectively).

The demographics, baseline disease characteristics, and prior treatments in the LKC and the LDCC were similar to those of the JTAC.

Results of the primary and sensitivity analyses show a significantly higher response rate and survival benefit in the JTAC compared with the ACC (see table below):

Table 45. Summary of Effectiveness Results, Adjusted for Stabilised IPTW or Real-World and JCAR017-Treated Analysis Cohorts, Primary and Sensitivity Analysis

	Primary Analysis			Sensitivity Analysis 1			Sensitivity Analysis 2		
	Estimate		RR/HR (95% CI), p-value	Estimate		RR/HR (95% CI), p-value	Estimate		RR/HR (95% CI), p-value
Endpoint	ACC (N = 407)	JTAC (N = 256)		ACC (N = 407)	JTAC-2L (N = 117)		sACC (N = 256)	JTAC (N = 256)	
ORR (%)	43.7	74.4	1.7 (1.4-2.0), < 0.0001	42.7	76.5	1.8 (1.5-2.1), < 0.0001	40.1	73.8	1.8 (1.5-2.2), < 0.0001
CR Rate (%)	21.0	49.6	2.4 (1.8-3.1), < 0.0001	21.8	51.3	2.4 (1.8-3.2), < 0.0001	22.4	50.0	2.2 (1.7-3.0), < 0.0001
Median DOR (months)	6.0	10.6	0.79 (0.57-1.09), 0.1514	5.7	10.6	0.75 (0.49-1.16), 0.1992	6.0	9.2	0.73 (0.43-1.25), 0.2559
Median PFS (months)	2.2	3.5	0.56 (0.45-0.71), < 0.0001	2.5	4.4	0.56 (0.41-0.78) 0.0005	2.2	3.5	0.59 (0.47-0.73) < 0.0001
Median OS (months)	9.4	20.5	0.63 (0.48-0.83), 0.0011	8.9	NR	0.51 (0.35-0.75), 0.0005	7.3	20.5	0.56 (0.43-0.73), < 0.0001

ACC = Analytic Comparator Cohort; BOR = best overall response; CI = confidence interval; CR = complete response; CPH = Cox Proportional Hazards; DOR = duration of response; FUP = follow-up period; HR = hazard ratio; IPTW = inverse probability of treatment weights; JTAC = JCAR017-treated Analysis Cohort; JTAC-2L = JCAR017-treated Analysis Cohort who received only 2 prior LOTs; LOT = line of therapy; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RR= relative risk ratio; sACC = stratified Analytic Comparator Cohort.

Notes: ORR was the percentage of subjects achieving a BOR of PR or CR as assessed by the investigator; CR rate was the percentage of subjects achieving a CR as assessed by the investigator. OS was the time from index date to all-cause death or the end of the FUP. PFS was the time from the index date (start of new therapy for the ACC and start of JCAR017 for the JTAC) to the first documented PD, relapse, death due to any cause, or end of the FUP, whichever occurred first. DOR was the duration of time from first investigator-assessed BOR (of PR or better) to documented PD, relapse, death from any cause, or end of FUP, whichever occurred first; analyses were based on responders only.

For all analyses, multiple imputation procedures created 25 datasets. Estimates were then obtained using Rubin's rules to combine the individual estimates from each dataset.

For ORR and CR rate, relative risk, p-value and CIs were based on a binomial regression with robust error variance, and used a log link function and stabilized IPTWs for the JTAC and the ACC/sACC.

For OS, PFS, and DOR, median of time to event was calculated from the CPH model. Hazard ratio and CI were based on a CPH model with study (ACC/sACC or respective Study 017001 cohort) as a term in the model and used the stabilized IPTWs (OS, PFS, and DOR [SA1 and SA2]) or stabilized IPTWs trimmed at the minimum of the maximum weight for the ACC or the JTAC (primary analysis of DOR).

Although DOR numerically favoured the JTAC over the ACC (HR <1), the comparison was not statistically significant (p=0.1514), most likely due to a relatively small proportion of responders in the ACC.

The results of the sensitivity analyses adjusted for inverse probability of treatment weights (IPTW) support the primary analysis.

Median follow-up times for surviving subjects in the LKC and LDCC were 15.0 months and 14.4 months, respectively. Overall survival was significantly longer in the LKC compared with the ACC (16.6 months vs. 9.4 months; HR=0.77; 95%CI 0.60-0.99; p=0.0436). Additionally, consistent with the primary analyses, median PFS was statistically significantly longer in the LKC compared with the ACC (4.6 months versus 2.2 months; HR=0.53; 95%CI 0.44-0.65; p<0.0001).

Consistent results were observed across subgroups, including age, sex, and bridging therapy (i.e., use of anticancer therapy for disease control).

In total, 323 of the 407 patients in the ACC had a first LBCL diagnosis in 2010 or later. Consistent with the primary analyses, the following were significantly higher in the JTAC compared with the RW patients with a first LBCL diagnosis in 2010 or later: ORR adjusted for stabilised IPTW (73.8% versus 47.7%; RR=1.5; 95%CI 1.2 - 2.0; p<0.0001); PFS (3.3 months vs 2.5 months; HR=0.64; 95%CI: 0.43 - 0.97; p = 0.0361) with median follow-up times of 10.6 months vs 6.1 months. The median OS in patients in the ACC with a first diagnosis in 2010 or later was numerically longer than that of the overall ACC (12.9 months versus 9.4 months, respectively) In this analysis, OS numerically favoured the JTAC over the

ACC, although the result did not reach statistical significance (20.5 versus 12.9 months; HR=0.76; 95% CI 0.51 - 1.15; p=0.1973).

Comparison with Real-World CAR T Patients

For subgroup analyses of RW CAR T patients, the index date was defined as the date of CAR T-cell infusion, in order to align with the index date for the JTAC. A summary of demographic and baseline disease characteristics for RW patients who received CAR T-cell therapy in the 3L+ LBCL multisource data asset and for those who met QCC eligibility criteria is presented in Table 46.

Real-world patients in the QCC who received CAR Tcell therapy ranged in age from 20 years old to 81 years old and approximately two-thirds were male. The majority of patients had a diagnosis of DLBCL not otherwise specified (NOS) and ECOG performance status of 1. The type of CAR T-cell therapy was unspecified for all but 2 patients who had received Yescarta (axi-cel).

Table 46. Selected Demographics and Baseline Disease Characteristics for Real-world Patients with CAR T-cell Therapy

Covariate	3L+ LBCL Multisource Data Asset (N = 61)	CAR T QCC (N = 34)
Age Range, years (Min, Max)	20.0, 85.0	20.0, 81.0
Sex, n (%)		
Female	19 (31.1)	12 (35.3)
Male	42 (68.9)	22 (64.7)
Prior LOT Range (Min, Max)	2.0, 8.0	2.0, 8.0
Outcome Assessment Availability[a], n (%)		
Yes	52 (85.2)	34 (100.0)
No	9 (14.8)	0
NHL Subtype, n (%)		
DLBCL NOS	44 (72.1)	28 (82.4)
DLBCL NOS (tFL)	1 (1.6)	0
HGL with DLBCL Histology	4 (6.6)	0
PMBCL	3 (4.9)	2 (5.9)
T-cell NHL	1 (1.6)	0
Not Reported	8 (13.1)	4 (11.8)
ECOG Performance Status at Screening, n (%)		
0	9 (14.8)	8 (23.5)
1	36 (59.0)	19 (55.9)
2	7 (11.5)	6 (17.6)
3	3 (4.9)	0
Missing	6 (9.8)	1 (2.9)
Type of CAR T-cell Therapy, n (%)		
Yescarta	7 (11.5)	2 (5.9)
Unspecified	54 (88.5)	32 (94.1)

3L+ = third line or later; CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; HGL = high-grade B-cell lymphoma; LBCL = large B-cell lymphoma; LOT = line of therapy; max = maximum; min = minimum; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal large B-cell lymphoma; QCC = Qualifying Comparator Cohort; tFL = DLBCL transformed from follicular lymphoma.

[a] Between the start of the CAR T-cell therapy and the next LOT

Source: D120 RWE Table 14.11.4 and Table 14.11.5

The insufficient number of RW patients and limited follow-up in these analyses does not allow for meaningful comparison of outcomes in the CAR T QCC and the JTAC. As such, no PS adjustments were made prior to the analysis of outcomes and no formal statistical testing was conducted. Unadjusted analyses for ORR, DOR, PFS, and OS are presented in the table below.

Table 47. Unadjusted Comparative Effectiveness Results for Real-world Patients with CAR T-cell Therapy

Parameter	CAR T QCC (N = 34)	JTAC (N = 257)
ORR[a], (%)		
Complete + Partial Response	70.6	73.5
95% CI[b]	52.5, 84.9	67.7, 78.8
OS[c] (Months)		
Median (95% CI)[d]	NR (10.7, NR)	NR (16.2, NR)
25th Percentile, 75th Percentile[d]	7.2, NR	5.9, NR
PFS[e] (Months)		
Median (95% CI)[d]	3.1 (1.1, 6.1)	3.9 (3.0, 5.9)
25th Percentile, 75th Percentile[d]	1.1, 9.3	1.8, 27.3
DOR[f] (Months)		
Median (95% CI)[d]	5.0 (3.1, 14.5)	10.4 (5.1, NR)
Follow-up Time for All Subjects (Months)		
Median	7.0	17.4
Q1, Q3	3.9, 10.7	5.6, 24.0
Min, Max	0.8, 18.2	0.2, 24.0
Follow-up Time for Surviving Subjects (Months)		
Median	8.1	24.0
Q1, Q3	5.9, 12.1	18.6, 24.0
Min, Max	1.0, 18.2	1.2, 24.0

BOR = best overall response; CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response; DOR = duration of response; JCAR017 = lisocabtagene maraleucel (liso-cel); JTAC = JCAR017-treated Analysis Set; max = maximum; min = minimum; NR = not reached; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; Q1 = first quartile; Q3 = third quartile; QCC = Qualifying Comparator Cohort.

[a] ORR: Percentage of subjects achieving a best response of PR or better as assessed by the investigator.

[b] 2-sided exact 95% CI. Response rate and CI were based on an exact test for a binomial proportion.

[c] OS: Time from index date to all-cause death or end of follow-up period.

[d] Calculated from Kaplan-Meier method.

[e] PFS: was defined as time from the index date to the first documented PD, relapse or death due to any cause or end of follow-up period.

[f] DOR: the duration of time from the first investigator-assessed BOR to documented PD, relapse, death from any cause, or end of the follow-up period, whichever occurred first. DOR analyses were based on responders only (response of CR or PR).

Given the potential population imbalances, unobserved confounding factors, and the differences in follow-up time between the CAR T QCC and the JTAC, these results must be interpreted with caution.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Studies 017001 and BCM-001

Pivotal study 017001 included a dose-finding and an expansion Phase, and was planned according to an adaptive seamless design, with preliminary data from the dose-finding cohorts informing enrolment in larger expansion and "confirmation" cohorts. Such seamless approaches are theoretically characterised by a higher risk of overestimating the true clinical effect. As highlighted in previous scientific advice (SA) procedures, consistency of results across different JCAR017 studies is, therefore, of pivotal importance.

Similar inclusion/exclusion criteria were adopted in studies 017001 and BCM-001 to select an adult patient population with r/r aggressive mature B-cell lymphomas. B-cell lymphomas with a large cell histology (as defined in the 2016 updated WHO classification of lymphoid neoplasms) are a broad class

of lymphoproliferative neoplasms which includes conditions characterised by distinct clinical/biological features and prognosis: high heterogeneity was, therefore, anticipated.

Histological confirmation of diagnosis was required, including CD19 expression for subjects who had received previous CD19-targeted therapies: limited data is currently available for patients with prior CD19-directed therapy and confirmed CD19-positive relapse (n=12), whereas no data is available for patients with no detectable CD19 tumour expression after prior CD19-directed therapy. Local testing to confirm CD19 expression in patients treated previously with CD19-targeted therapy is recommended to inform the decision to proceed with JCAR017 treatment. Data on patients previously treated with CD19-targeted therapy has been included in the SmPC Section 5.1, with additional information in Section 4.4, highlighting that clinical experience with JCAR017 in patients exposed to prior CD19-directed therapy is limited.

Only patients who had prior therapy with anthracyclines and rituximab (or other CD20-targeted agents) and with relapsed or refractory disease after at least 2 lines of therapy or after auto-HSCT were eligible. Limited information was available for subjects who received JCAR017 after prior allogeneic HSCT and for subjects who underwent allogeneic HSCT following JCAR017: this is reflected in section 5.1 of the SmPC.

The dose range allowed per current release specifications (44 to 120 x 10^6 CAR+ T cells) and recommended in SmPC section 4.2 reflects the clinical experience as observed at the assigned DL1 (administered dose range: 44 – 104 x 10^6 CAR T cells) and DL2 (administered dose range: 45 – 120 x 10^6 CAR T cells) in study 017001 and in study BCM-001 (administered dose range: 71 - 103 x 10^6 CAR T cells). Consistency of efficacy and safety was demonstrated across this dose range compared to the overall clinical experience with JCAR017 (DL1 + DL2 + DL3; administered dose range: 44 – 156 x 10^6 CAR T cells). With regard to efficacy, in study 017001 95%CIs for ORR, CR rate, median DOR, PFS and OS and probability of continued DOR, PFS and OS at all timepoints from 6 up to 24 months were overlapping, although some variability in point estimates could be observed in the smaller subgroups (e.g. lower point estimates for ORR and CR rate in lower and upper bounds, lower point estimates for median PFS and OS at the upper bounds). K-M plots for DOR, PFS and OS for all subgroups were also overlapping, showing a similar profile evolving towards a plateau phase. Consistency of efficacy was also observed between the ± 20% of assigned DL2, mid-range of recommended dose range and recommended dose range subgroups in study BCM-001 (in the upper range group, there were too few subjects to make meaningful comparisons). With regard to safety, subgroup analyses showed consistency of toxicity across the recommended dose range. In study 017001 a numerically higher incidence of all-grade CRS, all-grade iiNT, and Grade ≥ 3 infection was observed at assigned DL3 compared to the lower assigned dose levels (DL1 and DL2). This is consistent with retrospective logistic regression modelling which also suggested a potential relationship between increased administered dose and increased incidence of these AEs. Therefore, the recommended dose range excludes subjects assigned to DL3, which included subjects receiving the highest doses administered in Study 017001.

The available data support pooling of results across manufacturing process versions and LVV manufacturers; given the very limited data (n=7) currently available with JCAR017 manufactured using the LVV in its final commercial version for the EU patients, further clinical data with the intended commercial product version/vector will be provided post-approval from the post-authorisation registry study BCM-005 (with at least 750 subjects anticipated to receive JCAR017 manufactured with this LVV) and in the ongoing study BCM-001 (with 24 subjects anticipated to receive JCAR017 manufactured with this LVV).

JCAR017 is manufactured as two distinct CD4+ cell component and CD8+ cell component administered in a fixed 1:1 ratio; no other CD4+/CD8+ cell components ratio was prospectively investigated. However, due to overestimation issues with the indirect CAR+ T-cell quantification technique, patients in study 017001 received products with CD4+/CD8+ cell components ratios comprised between 0.73 and 2.20.

Multivariate and univariate logistic analyses showed that a 0.2 increase in the CD4+/CD8+ cell components ratio resulted in a 30% and 17% increase in the hazard for relapse or death in the DOR and PFS analyses, respectively. This finding can be potentially related to the association that was found between PK parameters (Cmax and AUC0-28) and the CD4+/CD8+ cell components ratio (see the Pharmacokinetics section). Efficacy and safety data were provided for the recommended dose range 44-120 x 10^6 CAR+ T cells in subgroups stratified by CD4+:CD8+ cell components ratio (0.8-1.2 [n = 209] vs. CD4+:CD8+ cell components ratio >1.2 [n = 19)]. No meaningful comparison was possible with patients who received JCAR017 at a CD4+:CD8+ components ratio <0.8, as there was only 1 patient in this subgroup. ORR and CRR in the group with CD4+:CD8+ cell components ratio >1.2 were numerically higher compared to the group with CD4+:CD8+ cell components ratio between 0.8–1.2, 95%, yet CIs were overlapping. Some differences suggestive for less favourable DOR, PFS and OS could be observed for the group that received a CD4+:CD8+ cell components ratio >1.2: although 95%CIs were overlapping, median DOR and median OS were shorter in this subgroup, and 95%CIs for probability of continued DOR and PFS at 24 months did not overlap; K-M plots for DOR, PFS and OS diverged over time and did not seem to evolve to the typical plateau phase that is observed for the group who received a CD4+:CD8+ cell components ratio between 0.8–1.2. These findings are consistent with the potential relationships between increasing CD4+:CD8+ cell components ratio and shorter DOR and PFS suggested by retrospective logistic regression modelling. With respect to safety, the available data stratified by CD4+:CD8+ cell components ratio do not indicate any relationship with the majority of key safety outcomes. Overall, although the sample size of the group who received a CD4+:CD8+ cell components ratio > 1.2 was reduced (especially at later timepoints), and the limits of the provided post-hoc analyses are recognised, the available data suggest that exerting a tighter control on the variability of the two JCAR017 product cell components ratio might be of relevance to preserve efficacy (see also the Quality AR). Therefore, a stringent 0.8-1.2 range for the CD4+/CD8+ cell components ratio has been included in the release specifications.

JCAR017 was only investigated in single-arm trials (SATs). In principle, randomised trials powered to detect superiority in terms of time-to-event endpoints are required to assess clinical benefit in non-Hodgkin lymphomas (NHLs); however, when the clinical development of JCAR017 was planned, no proper active control could be identified in the target population. Moreover, aggressive lymphomas are rapidly progressive neoplasms, and evidence on the encouraging anti-CD19 CARTs activity in NHLs was already available at the time, so it can be recognised that placebo or cross-over designs could have been challenging from an ethical perspective.

In line with the exploratory nature and single-arm design of studies 017001 and BCM-001, ORR by IRC, an objective measure of anti-tumour activity, was selected as primary endpoint. Reduction in tumour mass provides, in fact, a less biased estimation of anti-tumour activity in single-arm trials, yet the clinical relevance of ORR in aggressive lymphomas is limited, since sub-optimal responses are, usually, short-lasting. CRR by IRC was therefore collected as key secondary endpoint. Response to treatment was adjudicated based on the 2014 Lugano criteria, which is in accordance with standard clinical practice.

DOR, PFS, EFS (in study BCM-001) and OS were included as secondary endpoints to further characterise the efficacy of JCAR017. Although the interpretation of time-to-event endpoints in the absence of direct controls is problematic, these analyses are still considered useful to further weigh clinical benefit.

Sample size calculations for the primary analysis in study 017001 were agreed and the assumed thresholds for efficacy (i.e. ORR 40%, CRR 20%) was considered acceptable in the context of the available treatment options at the time both studies were designed.

Primary efficacy analyses in studies 017001 and BCM-001 were performed on subjects from the DLBCL cohort (study 017001) or Cohort 1 (study BCM-001) who had PET-positive disease before JCAR017 administration, received JCAR017 and had at least one post-infusion response assessment: this is

acceptable to control possible confounding factors unrelated to JCAR017 activity. Results from the leukapheresed/enrolled set including all leukapheresed subjects irrespectively on whether they actually received JCAR017 are, in turn, more in line with the ITT principle and with real world clinical practice.

The planned statistical methods used for time-to-event and binary endpoints analyses are standard and acceptable.

Changes in health-related quality of life (HR-QoL) were also investigated using the validated EORTC QLQ-C30, EQ-5D-5L, and FACT-LymS questionnaires. The overall methodology to analyse categorical and time-to-event variables in the PRO analysis is, in principle, adequate; however, the lack of any strategy to control for multiplicity and the uncontrolled/unblinded nature of the data limit PROs reliability and do not allow for HR-QoL-based claims.

Preliminary analyses from study BCM-001 showed numerically relevant differences in efficacy outcomes compared to larger study 017001. An exploratory "post-hoc" bridging analysis was, therefore, provided, using ORR and CRR at months 1 and 3 as primary endpoints and DoR, PFS and OS as secondary endpoints. The proposed statistical approach is reasonable, although the limits introduced by reduced sample size and shorter follow-up in the BCM-001 trial cannot be overcome. A choice of patient, disease and treatment-related variables were included in the model as potential confounders: the role of age, ECOG score, high LDH, number of prior lines of therapy and response to last therapy as prognostic factors in large B-cell lymphomas has been extensively described in literature and is not controversial. The rationale to include the need for bridging therapy before JCAR017 infusion as independent variable is also understood, based on the available evidence suggesting that disease progression during manufacturing time has a significant impact on clinical outcomes with CARTs. The inclusion of C-Reactive Protein (CRP) and sum of products of perpendicular diameters (SPD) in the model was, however, not supported: neither is currently included in validated prognostic tools for DLBCL and their possible predictive role is only supported by post-hoc analyses in study 017001, since no similar effect was observed in Phase II study BCM-001 nor in other CAR-T trials. In response to CAT/CHMP requests, the applicant has included updated sensitivity analyses from two additional models which included IPI score components (together or separated) and excluded CRP and SPD.

Even though some variability in patient and disease characteristics could be observed across patient groups defined by protocol versions for study 017011, the study population remained consistent with the target indication and the overall impact of protocol changes on the observed outcomes appears to be limited.

With respect to study BCM-001, 3 major protocol amendments had been issued at the time of the data cut-off date. Under protocol amendment 2, subjects with vascular tumour invasion, DVT or PE within 3 months or with DVT/PE requiring therapeutic levels of anticoagulation were excluded from study participation out of safety concerns. These strict limitations were, however, mitigated under Amendment 3.

Historical studies

External historical data were used to set-up a benchmark for the main efficacy endpoints observed in JCAR017 studies. The use of external controls (including historical controls) is discussed in ICH Topic E10 (CHMP ICH/364/96) and it is concluded that "*the inability to control bias restricts use of the external control design to situations where the treatment effect is dramatic and the usual course of the disease highly predictable*". When the significant clinical and biological heterogeneity of aggressive large B-cell lymphomas is considered, results from these indirect comparisons can only be accepted to "contextualise" the results observed with JCAR017, yet their contribution to inform B/R evaluations is necessarily limited.

Efficacy data and additional analyses

At the time of the 19 Jun 2020 data cut-off date, 427 and 69 patients were screened in studies 017001 and BCM-001, respectively. A similar fraction of subjects (~14%) was excluded from trial participation due to screening failure in the two studies yet, compared to study BCM-001, more subjects in study 017001 (~20%) failed screening procedures due to issues in their ability to comply with study protocol. This difference did not result, however, in an enrichment in physically fitter subjects in the US study, as demonstrated by the similar rates of subjects excluded because of ECOG PS score ≥2 at screening in both studies (15.2% vs. 18.2% in study 017001 and BCM-001, respectively); the baseline characteristics of leukapheresed subjects in studies 017001 and BCM-001 were also generally consistent. Although the possibility of selection bias cannot be completely ruled out, its impact on study outcomes seems limited.

Approximately 22-25% of subjects who underwent leukapheresis in studies 017001 and BCM-001 did not receive JCAR017. The high dropout rate before infusion of JCAR017 conforming product could be explained by 2 major causes:

- the first one is disease-related, since 9.6% of patients died while waiting for JCAR017 (n=33; 27 subjects died because of PD, 3 from unknown reasons, 1 from bowel perforation, 1 from cardiogenic shock and 1 from AE) despite the possibility to receive bridging therapy, and 1.7% (n=6) dropped out because of disease-related complications. Analyses in patients infused across JCAR017 studies showed, however, no clear relationship between the time from leukapheresis to JCAR017 infusion and risk of early death. In this regard, the median time from leukapheresis to JCAR017 availability in the US study was 24 days (range 17-51 days), which is in line with the available turnaround time data for the approved CARTs. The manufacturing process for EU patients is characterised, however, by additional steps (e.g. shipment to the US manufacturing site and back) and data from Cohort 1 of EU study BCM-001 showed a slightly longer median time from leukapheresis to JCAR017 availability (i.e. 28 days, range 24-38 days). Based on the available data, however, the impact of this finding on the rate of leukapheresed subjects who actually received JCAR017 seems limited, although the fraction of patients who needed bridging therapy in study BCM-001 was higher than that in study 017001 (75% vs. 58.9%, respectively).

- the second major cause is that JCAR017 manufacturing failed in 11.4% and 8.9% of leukapheresed patients in studies 017001 and BCM-001, respectively. Sixteen and 6 patients eventually received nonconforming products in studies 017001 and BCM-001, respectively. The limited number of patients in subgroups did not allow to draw meaningful conclusions as regards baseline patient/disease/immune cells characteristics that could have contributed to the failure of one or both cell components. A recommendation is provided by the CAT/CHMP to further investigate this issue post-approval with data to be captured in the periodic safety update reports (PSURs).

Overall, 58.6% of patients in study 017001 received bridging anticancer therapy after leukapheresis and prior to infusion. The possibility that bridging therapy might induce changes in the tumour microenvironment that might have an impact on CAR T-cell activity, however, cannot be excluded at present. In this regard, subjects who needed bridging therapy for disease control in study 017001 (n=150) fared worse than patients who did not require additional treatments before JCAR017 infusion, with lower ORR and CRR (66.7% 44%, respectively) and shorter DoR, PFS and OS (9.1, 4.6 and 13.3 months, respectively). Nonetheless, durable remissions could still be observed, and the B/R in this subpopulation is not considered different from that established in the overall population.

Demographic characteristics were similar across JCAR017 studies and, overall, in line with the known epidemiology of DLBCL.

A similar fraction of patients (~18%) in studies 017001 and BCM-001 had moderately impaired renal function at baseline, and approximately 5% of patients had LVEF ≥40% to <50% in the US study. The inclusion of subjects with clinically relevant comorbidities could increase, in principle, the generalisability

of the results, yet the available data are not sufficient to fully characterise the B/R of JCAR017 in frailer subjects with renal or cardiac comorbidities. It is recognised, however, that some of these patients experienced durable benefit. Analyses in subgroups of patients with impaired cardiac (e.g. left ventricular ejection fraction <50%, coronary artery disease, congestive heart failure, or myocardial infarction) or renal function (i.e. serum creatinine > 2 mg/dL or > 177 µmol/L, on dialysis, or prior renal transplantation) are pre-specified in PASS study BCM-005: this is acceptable.

In line with the broad indication pursued, a heterogeneous patient population was enrolled in study 017001, with DLBCL NOS representing approximately 50% of all patients, followed by DLBCL arising from indolent lymphomas (tIL, ~30%) and HGL (~13%). In the tIL subgroup most clinical information came from patients with transformed follicular lymphoma (tFL, ~75% of all tIL patients) and marginal zone lymphoma (tMZL, ~15% of all tIL patients). Only 5 patients had Richter syndrome (RS). DLBCL NOS was the most common histology also in study BCM-001 (81.5%), followed by HGL (14.8%).

Overall, the studied population can be considered representative of the targeted advanced setting of relapse. In this regard, in light of the increased need for bridging therapy observed in study BCM-001 compared to study 017001 (75% vs. 58.9%, respectively), it cannot be excluded that subjects in the EU trial might be representative of a population at higher risk for rapid progression.

Baseline characteristics in the ITT (i.e. leukapheresed) sets in JCAR017 studies were not significantly dissimilar compared to those in the treated sets.

Consistently with what observed with other CARTs, complete responders had a significantly longer DOR, PFS and OS compared to subjects with a BOR of PR (median DOR NR vs. 1.9 months, median PFS NR vs. 2.8 months, median OS NR vs. 9.0 months, respectively). KM curves for time-to-event endpoints showed a plateau phase starting approximately from month 12-18 onwards, suggesting the possibility for long-term disease control in a subset of patients. Median DOR (9.1 months) in the DL2S v4 subset was shorter, despite similar median PFS (5.9 months) and OS (17.1 months). Updated analyses (19 Jun 2020) showed that mDoR (11.1 vs. 19 months), mPFS (6 vs. 6.8 months) and mOS (27.3 vs. 21.4 months) were still shorter in the DL2Sv4 set compared to the overall DL2S population, yet such differences resulted from minimal variations in the plateau portion of otherwise superimposable KM curves.

Shorter median DOR and PFS were also observed in the analyses by Investigator (i.e. 9.2 months and 3.9 months, respectively). However, the main reason for such discrepancies was that, in the case of PD adjudication by the Investigator or start of a subsequent anticancer therapy, no subsequent radiographic evaluation was required by study protocol and, if performed, submission to the IRC was not mandatory. This was particularly relevant when the EMA censoring rules were applied, since the start of a new subsequent anti-lymphoma therapy before PD or death was no reason for censoring.

In study 017001, ITT analyses showed shorter survival (with overlapping CIs) compared to the primary analysis in the DLBCL Efficacy Set, for both OS (14.0 vs. 21.1 months) and PFS (4.8 vs. 6.0 months), although the median follow-up time for these endpoints in the ITT analyses was similar to the primary analysis. Sensitivity analyses for PFS and OS in the DLBCL Efficacy Set with PFS and OS defined as starting from the date of leukapheresis were provided and, although differences were still observed, confidence intervals were overlapping.

Overall, results from study 017001 indicate that a subset of subjects who received JCAR017 is expected to receive significant clinical benefit, especially in terms of sustained disease control.

Cohort 1 of Phase II study BCM-001 was designed to further explore the efficacy and safety of JCAR017 in EU patients and to confirm the feasibility of the "EU manufacturing process". Preliminary efficacy results from study BCM-001 (data cut-off date 13 Sep 2019) were, however, less convincing than those observed in the US study: the **ORR by IRC** (**48.1%**, 95%CI 28.7 - 68.1) and the **CRR by**

IRC (**25.9%**, 95%CI 11.1 - 46.3) were lower than those reported in study 017001 and did not allow to reject the study null hypothesis. With a shorter median follow-up (3.38 months in the overall population)), time-to-event outcomes were considered too immature to make meaningful comparisons relative to study 017001 **median DOR** in the EU cohort of study BCM-001 was **2.53 months** (95%CI 1.08, 9.23), **median PFS 2.99 months** (95%CI 2.00, 5.22) and **median EFS 2.00 months** (95%CI 1.38, 2.99). **Median OS** was **8.34 months** (95%CI 3.38, NR), with a 12-month OS rate of approximately 30%.

Updated results from the planned **primary analysis of study BCM-001** were provided with a data cut-off date 19 Jun 2020. Compared to the initial submission, data from 9 additional subjects in study BCM-001 Cohort 1 were available, and the median on-study follow-up was 8.13 months.

Subjects in the final dataset from study BCM-001 Cohort 1 were slightly older than the population in the preliminary analysis (median age 59 vs. 61.5 years, subjects aged 65 to 75 years 29.6% vs. 38.9% in the initial MAA and in updated dataset, respectively), markers of higher disease burden/aggressive clinical behaviour were less represented (SPD <50 cm^2 63% vs. 69.4%; high-intermediate/high risk IPI 59.2% vs. 50%; Ann Arbor stage III/IV 77.8% vs. 63.9%, LDH ≥500 U/L 29.6% vs. 22.2%, respectively) and the fraction of subjects with ≤2 previous lines of therapy was increased (i.e. 40.7% vs. 52.8%). The updated patient population included in the primary analysis of study BCM-001 was, therefore, less representative of a higher risk population compared to patients in the preliminary analysis and more in line with subjects treated in study 017001, although an increased need for bridging therapy was still observed (75% vs. 58.9% in studies BCM-001 and 017-001, respectively).

Consistently with this shift towards lower risk clinical features, efficacy outcomes in study BCM-001 were improved compared to the previous data cut-off and less divergent from those observed in study 017001: the updated **ORR** in the BCM-001 Cohort 1 JCAR017-treated set was **61.1%** (95%CI 43.5, 76.9; ITT set 55.6%) and **CRR** was **33.3%** (95%CI 18.6, 51; ITT set 31.1%). Measures of response duration were also improved, although still shorter than those observed in the larger US study: **mDoR** in the BCM-001 Cohort 1 JCAR017-treated set was **3.50 months** (95%CI 2.20, NR; ITT set 3.35 months) and **mPFS 3.25 months** (95%CI 2.89, 5.36; ITT set 4.53 months). OS data were less divergent from those in study 017001, with a **mOS** in the BCM-001 Cohort 1 JCAR017-treated set of **18.6 months** (95%CI 5.82, NR; ITT set 12.1 months).

The updated **Bridging Analysis for studies BCM-001 and 017001** (data cut-off 19 Jun 2020) confirmed that differences in baseline characteristics across studies were reduced compared to earlier analyses and the distribution of factors with a possible impact on JACR017 efficacy (e.g. SPD, LDH and CRP) more balanced. The applicant explored, however, possible imbalances in additional variables with a potential prognostic effect (e.g. the 5 IPI score components) confirming that EU patients were more likely to have extensive extranodal involvement, bulky disease, elevated LDH and IPI scores >2. Overall, response rates at month 3 in the bridging analysis were similar across studies and, in general, the updated bridging analysis showed that patient populations in studies 017001 and BCM-001 were less divergent, resulting in more similar response rates and median OS across studies. Further updated efficacy data from study BCM-001 (data cut-off date 04 Jan 2021), with a median survival follow-up of 16.4 months, were consistent with those observed in the primary analysis. Data from the EBMT registry (PASS BCM-005) will be used to provide further information for patients treated in the EU who will receive the commercial product (expected number of EU patients N=200).

Regarding the contextualisation of results from uncontrolled pivotal study 017001 with respect to current clinical practice, efficacy data in study 017001 compared favourably with the outcomes reported with CARTs and conventional treatments in the provided **SLR,** and also with the results from a recent meta-analysis investigating the efficacy of second-generation CAR T-cell therapy in DLBCL (see Al-Mansour M et al, Mol Clin Oncol 2020).

With the intrinsic limits of such indirect comparisons, the provided **MAIC analysis** comparing the results with JCAR017 in study 017001 with efficacy data from the registrational studies of the CARTs currently approved for the treatment of 3rd line DLBCL was also reassuring, showing at least comparable efficacy between JCAR017 and tisagenlecleucel/axicabtagene ciloleucel.

Adjusted analyses from historical study **NDS-NHL-001** consistently showed significantly higher ORR, CRR, PFS and OS in the reference dataset from study 017001 compared to the historical cohort. To further support the external validity and generalisability of the results obtained in the JCAR017 clinical development programme in the EU treatment landscape for 3rd line large B cell lymphomas, the applicant has submitted additional RWE analyses:

- demographic/disease characteristics and efficacy outcomes were compared between EU and US subjects in study NDS-NHL-001, showing that significant differences in characteristics and outcomes of 3rd line DLBCL patients treated in EU and US are unlikely.

- the applicant has also conducted additional updated comparisons between subjects in the RWE study cohorts (i.e. RW EU cohort [n=94], the JTAC [n=257] and the BCM-001 cohort [n=36]), showing that RW patients from the EU were generally younger and more likely to have refractory/primary refractory disease, a shorter time from diagnosis, higher baseline LDH levels and ECOG PS scores.

This is not unexpected since, despite the efforts to super-impose inclusion/exclusion criteria from JCAR017 trials to the historical data, patient selection for CAR T-cell treatments is known to involve clinical decisions not completely standardised and hardly captured by fixed criteria. The DLBCL CART-eligible population should be considered, therefore, as a distinct subgroup of patients defined by clinical features (e.g. overall "fitness", absence of rapidly progressing disease and/or elevated disease bulk etc.) that, in the opinion of the treating physician/investigator, can shift the B/R of this treatment option to more favourable positions (see e.g. Cahill KE et al, Leuk Lymphoma 2020 and Yassine F et al, Current Research in Translational Medicine 2020). To confirm that subjects who received JCAR017 in pivotal study 017001 were indeed representative of the "RW CART-eligible population", the applicant has provided additional **indirect comparisons vs. RW DLBCL patients** in study NDS-NHL-001 (n=34) and vs. patients who received CARTs in 5 French Lymphoma Study Association Centres (n=116, see Vercellino L. et al, Blood Adv 2020) and in the UK national programme (n=183, see Kuhnl A. et al, EHA Annual Congress 2020, Abstract S243). The results showed that no significant divergencies in patient/disease characteristics and clinical outcomes could be observed across CARTs cohorts, although limited numbers and disease heterogeneity should be taken into account.

A broad indication is claimed for JCAR017, encompassing all DLBCL subtypes (including, e.g., HGL, which is now classified as a distinct entity, and DLBCL arising from transformed indolent lymphomas), PMBCL and FL3B. Overall, JCAR017 was able to induce disease remission in ~40-60% of subjects across all disease subtypes, and durable responses were observed in all histology subgroups. In this regard, particularly favourable results were observed in patients with PMBCL (n=15, ORR 78.6% and CRR 50%), with KM-plots showing a high rate of durable responses.

FL3B is a rare form of aggressive B-cell lymphoma and an unmet medical need for patients who have received at least 2 prior lines of therapy can be recognised. Clinical and biological data from published literature support the dignity of FL3B as a distinct condition, yet heterogeneity in clinical behaviour, phenotype and genetic background can be expected (see e.g. Barraclough A et al, Br J Haematol. 2021, Swerdlow SH et al, 2008 WHO classification of Tumours of Haematopoietic and Lymphoid Tissues, Katzenberger OG et al, Blood 2002; Koch K et al, Ann Oncol 2016; Kikkeri NN et al, Haematologica 2007) and it cannot be excluded that the variability observed in how the WHO diagnostic criteria for FL3B were applied in studies 017001 and BCM-001 might eventually reflect real-world clinical practice. The number of patients (n = 4 from study 017001; n = 2 from study BCM-001) is, per se, too limited for self-standing B/R evaluations, even though promising responses have been observed. It is noted, however, that the

distinction between FL3B and DLBCL is mainly based on histology but that there is a large overlap in gene expression profile, clinical presentation and behaviour/biology. Importantly, the same treatment options are available for FL3B and DLBCL and response to treatment appears to be similar. The long-lasting remissions observed with JCAR017 in patients with R/R FL3B, despite failure of multiple prior lines of chemotherapy, are suggestive of an efficacy that is at least similar to that observed in DLBCL NOS. Based on these similarities, the results observed with JCAR017 in the overall study population are considered to provide support for the efficacy seen in the very few FL3B patients and the inclusion of FL3B in section 4.1 can be, therefore, accepted. Limited additional data in FL3B can be expected from ongoing clinical trials and in the post-marketing setting, as expected considering the rarity of this condition. Information will nonetheless be collected post-approval from the CIBMTR and EBMT registries (PASS BCM-005) to further characterise patients with FL3B.

Although the number of patients was limited, apparently reduced efficacy was observed in DLBCL arising from indolent NHLs other than tFL (i.e. the tIL subset), which is a heterogenous group of aggressive lymphomas arising from different indolent conditions, including CLL/SLL (i.e. Richter's syndrome, RS). The majority of the responses in this subgroup were observed in subjects with tMZL (n=10, month-3 ORR and CRR 5/10 and 4/10, respectively), with some responses being durable. Conversely, patients with RS (n=5) who received JCAR017 in study 017001 fared significantly worse, with 3/5 showing at least a PR (1/5 with CR) yet no durable response beyond the 3-month timepoint. Only 2 patients with tWM received JCAR017 in study 017001, the ORR was 50% (1/2 subjects) with a maximal response duration of 5.3 months and no subjects achieving a CR. Based on the available data, it is uncertain whether the anti-tumour activity of JCAR017 in RS/tWM, as observed in terms of ORR/CRR, can be translated in prolonged remission, which is the ultimate measure of clinical benefit in such advanced stages of disease. This uncertainty is reflected in the SmPC, specifying that although durable remissions (i.e. DoR ≥12 months) were reported for subjects with tFL and tMZL, the experience in patients with tCLL/SLL and tWM is very limited and shorter remissions (maximal DoRs of 2 and 5.3 months, respectively) were observed.

A consistent treatment effect in terms of response rates and time-to event endpoints was observed in all the other pre-specified subgroups, yet results have to be interpreted with caution because of the reduced sample size in most subsets. The impact of high ECOG score at baseline was explored in study 017001: overall, responses in subjects with baseline ECOG score of 2 (n=9) were short-lasting and no subject was still alive at the time of the data cutoff date. Further, under Amendment 5 subjects with baseline ECOG score >1 were excluded from JCAR017 trials out of safety concerns: clinical benefit in patients with higher baseline ECOG PS scores is not considered characterised, as currently stated in section 5.1 of the SmPC. The efficacy of JCAR017 in higher risk patients (e.g. because of high IPI score, extranodal involvement and/or ECOG PS score ≥2) will be further characterised in PASS BCM-005.

Only 8 subjects in JCAR017 studies had secondary CNS disease at first infusion; 5/8 were able to achieve CR and two subjects were still in remission with a DoR of approximately 23 months: such results in this high unmet need population are encouraging, yet currently too limited for specific B/R evaluations. A statement in section 4.4 of the SmPC has been included to specify that clinical experience in subjects with secondary CNS involvement is currently limited, and all the available clinical data in subjects with secondary CNS lymphoma who received JCAR017 in clinical studies were reflected in section 5.1 of the SmPC. Further efficacy/safety data in subjects with secondary CNS lymphoma will be collected in registry study BCM-005 (PASS).

JCAR017 could be manufactured also in presence of low absolute lymphocyte counts (ALCs) at the time of leukapheresis. Patients with low ALC (i.e. $<0.3 \times 10^9$/L) had lower chances to achieve CR (37% vs. 54%, respectively) and long-term disease control (median DOR was 5.3 vs. 20.2 months, respectively) compared to subjects with ALC $\geq 0.3 \times 10^9$/L. Whether this reduced treatment effect should be ascribed to the product or to underlying biological/clinical differences is uncertain. A secondary objective to the

post-authorisation registry study BCM-005 has been included to assess effectiveness in the subgroup of patients with pre-leukapheresis ALC $<0.3 \times 10^9$/L. Study JCAR017-BCM-005 will also allow for the evaluation of the relationship between the administered CD4+:CD8+ cell components ratio and the pre-leukapheresis ALC, using data from the CIBMTR registry. Since the CD4+:CD8+ cell components ratio will be controlled at the manufacturing level (range 0.8 – 1.2) and is expected to be independent from the pre-leukapheresis ALC count, limited variability is however anticipated.

2.6.7. Conclusions on the clinical efficacy

Overall, the ORR/CRR rates reported from registrational studies 017001 and BCM-001 in a relatively important number of patients in advanced settings of relapse are reasonably supporting that clinical benefit would be expected with a meaningful disease control in a substantial proportion of patients. Uncertainties remain, however, on longer-term efficacy.

The available results are considered generalizable to the population to be treated. Full approval in the broad target indication is supported by the totality of data.

The CAT considers the following measures necessary to address issues related to efficacy:

Given the limitations associated with efficacy at long term and in certain sub-populations, the CAT/CHMP considers the following measures necessary to address issues related to efficacy:

- In order to further characterise the long-term efficacy and safety of Breyanzi in patients treated for relapsed or refractory DLBCL, PMBCL, FL3B after at least 2 prior therapies, the MAH should submit 24 months post Breyanzi infusion follow-up data (in the enrolled and treated population) of the study 017001.
- In order to further characterise the long-term efficacy and safety of Breyanzi in patients treated with relapsed or refractory DLBCL, PMBCL, FL3B after at least 2 prior therapies, the MAH should submit 24 months post Breyanzi infusion follow-up data (in the enrolled and treated population) of the study JCAR017-BCM-001 Cohort 1.

Data in more rare subgroups will become available from the ongoing JCAR017-BCM-003 study. Furthermore, remaining efficacy uncertainties will be further investigated in the post-approval setting in LTFU study GC-LTFU-001 (category 3 PASS study) and in registr- imposed PASS BCM-005, with the prespecified analyses as per an agreed protocol for efficacy which includes OS, DOR, PFS, ORR, CRR and TTNT. Effectiveness analyses will be provided as part of the interim reports to be prepared at Years 5, 10, and 15, as well as part of the final study report, currently targeted for Q4 2042.

Although reasons for pre-infusion treatment failure will not be collected as part of the imposed PASS, since registries only collect data on patients who receive JCAR017, data collected in the applicant's manufacturing database will be provided post-approval to further investigate the reasons for early treatment failures. The applicant committed to provide all available information on the rate and reasons for Breyanzi manufacturing failures that occur in the post-approval setting in the periodic safety update reports (PSURs).

In addition, the CAT recommended the following point for consideration:

- In order to further characterise the efficacy and safety of Breyanzi in patients with relapsed or refractory DLBCL, PMBCL, FL3B after at least 2 prior therapies, the MAH should submit the results of the study JCAR017-BCM-003.

The CHMP endorses the CAT conclusion on clinical efficacy as described above.

2.6.8. Clinical safety

The safety evaluation is primarily based on pooled safety results from 349 subjects treated with JCAR017, across all dose regimens, from 4 ongoing studies as per the table below

Table 48. Overview of Studies Included in the Summary of Clinical Safety in the Pooled 3L+ DLBCL Set – JCAR017-treated Set

Study	Phase	Study Start[a] / Data Cutoff	Cohort(s)	Assigned Dose Level[b] ($\times 10^6$ CAR+ T cells)	Subjects Exposed to JCAR017	
					By Dose Level / Cohort	By Study
017001	1	06 Jan 2016 to 12 Aug 2019	DLBCL Cohort	50 100 150	51 177 41	269
JCAR017-BCM-001	2	05 Jun 2018 to 13 Sep 2019	Cohort 1 / Cohort 3	100 / 100	27 10	37
017007	2	29 Nov 2018[c] to 01 Aug 2019	NA	100	17	17
JCAR017-BCM-002	1/2	28 Nov 2017 to 01 Aug 2019	NA (up to Day 29)[d]	50 100	8 18	26
Total number of subjects exposed to JCAR017 in the Pooled 3L+ DLBCL Set						**349**

3L+ = third and later line; CAR+ = chimeric antigen receptor positive; DLBCL = diffuse large B-cell lymphoma; IV = intravenous; NA = not applicable; SPM = second primary malignancy.

[a] Time from first subject consent date to data cutoff date.

[b] CAR+ T cells were provided in a defined composition. For example, a dose level of 100×10^6 CAR+ T cells included 50×10^6 CD8+ CAR+ and 50×10^6 CD4+ CAR+ T cells. JCAR017 was administered as separate IV infusions of CD8+ CAR+ and CD4+ CAR+ T cells (JCAR017 CD8+ drug product component administered first, followed by the JCAR017 CD4+ drug product component).

[c] Data on file.

[d] Includes data up to the start of combination therapy (approximately 30 days post JCAR017 infusion), with the exceptions of death and adverse events of special interest reported beyond the treatment-emergent period (SPM, autoimmune disorders, and hypogammaglobulinemia).

Note: The Pooled 3L+ DLBCL Set includes all subjects with 3L+ large B-cell lymphoma, as described in Section 1.1.2.2.

Sources: Clinical study protocols; CSR 017001 Table 14.1.2.a and Listing 16.2.1.1; SCS Table 1.1.1.1; CSR BCM-001 Listing 16.2.1.3 and Listing 16.2.2; and SCS Study BCM-002 Listing 16.2.1.2 and Listing 16.2.5.2.

JCAR017 safety profile for the treatment of adult patients with R/R large B-cell lymphoma after at least 2 prior therapies was also provided with data cutoff date 19 Jun 2020 for Studies 017001 and BCM-001, with 10 new subjects added (9 from BCM-001 Cohort 1 and 1 from the 017001 DLBCL cohort) to the Pooled 3L+ DLBCL Treated Set (D120 Safety Update section).

All subjects who completed study treatment and the 2-year on-study follow-up or who discontinued the study for any reason were encouraged to enrol in the long-term follow-up Study GC-LTFU-001 to evaluate long-term safety and survival for up to 15 years post-infusion.

Subject disposition

The subject disposition is shown in the table below.

Table 49: Set Subject Disposition in Study 017001, Study BCM-001, Study 017007, Study BCM-002, and the Pooled 3L+ DLBCL Screened Set

	017001 DLBCL Cohort n (%)	BCM-001		017007 n (%)	BCM-002 n (%)	Total n (%)
		Cohort 1 n (%)	Cohort 3 n (%)			
Subjects screened (N)	347	52	16	37	39	491

	017001 DLBCL Cohort n (%)	BCM-001		017007 n (%)	BCM-002 n (%)	Total n (%)
		Cohort 1 n (%)	Cohort 3 n (%)			
Failure[a]	6 (1.7)	8 (15.4)	2 (12.5)	6 (16.2)	7 (17.9)	29 (5.9)
Success[a]	341 (98.3)	44 (84.6)	14 (87.5)	31 (83.8)	32 (82.1)	462 (94.1)
Subjects underwent leukapheresis[a]	344 (99.1)[b]	43 (82.7)	14 (87.5)	28 (75.7)	33 (84.6)[b]	462 (94.1)
Subjects received LDC[c]	298 (86.6)	35 (81.4)	12 (85.7)	17 (60.7)	27 (81.8)	389 (84.2)
Subjects didn't receive JCAR017 infusion or nonconforming product[c]	50 (14.5)	12 (27.9)	2 (14.3)	11 (39.3)	6 (18.2)	81 (17.5)
Leukapheresed and waiting for product or not eligible for JCAR017 infusion	2 (0.6)[d]	7 (16.3)[d]	0	10 (35.7)[d]	0	19 (4.1)
Discontinued from study	48 (14.0)	5 (11.6)	2 (14.3)	1 (3.6)	6 (18.2)	62 (13.4)
Adverse event	0	1 (2.3)	0	0	0	1 (0.2)
Could not manufacture JCAR017	2 (0.6)	0	1 (7.1)	0	0	3 (0.6)
Death	33 (9.6)	4 (9.3)	0	1 (3.6)	3 (9.1)	41 (8.9)
Disease-related complications	6 (1.7)	0	0	0	0	6 (1.3)
Failure to meet treatment criteria	0	0	1 (7.1)	0	3 (9.1)	4 (0.9)
Ineligible for other reasons	3 (0.9)	0	0	0	0	3 (0.6)
Other	2 (0.6)	0	0	0	0	2 (0.4)
Withdrew consent	2 (0.6)	0	0	0	0	2 (0.4)
Subjects received JCAR017 or nonconforming product[c]	294 (85.5)	31 (72.1)	12 (85.7)	17 (60.7)	27 (81.8)	381 (82.5)
Subjects received nonconforming product[c]	25 (7.3)	4 (9.3)	2 (14.3)	0	1 (3.0)	32 (6.9)
Subjects received JCAR017 infusion[c]	269 (78.2)	27 (62.8)	10 (71.4)	17 (60.7)	26 (78.8)	349 (75.5)
Ongoing	103 (29.9)	15 (34.9)	7 (50.0)	17 (60.7)	16 (48.5)	158 (34.2)
Completed study (24 months)	35 (10.2)	0	0	0	0	35 (7.6)
Discontinued from study	131 (38.1)	12 (27.9)	3 (21.4)	0	10 (30.3)	156 (33.8)
Death	121 (35.2)	6 (14.0)	1 (7.1)	0	8 (24.2)	136 (29.4)
Lost to follow-up	2 (0.6)	0	0	0	0	2 (0.4)
Other	1 (0.3)	3 (7.0)	0	0	1 (3.0)	5 (1.1)
Withdrew consent	7 (2.0)	3 (7.0)	2 (14.3)	0	1 (3.0)	13 (2.8)
Consented to long-term follow up[c]	23 (6.7)[e]	0	0	0	0	23 (5.0) [e]

3L+ = third line or later; DLBCL = diffuse large B-cell lymphoma; LDC = lymphodepleting chemotherapy.

[a] Percentages are based on the numbers in row of 'Subjects screened'.

[b] There were subjects who were retrospectively determined to not have met entry criteria but who had already been leukapheresed. For this reason, the number of subjects who underwent leukaphereses is higher than the subjects who screened successfully.

[c] Percentages are based on the numbers in row of 'Subjects underwent leukapheresis."

[d] In Study 017001, 2 subjects were leukapheresed but not eligible for JCAR017 infusion. As of the data cutoff dates, in Study BCM-001 and Study 017007, 7 and 10 subjects, respectively, were leukapheresed and waiting for product.

[e] Includes only subjects in the 017001 DLBCL Screened Set who consented during Study 017001 (including Subject 00X-XXXX, who consented but did not enroll in the long-term follow-up [LTFU] study) (CSR 017001 Listing 16.2.1.1). Six additional subjects in the 017001 DLBCL Screened Set consented to the LTFU study after their final visit in Study 017001; that information is not available in the Study 017001 database but is found in Study GC-LTFU-001 Listing 16.2.1.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 1.1.1.1.

2.6.8.1. Patient exposure

Demographic and other characteristics of Study Population in the different Safety Datasets are reported in Table 50 and Table 51.

Table 50. Demographics and Baseline Characteristics - Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001		017007 (N = 17)	BCM-002 (N = 26)	Total (N = 349)
	(N = 269)	DL2S v4 (N = 126)	Cohort 1 (N = 27)	Cohort 3 (N = 10)			
Age (years)[a]							
n	269	126	27	10	17	26	349
Mean (StD)	60.1 (13.35)	59.5 (14.48)	58.4 (9.13)	60.4 (9.03)	66.4 (11.86)	65.5 (10.89)	60.7 (12.82)
Median	63.0	63.0	59.0	57.0	68.0	66.0	63.0
Q1, Q3	54.0, 70.0	54.0, 70.0	52.0, 65.0	55.0, 72.0	60.0, 78.0	62.0, 73.0	55.0, 70.0
Min, Max	18, 86	18, 79	40, 72	47, 73	43, 81	27, 83	18, 86
Age Group, n (%)							
< 65 years	157 (58.4)	74 (58.7)	19 (70.4)	7 (70.0)	8 (47.1)	7 (26.9)	198 (56.7)
≥ 65 years	112 (41.6)	52 (41.3)	8 (29.6)	3 (30.0)	9 (52.9)	19 (73.1)	151 (43.3)
< 75 years	242 (90.0)	113 (89.7)	27 (100)	10 (100)	11 (64.7)	21 (80.8)	311 (89.1)
≥ 75 years	27 (10.0)	13 (10.3)	0	0	6 (35.3)	5 (19.2)	38 (10.9)
Sex, n (%)							
Male	174 (64.7)	84 (66.7)	18 (66.7)	6 (60.0)	11 (64.7)	19 (73.1)	228 (65.3)
Female	95 (35.3)	42 (33.3)	9 (33.3)	4 (40.0)	6 (35.3)	7 (26.9)	121 (34.7)
Race, n (%)							
White	232 (86.2)	105 (83.3)	22 (81.5)	0	15 (88.2)	24 (92.3)	293 (84.0)
African American	12 (4.5)	5 (4.0)	0	0	0	1 (3.8)	13 (3.7)
Asian	11 (4.1)	7 (5.6)	0	10 (100)	0	0	21 (6.0)
Other	3 (1.1)	2 (1.6)	0	0	0	1 (3.8)	4 (1.1)
Unknown	11 (4.1)	7 (5.6)	5 (18.5)	0	2 (11.8)	0	18 (5.2)
Region, n (%)							
US	269 (100)	126 (100)	0	0	17 (100)	26 (100)	312 (89.4)
Europe	0	0	27 (100)	0	0	0	27 (7.7)
Japan	0	0	0	10 (100)	0	0	10 (2.9)
ECOG at Screening, n (%)							
0	110 (40.9)	46 (36.5)	15 (55.6)	6 (60.0)	8 (47.1)	17 (65.4)	156 (44.7)
1	155 (57.6)	80 (63.5)	11 (40.7)	4 (40.0)	9 (52.9)	9 (34.6)	188 (53.9)
2	4 (1.5)	0	1 (3.7)	0	0	0	5 (1.4)

3L+ = third line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; StD = standard deviation; US = United States.

[a] Age (years) = (date of first JCAR017 infusion – date of birth + 1) / 365.25 (rounded down to an integer).

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 1.2.1.1 and SCS Table 1.2.2.1.b.

Table 51. Summary of Disease Characteristics - Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269)	DL2S v4 (N = 126)	Cohort 1 (N = 27)	Cohort 3 (N = 10)	017007 (N = 17)	BCM-002 (N = 26)	Total (N = 349)
NHL subtype, n (%)							
DLBCL NOS	137 (50.9)	69 (54.8)	16 (59.3)	6 (60.0)	10 (58.8)	12 (46.2)	181 (51.9)
HGL, including double/triple hit	36 (13.4)	18 (14.3)	4 (14.8)	0	4 (23.5)	5 (19.2)	49 (14.0)
DLBCL transformed from indolent lymphoma	78 (29.0)	25 (19.8)	6 (22.2)	3 (30.0)	3 (17.6)	7 (26.9)	97 (27.8)
Follicular lymphoma	60 (22.3)	23 (18.3)	6 (22.2)	3 (30.0)	3 (17.6)	3 (11.5)	75 (21.5)
CLL/SLL	5 (1.9)	1 (0.8)	0	0	0	0	5 (1.4)
MZL	10 (3.7)	1 (0.8)	0	0	0	1 (3.8)	11 (3.2)
Other	3 (1.1)	0	0	0	0	3 (11.5)	6 (1.7)
FL3B	3 (1.1)	2 (1.6)	1 (3.7)	1 (10.0)	0	2 (7.7)	7 (2.0)
PMBCL	15 (5.6)	12 (9.5)	0	0	0	0	15 (4.3)
Cell of origin, n (%)							
GCB	119 (44.2)	57 (45.2)	17 (63.0)	4 (40.0)	13 (76.5)	11 (42.3)	164 (47.0)
non-GCB	76 (28.3)	33 (26.2)	7 (25.9)	5 (50.0)	3 (17.6)	7 (26.9)	98 (28.1)
Unknown	56 (20.8)	22 (17.5)	2 (7.4)	0	1 (5.9)	6 (23.1)	65 (18.6)
Missing	18 (6.7)	14 (11.1)	1 (3.7)	1 (10.0)	0	2 (7.7)	22 (6.3)

	017001 DLBCL Cohort		BCM-001				
	(N = 269)	DL2S v4 (N = 126)	Cohort 1 (N = 27)	Cohort 3 (N = 10)	017007 (N = 17)	BCM-002 (N = 26)	Total (N = 349)
Disease status to last prior therapy, n (%)							
Refractory[a]	213 (79.2)	101 (80.2)	20 (74.1)	7 (70.0)	15 (88.2)	11 (42.3)	266 (76.2)
Relapsed[a]	56 (20.8)	25 (19.8)	7 (25.9)	3 (30.0)	2 (11.8)	14 (53.8)	82 (23.5)
Time since eligible diagnosis[b] to JCAR017 infusion (months)							
n	269	126	27	10	17	18	341
Mean (StD)	31.4 (36.37)	35.0 (40.01)	27.5 (18.34)	39.7 (45.72)	23.4 (21.20)	73.8 (79.27)	33.1 (39.47)
Median	18.4	18.5	24.0	22.2	16.3	34.3	19.2
Q1, Q3	11.1, 34.5	11.4, 37.7	14.4, 39.8	11.3, 51.3	12.3, 23.4	20.2, 89.4	11.7, 35.9
Min, Max	5, 259	5, 202	2, 75	8, 157	4, 82	12, 301	2, 301
Prior HSCT, n (%)							
Yes	94 (34.9)	45 (35.7)	11 (40.7)	2 (20.0)	4 (23.5)	9 (34.6)	120 (34.4)
No	175 (65.1)	81 (64.3)	16 (59.3)	8 (80.0)	13 (76.5)	17 (65.4)	229 (65.6)
Prior allogeneic HSCT, n (%)							
Yes	9 (3.3)	3 (2.4)	0	0	0	0	9 (2.6)
No	260 (96.7)	123 (97.6)	27 (100)	10 (100)	17 (100)	26 (100)	340 (97.4)
Prior autologous HSCT, n (%)							
Yes	90 (33.5)	45 (35.7)	11 (40.7)	2 (20.0)	4 (23.5)	9 (34.6)	116 (33.2)
No	179 (66.5)	81 (64.3)	16 (59.3)	8 (80.0)	13 (76.5)	17 (65.4)	233 (66.8)
Best response to any prior therapy, n (%)							
Complete response	150 (55.8)	73 (57.9)	17 (63.0)	4 (40.0)	8 (47.1)	18 (69.2)	197 (56.4)
Partial response	83 (30.9)	38 (30.2)	5 (18.5)	3 (30.0)	7 (41.2)	6 (23.1)	104 (29.8)
Stable disease	18 (6.7)	7 (5.6)	1 (3.7)	2 (20.0)	1 (5.9)	1 (3.8)	23 (6.6)
Progressive disease	18 (6.7)	8 (6.3)	3 (11.1)	1 (10.0)	1 (5.9)	0	23 (6.6)
Not evaluable	0	0	0	0	0	1 (3.8)	1 (0.3)
CNS involvement by lymphoma at first JCAR017 dosing, n (%)							
Yes	7 (2.6)	4 (3.2)	0	0[e]	1 (5.9)	0	8 (2.3)
No	262 (97.4)	122 (96.8)	27 (100)	9 (90.0)	16 (94.1)	0	314 (90.0)
Missing	0	0	0	1 (10.0)	0	26 (100)	27 (7.7)
LDH prior to LDC[c], U/L							
n	269	126	27	10	17	26	349
Mean (StD)	460.2 (877.06)	459.0 (1073.39)	502.8 (482.45)	454.2 (433.56)	397.0 (238.57)	401.2 (505.68)	455.9 (797.63)
Median	266.0	255.5	337.0	259.5	294.0	242.5	270.0
Q1, Q3	197.0, 462.0	196.0, 370.0	206.0, 543.0	185.0, 386.0	201.0, 617.0	177.0, 318.0	196.0, 467.0
Min, Max	112, 11933	116, 11933	166, 2100	181, 1338	128, 933	140, 2291	112, 11933
≥ 500 U/L, n (%)	58 (21.6)	24 (19.0)	8 (29.6)	2 (20.0)	6 (35.3)	4 (15.4)	78 (22.3)
< 500 U/L, n (%)	211 (78.4)	102 (81.0)	19 (70.4)	8 (80.0)	11 (64.7)	22 (84.6)	271 (77.7)
SPD per investigator assessment prior to LDC[c], cm^2							
n	265	124	27	10	17	26	345
Mean (StD)	54.4 (64.44)	57.5 (69.72)	59.1 (50.42)	39.2 (43.08)	39.1 (33.13)	22.2 (18.92)	51.1 (59.94)
Median	31.2	34.9	39.8	16.2	28.5	21.4	30.4
Q1, Q3	13.6, 72.3	15.2, 78.6	20.9, 81.7	12.0, 85.8	20.8, 51.9	5.8, 30.0	13.1, 69.1
Min, Max	1, 485	1, 485	4, 178	5, 121	1, 118	1, 73	1, 485
≥ 50 cm^2, n (%)	92 (34.7)	46 (37.1)	12 (44.4)	3 (30.0)	5 (29.4)	2 (7.7)	114 (33.0)
< 50 cm^2, n (%)	173 (65.3)	78 (62.9)	15 (55.6)	7 (70.0)	12 (70.6)	24 (92.3)	231 (67.0)

	017001 DLBCL Cohort		BCM-001				
	(N = 269)	DL2S v4 (N = 126)	Cohort 1 (N = 27)	Cohort 3 (N = 10)	017007 (N = 17)	BCM-002 (N = 26)	Total (N = 349)
Baseline[d] CRP (mg/L)							
n	268	126	27	10	17	26	348
Mean (StD)	83.4 (222.65)	83.2 (194.62)	28.9 (39.42)	20.4 (49.00)	39.7 (46.48)	24.1 (45.43)	70.8 (197.77)
Median	27.6	29.5	13.2	4.1	18.0	8.1	20.6
Q1, Q3	7.9, 81.6	8.0, 93.8	6.8, 31.5	2.2, 6.6	11.0, 42.0	3.0, 16.1	6.8, 72.4
Min, Max	0, 2158	0, 1503	1, 175	0, 159	2, 160	0, 186	0, 2158
< 20 mg/L, n (%)	117 (43.7)	55 (43.7)	16 (59.3)	9 (90.0)	9 (52.9)	21 (80.8)	172 (49.4)
≥ 20 mg/L, n (%)	151 (56.3)	71 (56.3)	11 (40.7)	1 (10.0)	8 (47.1)	5 (19.2)	176 (50.6)

3L+ = third line or later; CLL = chronic lymphocytic leukemia; CNS = central nervous system; CR = complete response; CRF = case report form; CRP = C-reactive protein; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; FL3B = follicular lymphoma, Grade 3B; GCB = germinal center B-cell; HGL = high-grade lymphoma; HSCT = hematopoietic stem cell transplantation; LDC = lymphodepleting chemotherapy; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PD = progressive disease; PMBCL = primary mediastinal B-cell lymphoma; PR = partial response; Q1 = first quartile; Q3 = third quartile; SD = stable disease; SLL = small lymphocytic lymphoma; SPD = sum of product of perpendicular diameters; StD = standard deviation.

[a] Relapsed versus Refractory is defined as best response of CR versus best response of PR, SD, or PD to last systemic or transplant treatment with curative intent. Determined by the response to the CRF question 'Was disease relapsed or refractory to last therapy?'

[b] Eligible diagnosis is defined as a subject's large B-cell lymphoma diagnosis which met eligibility for the clinical trial. The date of this diagnosis captured in the database is used for calculating the time from diagnosis. If a subject had previous indolent lymphoma (eg follicular lymphoma), the date of the qualifying transformation diagnosis (eg, DLBCL transformed from follicular lymphoma) was used, not the initial indolent lymphoma diagnosis date.

[c] Prior to LDC is the latest measurement taken prior to the start date of LDC closest to the JCAR017 infusion or on the start date of LDC but prior to LDC administration.

[d] Baseline is the latest measurement taken prior to the date of the JCAR017 infusion or on the date of the JCAR017 infusion but prior to JCAR017 administration.

[e] One subject in Study BCM-001 Cohort 3 was identified as having CNS lymphoma involvement after screening and prior to JCAR017 administration, but this subject is not represented in the table above, as CNS involvement is determined based on data collected at screening in Study BCM-001. See BCM-001 Narrative 6011008 for details.

Note: Per protocol, Study BCM-001 did not allow subjects with PMBCL to enroll in these studies.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 1.2.1.1, SCS Table 1.3.1.1, SCS Table 1.3.2.1.b, and SCS Table 1.2.2.1.b.

Some clinically relevant comorbidities were permitted by the eligibility criteria in Study 017001; 19.0% had a calculated creatinine clearance (CrCl) between 25 and 60 mL/min and 4.8% had screening left ventricular ejection fraction (LVEF) < 50% but ≥ 40%. In addition, 17.8% of subjects had laboratory-based Grade ≥ 3 cytopenia prior to receiving LDC.

Anticancer treatment (Table 52). In the total 017001 DLBCL Treated Set, systemic therapy only was used in 88.1%, radiotherapy only was used in 3.8%, and both systemic therapy and radiotherapy were used in 8.2% of subjects.

Table 52. Anticancer Treatment for Disease Control - Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Received Anticancer Treatment[a]							
Yes	159 (59.1)	63 (50.0)	21 (77.8)	10 (100)	8 (47.1)	12 (46.2)	210 (60.2)
No	110 (40.9)	63 (50.0)	6 (22.2)	0	9 (52.9)	14 (53.8)	139 (39.8)

3L+ = third line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma.

[a] The case report form captured new anticancer treatment for disease control that was started after consent and prior to lymphodepleting chemotherapy.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 1.4.1.1 and SCS Table 1.4.2.1.b.

Lymphodepleting Chemotherapy

In the 017001 DLBCL Treated Set, most subjects (92.2%) received the full specified dose of fludarabine and cyclophosphamide at the planned time with no missing doses. This was consistent across NHL subtypes. The median time from the last LDC to JCAR017 treatment was 4.0 days (range 3 to 9 days).

Table 53. Lymphodepleting Chemotherapy - Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
Subjects Received	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Full dose of Fludarabine and Cyclophosphamide[a]	248 (92.2)	116 (92.1)	21 (77.8)	6 (60.0)	15 (88.2)	20 (76.9)	310 (88.8)

3L+ = third line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma.

[a] Received both fludarabine and cyclophosphamide at full dose, no missing doses.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 2.1.1.1 and Table 2.1.1.1.b.

JCAR017 Administration

Table 54. Administered JCAR017 Dose, 017001 DLBCL Treated Set

Subjects Received	DL2S (N=177)	DL1S (N=45)	DL1D (N=6)	DL3S (N=41)	Total (N=269)
CD8 Cell Dose (10^6 cells)					
Mean (StD)	44.6 (6.73)	25.3 (1.86)	30.5 (10.96)	62.9 (8.88)	43.9 (12.72)
Median	45.8	25.2	26.5	64.1	45.2
Q1, Q3	40.9, 48.3	24.6, 25.9	25.1, 26.8	58.8, 67.6	36.1, 50.0
Min, Max	20, 65	20, 30	25, 53	35, 80	20, 80
CD4 Cell Dose (10^6 cells)					
Mean (StD)	45.7 (5.17)	24.8 (1.17)	30.0 (10.22)	65.7 (6.25)	44.9 (12.83)
Median	45.7	25.0	25.9	65.0	45.4
Q1, Q3	42.2, 49.3	24.5, 25.4	25.5, 26.7	62.8, 67.5	39.4, 50.6
Min, Max	21, 66	20, 27	25, 51	52, 82	20, 82
Total Cell Dose (10^6 cells)					
Mean (StD)	90.3 (10.17)	50.1 (2.48)	60.5 (21.18)	128.5 (11.77)	88.7 (24.70)
Median	91.1	50.1	52.4	128.9	90.6
Q1, Q3	84.1, 97.0	49.5, 51.3	50.8, 53.5	122.4, 135.1	78.6, 99.6
Min, Max	45, 120	44, 56	50, 104	87, 156	44, 156

DL1D = Dose Level 1, 2 Dose; DL1S = Dose Level 1, Single Dose; DL2S = Dose Level 2, Single Dose; DL3S = Dose Level 3, Single Dose; DLBCL = diffuse large B-cell lymphoma; Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; StD = standard deviation.
Note: Additional doses and retreatment with JCAR017 were not included in this table.
Data as of the 12 Aug 2019 cutoff date.
Source: CSR 017001 Table 14.3.1.1.8.a.

Table 55. Range of Administered JCAR017 Doses and Components Ratios Across Single-dose Regimens, 017001 DLBCL Treated Set

Parameter	Administered Dose (CAR+ viable T cells) (N = 263)
Median	91.1×10^6
Range	43.9 to 156.0×10^6
Q1, Q3	79.6×10^6, 99.9×10^6
Parameter	**Administered Component Ratio (CD4:CD8) (N = 263)**
Median	1.00
Range	0.73 to 2.20
Q1, Q3	0.94, 1.07

CAR = chimeric antigen receptor; DLBCL = diffuse large B cell lymphoma; Q1 = first quartile; Q3 = third quartile.
Data cutoff date: 12 Aug 2019.
Source: 017001 DOVER Table 14.3.6.1.1.

Table 56. JCAR017 Administered Dose in Study 017001, by NHL Subtype in the DLBCL Cohort – JCAR017-treated Set

Subjects Received	DLBCL Cohort Total (N = 269)	DLBCL Histology Subgroup						
		DLBCL Subgroup Total (NOS, HGL, tFL, tiNHL) (N = 251)	DLBCL NOS (N = 137)	HGL (N = 36)	tFL (N = 60)	tiNHL (N = 18)	PMBCL (N = 15)	FL3B (N = 3)
CD8 Cell Dose (10^6 cells)								
Mean (StD)	43.9 (12.72)	43.7 (12.99)	44.3 (12.62)	42.7 (11.51)	43.2 (14.07)	43.6 (15.57)	45.9 (6.66)	42.7 (15.26)
Median	45.2	44.9	45.5	44.4	43.7	46.1	47.0	49.8
Q1, Q3	36.1, 50.0	34.8, 50.0	37.8, 50.4	39.2, 47.2	27.2, 50.4	25.3, 58.7	42.7, 50.1	25.2, 53.2
Min, Max	20, 80	20, 80	20, 77	22, 77	23, 80	24, 68	29, 54	25, 53
CD4 Cell Dose (10^6 cells)								
Mean (StD)	44.9 (12.83)	45.1 (13.12)	45.6 (12.15)	43.8 (12.49)	44.5 (14.35)	45.3 (17.52)	43.1 (6.35)	37.4 (12.47)
Median	45.4	45.6	45.9	45.1	43.7	47.8	44.4	38.8
Q1, Q3	39.4, 50.6	39.3, 50.9	41.0, 50.7	38.8, 50.0	36.8, 51.0	25.3, 55.4	40.5, 46.7	24.3, 49.1
Min, Max	20, 82	20, 82	23, 80	24, 74	21, 76	20, 82	25, 50	24, 49
Total Cell Dose (10^6 cells)								
Mean (StD)	88.7 (24.70)	88.8 (25.28)	89.9 (23.75)	86.5 (23.24)	87.7 (27.88)	88.9 (32.40)	89.1 (12.07)	80.1 (26.75)
Median	90.6	90.5	91.1	87.3	87.4	94.7	91.4	92.0
Q1, Q3	78.6, 99.6	78.0, 100.2	80.5, 99.9	80.4, 96.2	64.2, 102.2	50.3, 121.4	86.5, 95.8	49.5, 98.9
Min, Max	44, 156	44, 156	46, 145	46, 144	45, 156	44, 141	54, 105	49, 99

DLBCL = diffuse large B-cell lymphoma; FL3B = follicular lymphoma, Grade 3B; HGL = high-grade lymphoma; Max = maximum; Min = minimum; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal B-cell lymphoma; Q1 = first quartile; Q3 = third quartile; StD = standard deviation; tCLL/SLL = DLBCL transformed from chronic lymphocytic leukemia/small lymphocytic lymphoma; tFL = DLBCL transformed from follicular lymphoma; tiNHL = DLBCL transformed from indolent non-Hodgkin lymphoma (tMZL + tCLL/SLL + tOther); tMZL = DLBCL transformed from marginal zone lymphoma; tOther = DLBCL transformed from other indolent lymphomas, including Waldenstrom macroglobulinemia.
Data cutoff date: 12 Aug 2019.
Source: SCS Table 2.2.2.1.

Additional Cycles and Retreatment Cycles of JCAR017 in Study 017001

Under the original Study 017001 protocol and Amendments 1 through 5, subjects could receive additional cycles of JCAR017 if SD or PR was their BOR after the initial response assessment. Throughout the study, subjects could receive retreatment cycles with JCAR017 if PD occurred following CR to JCAR017 (Table 57).

Table 57. Subjects Receiving Additional Cycles or Retreatment Cycles in Study 017001, by NHL Subtype in the DLBCL Cohort – JCAR017-treated Set

	DLBCL Cohort Total (N = 269) n (%)	DLBCL Histology Subgroup						
		DLBCL Subgroup Total (NOS, HGL, tFL, tiNHL) (N = 251) n (%)	DLBCL NOS (N = 137) n (%)	HGL (N = 36) n (%)	tFL (N = 60) n (%)	tiNHL (N = 18) n (%)	PMBCL (N = 15) n (%)	FL3B (N = 3) n (%)
Subjects received additional cycles[a]	7 (2.6)	7 (2.8)	3 (2.2)	2 (5.6)	2 (3.3)	0	0	0
Subjects received retreatment cycles[b]	16 (5.9)	15 (6.0)	9 (6.6)	3 (8.3)	1 (1.7)	2 (11.1)	1 (6.7)	0

DLBCL = diffuse large B-cell lymphoma; FL3B = follicular lymphoma, Grade 3B; HGL = high-grade lymphoma; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PD = progressive disease; PMBCL = primary mediastinal B-cell lymphoma; tCLL/SLL = DLBCL transformed from chronic lymphocytic leukemia/small lymphocytic lymphoma; tFL = DLBCL transformed from follicular lymphoma; tiNHL = DLBCL transformed from indolent non-Hodgkin lymphoma (tMZL + tCLL/SLL + tOther); tMZL = DLBCL transformed from marginal zone lymphoma; tOther = DLBCL transformed from other indolent lymphomas, including Waldenstrom macroglobulinemia.

[a] In Study 017001, subjects may have received multiple infusions of JCAR017 if they had JCAR017-responsive lymphoma but had not achieved a complete response (CR).

[b] In Study 017001, retreatment with JCAR017 was allowed for subjects who achieved a CR after JCAR017 treatment and subsequently had PD.

Data cutoff date: 12 Aug 2019.
Source: SCS Table 2.2.2.1.

Study BCM-001

All subjects in Study BCM-001 were assigned to treatment at 100 × 10^6 CAR+ T cells. The median CD4+:CD8+ cell components ratio was 0.99 (range 0.88 to 1.44; Q1, Q3 = 0.95, 1.03).

Pooled 3L+ DLBCL Treated Set

The median administered dose of JCAR017 in the Pooled 3L+ DLBCL Set (N = 349) was 90.8 × 10^6 CAR+ viable T cells (range, 37 × 10^6 to 203 × 10^6; Table 12). Of note, 8 out of 26 subjects in BCM-002 were assigned to DL1S (50 × 10^6 CAR+ T cells) per protocol and the remaining 18 to DL2S (100 × 10^6 CAR+ T cells) (Table 58).

Table 58. JCAR017 Administered Dose – Pooled 3L+ DLBCL Set

Subjects Received	017001 DLBCL Cohort (N = 269)	017001 DLBCL Cohort DL2S v4 (N = 126)	BCM-001 Cohort 1 (N = 27)	BCM-001 Cohort 3 (N = 10)	017007 (N = 17)	BCM-002 (N = 26)	Total (N = 349)
CD8 Cell Dose (10^6 cells)							
Mean (StD)	43.9 (12.72)	42.3 (6.16)	45.3 (5.10)	47.7 (6.72)	51.1 (14.90)	35.7 (11.28)	43.8 (12.46)
Median	45.2	43.4	46.2	49.8	50.0	38.4	45.6
Q1, Q3	36.1, 50.0	39.8, 46.6	42.5, 49.3	46.7, 51.2	49.1, 50.3	23.9, 41.8	37.4, 50.0
Min, Max	20, 80	20, 53	33, 52	34, 56	31, 105	16, 57	16, 105
CD4 Cell Dose (10^6 cells)							
Mean (StD)	44.9 (12.83)	43.7 (4.60)	45.7 (3.51)	47.9 (3.23)	51.2 (12.65)	37.9 (12.19)	44.8 (12.32)
Median	45.4	44.1	46.2	49.1	50.0	42.3	45.7
Q1, Q3	39.4, 50.6	41.3, 46.0	43.2, 49.1	45.4, 49.9	48.5, 50.5	23.0, 48.7	40.1, 50.3
Min, Max	20, 82	21, 66	38, 51	41, 52	39, 98	20, 57	20, 98
Total Cell Dose (10^6 cells)							
Mean (StD)	88.7 (24.70)	86.0 (8.29)	90.9 (7.54)	95.6 (9.18)	102.3 (27.38)	73.6 (22.48)	88.6 (23.98)
Median	90.6	86.8	91.6	99.6	99.5	83.2	90.8
Q1, Q3	78.6, 99.6	81.4, 91.8	87.2, 95.6	93.9, 101.7	98.7, 100.4	45.2, 87.3	80.3, 99.6
Min, Max	44, 156	45, 103	71, 103	79, 103	70, 203[a]	37, 105	37, 203[a]

3L+ = third line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; eCRF = electronic case report form; Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; StD = standard deviation.

[a] Cell dose is derived from the volume of JCAR017 component administered and recorded by the site in the eCRF, and the cell concentration of JCAR017 component. The maximum cell dose for CD8 (105 × 10^6), CD4 (98 × 10^6), and Total Cell Dose (203 × 10^6) for one subject in Study 017007 was derived based on incorrect CD4 and CD8 component volumes as the result of a transcription error by the site when entering administered component volumes in the eCRF. The transcription error was identified and corrected following the database lock. Corrected administered volumes for this subject in the clinical database (1.6 mL for CD8 and 1.7 mL for CD4) result in administered CD4 and CD8 Cell Doses of 51 × 10^6 and 49 × 10^6, respectively, and a Total Cell Dose of 100 × 10^6 for this subject (data on file). Therefore, in this table, the mean, standard deviation, and the maximum are overestimated for Study 017007 and the Total column.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 2.2.1.1 and Table 2.2.1.1.b.

Study Duration

Study 017001

Total on-study follow-up time for the 017001 DLBCL Treated Set was 278.4 patient-years. Total median on-study follow-up time in the 017001 DLBCL Treated Set was 11.50 months (range 0.2 to 35.0 months). Among the NHL subtypes, follow-up time ranged from a median of 6.49 months for tiNHL to 14.05 months for tFL. In the Study 017001 DLBCL Cohort, in the approximately 10 months between the data cutoff dates of the original MAA and the Day 120 update (12 Aug 2019 to 19 Jun 2020), the median on-study follow-up time increased from 11.50 to 19.06 months, and the total on-study follow-up from 278.4 to 343.6 patient-years (for details, see Day 120 Safety Update section).

BCM-001

Median on-study follow-up for subjects in BCM-001 Cohort 1 JCAR017-treated Set was 2.40 months (range: 0.1 to 12.1 months). Total on-study follow-up time for BCM-001 Cohort 1 was 10.2 patient-years. In Study BCM-001 Cohort 1, in the approximately 9 months between the data cut-off dates of the original MAA and the Day 120 update (13 Sep 2019 to 19 Jun 2020), the median on-study follow-up time increased from 2.40 to 6.36 months, and the total on-study follow-up from 10.2 to 23.5 patient-years.

Studies in the Pooled 3L+ DLBCL Set

In the Pooled 3L+ DLBCL Set, median on-study follow up time was 9.17 months (range 0.1, 35.0 months) (Table 59). At cutoff date of 19 Jun 2020, in the Pooled 3L+ DLBCL Treated Set, the median on-study follow-up time increased from 9.17 to 10.74 months, and the total on-study follow-up from 313.6 to 395.7 patient-years.

Table 59. Study Duration – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269)	DL2S v4 (N = 126)	Cohort 1 (N = 27)	Cohort 3 (N = 10)	017007 (N = 17)	BCM-002 (N = 26)	Total (N = 349)
On-study Follow-up Time [a] (months)							
Mean (StD)	12.42 (7.836)	11.09 (6.195)	4.52 (3.964)	4.87 (2.706)	2.60 (1.543)	7.93 (5.489)	10.78 (7.805)
Median	11.50	12.50	2.40	4.42	2.66	7.20	9.17
Q1, Q3	5.55, 18.86	5.39, 16.99	1.28, 7.95	3.15, 7.59	1.94, 3.81	3.22, 11.10	3.91, 16.99
Min, Max	0.2, 35.0	0.2, 22.5	0.1, 12.1	1.1, 9.3	0.1, 5.0	0.8, 18.7	0.1, 35.0
Duration of On-study Follow-up[a]							
≥ 1 Day, n (%)	269 (100)	126 (100)	27 (100)	10 (100)	17 (100)	26 (100)	349 (100)
≥ 29 Days, n (%)	259 (96.3)	121 (96.0)	23 (85.2)	10 (100)	13 (76.5)	25 (96.2)	330 (94.6)
≥ 2 Months, n (%)	245 (91.1)	118 (93.7)	15 (55.6)	8 (80.0)	10 (58.8)	23 (88.5)	301 (86.2)
≥ 3 Months, n (%)	233 (86.6)	110 (87.3)	13 (48.1)	8 (80.0)	8 (47.1)	21 (80.8)	283 (81.1)
≥ 6 Months, n (%)	199 (74.0)	88 (69.8)	10 (37.0)	3 (30.0)	0	14 (53.8)	226 (64.8)
≥ 9 Months, n (%)	164 (61.0)	74 (58.7)	5 (18.5)	1 (10.0)	0	10 (38.5)	180 (51.6)
≥ 12 Months, n (%)	131 (48.7)	65 (51.6)	1 (3.7)	0	0	6 (23.1)	138 (39.5)
≥ 18 Months, n (%)	71 (26.4)	18 (14.3)	0	0	0	2 (7.7)	73 (20.9)
≥ 24 Months, n (%)	29 (10.8)	0	0	0	0	0	29 (8.3)
Total on-study follow-up time (patient years)	278.4	116.5	10.2	4.1	3.7	17.2	313.6

3L+ = third line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; Max = maximum; Min = minimum; Q1 = first quartile; Q3 = third quartile; StD = standard deviation.

[a] On-study follow-up time was defined as the end of study (EOS) date minus first JCAR017 dose date plus 1. If subjects were continuing on study, the data cut-off date was used to impute the EOS date for the purpose of calculation. Months = Days/30.4375; Years = Days/365.25.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 2.3.1.1 and Table 2.3.1.1.b.

2.6.8.2. Adverse events

Summary of adverse events

For Studies 017001 and BCM-001, AEs were mapped into the following time periods:

- Screening to the day before leukapheresis (Study 017001 only)
- Leukapheresis to the day before LDC
- Start of LDC to the day before the first JCAR017 infusion
- TEAE reporting period: from the first JCAR017 infusion through the TEAE reporting period
- Post-treatment-emergent period

Treatment-emergent Adverse Events (TEAE)

A TEAE was defined as an AE that started any time from initiation of JCAR017 administration through and including 90 days following the final cycle (i.e., final infusion) of JCAR017. Any AE occurring after the initiation of subsequent anticancer therapy, JCAR017 retreatment, or start of combination therapy (Study BCM-002) was not considered a TEAE.

Table 60. Overview of Treatment-emergent Adverse Events in Study 017001, by NHL Subtype in the DLBCL Cohort-JCAR017-treated Set

	DLBCL Cohort Total (N = 269) n (%)	DLBCL Histology Subgroup					
		DLBCL Subgroup Total (NOS, HGL, tFL, tiNHL) (N = 251) n (%)	DLBCL NOS (N = 137) n (%)	HGL (N = 36) n (%)	tFL (N = 60) n (%)	tiNHL (N = 18) n (%)	PMBCL (N = 15) n (%)	FL3B (N = 3) n (%)
Subjects with any TEAE	267 (99.3)	249 (99.2)	136 (99.3)	36 (100)	59 (98.3)	18 (100)	15 (100)	3 (100)
Grade ≥ 3 TEAE	213 (79.2)	200 (79.7)	108 (78.8)	30 (83.3)	48 (80.0)	14 (77.8)	10 (66.7)	3 (100)
Grade 5 TEAE	7 (2.6)	7 (2.8)	3 (2.2)	3 (8.3)	1 (1.7)	0	0	0
Treatment-emergent SAE	122 (45.4)	112 (44.6)	65 (47.4)	14 (38.9)	24 (40.0)	9 (50.0)	10 (66.7)	0
Any JCAR017-related TEAE	201 (74.7)	188 (74.9)	96 (70.1)	27 (75.0)	51 (85.0)	14 (77.8)	11 (73.3)	2 (66.7)
JCAR017-related Grade ≥ 3 TEAE	93 (34.6)	91 (36.3)	44 (32.1)	19 (52.8)	24 (40.0)	4 (22.2)	2 (13.3)	0
JCAR017-related Grade 5 TEAE	4 (1.5)	4 (1.6)	2 (1.5)	2 (5.6)	0	0	0	0
JCAR017-related treatment-emergent SAE	79 (29.4)	72 (28.7)	43 (31.4)	9 (25.0)	16 (26.7)	4 (22.2)	7 (46.7)	0
Any LDC-related TEAE	235 (87.4)	220 (87.6)	119 (86.9)	34 (94.4)	52 (86.7)	15 (83.3)	12 (80.0)	3 (100)
LDC-related Grade ≥ 3 TEAE	197 (73.2)	185 (73.7)	100 (73.0)	28 (77.8)	43 (71.7)	14 (77.8)	9 (60.0)	3 (100)
LDC-related Grade 5 TEAE	6 (2.2)	6 (2.4)	3 (2.2)	3 (8.3)	0	0	0	0
LDC-related treatment-emergent SAE	46 (17.1)	44 (17.5)	28 (20.4)	7 (19.4)	7 (11.7)	2 (11.1)	2 (13.3)	0

DLBCL = diffuse large B-cell lymphoma; FL3B = follicular lymphoma Grade 3B; HGL = high-grade lymphoma; LDC = lymphodepleting chemotherapy; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal B-cell lymphoma; SAE = serious adverse event; tCLL/SLL = DLBCL transformed from chronic lymphocytic leukemia/small lymphocytic lymphoma; TEAE = treatment-emergent adverse event; tFL = DLBCL transformed from follicular lymphoma; tiNHL = DLBCL transformed from indolent non-Hodgkin lymphoma (tMZL + tCLL/SLL + tOther); tMZL = DLBCL transformed from marginal zone lymphoma; tOther = DLBCL transformed from other indolent lymphomas, including Waldenstrom macroglobulinemia.

A TEAE was defined as an adverse event that started any time from initiation of JCAR017 administration through and including 90 days following the final cycle of JCAR017. Any adverse event occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment was not considered a TEAE.

Data cutoff date: 12 Aug 2019.

Source: SCS Table 3.1.2.1.

Results in the 017001 DLBCL Treated Set (n = 269), and in the subset of subjects in the 017001 DLBCL Treated Set who were treated with DL2S v4 (n = 126), were similar to the results observed in the Pooled 3L+ DLBCL Set (Table 61).

Table 61. Overview of Treatment-emergent Adverse Events – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Subjects with any TEAE	267 (99.3)	126 (100)	27 (100)	10 (100)	17 (100)	26 (100)	347 (99.4)
Grade ≥ 3 TEAE	213 (79.2)	102 (81.0)	25 (92.6)	9 (90.0)	15 (88.2)	19 (73.1)	281 (80.5)
Grade 5 TEAE	7 (2.6)	4 (3.2)	2 (7.4)	0	0	2 (7.7)	11 (3.2)
Treatment-emergent SAE	122 (45.4)	60 (47.6)	11 (40.7)	1 (10.0)	8 (47.1)	12 (46.2)	154 (44.1)
Any JCAR017-related TEAE	201 (74.7)	98 (77.8)	26 (96.3)	8 (80.0)	13 (76.5)	17 (65.4)	265 (75.9)
JCAR017-related Grade ≥ 3 TEAE	93 (34.6)	42 (33.3)	15 (55.6)	7 (70.0)	11 (64.7)	4 (15.4)	130 (37.2)
JCAR017-related Grade 5 TEAE	4 (1.5)	3 (2.4)	2 (7.4)	0	0	0	6 (1.7)
JCAR017-related treatment-emergent SAE	79 (29.4)	35 (27.8)	9 (33.3)	0	8 (47.1)	8 (30.8)	104 (29.8)
Any LDC-related TEAE	235 (87.4)	112 (88.9)	21 (77.8)	8 (80.0)	17 (100)	22 (84.6)	303 (86.8)
LDC-related Grade ≥ 3 TEAE	197 (73.2)	90 (71.4)	20 (74.1)	8 (80.0)	13 (76.5)	17 (65.4)	255 (73.1)
LDC-related Grade 5 TEAE	6 (2.2)	4 (3.2)	1 (3.7)	0	0	1 (3.8)	8 (2.3)
LDC-related treatment-emergent SAE	46 (17.1)	25 (19.8)	1 (3.7)	0	1 (5.9)	4 (15.4)	52 (14.9)

3L+ = third-line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; LDC = lymphodepleting chemotherapy; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: A TEAE was defined as an adverse event that started any time from initiation of JCAR017 administration through and including 90 days following the final cycle of JCAR017. Any adverse event occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (Study BCM-002) was not considered a TEAE.
Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: SCS Table 3.1.1.1 and SCS Table 3.1.2.1.b.

Treatment-emergent Adverse Events by SOC and PT

Among the individual subtypes in the DLBCL histology subgroup, frequently reported TEAEs were generally similar across these subtypes. However, some differences (i.e., ≥ 20% difference) were observed for the tiNHL subtype compared to the other subtypes: at the level of the SOC, Gastrointestinal Disorders were reported less frequently in the tiNHL subtype (61.1%) compared with the tFL subtype (81.7%). Musculoskeletal and Connective Tissue Disorders were reported more frequently in the tiNHL subtype (61.1%) than in the HGL subtype (33.3%), and Cardiac Disorders were reported more frequently in the tiNHL subtype (50.0%) than in the tFL subtype (25.0%). Skin and Subcutaneous Tissue Disorders were also reported more frequently in subjects with tiNHL (50.0%) compared to the other subtypes (19.4% to 30.7%).

No clear differences were noted in the frequencies or types of TEAEs reported in the subset of subjects treated with DL2S v4 compared with those of the total 017001 DLBCL Treated Set. Nevertheless, TEAEs were reported most frequently in the SOC of General Disorders and Administration Site Conditions (78.6%) rather than Blood and Lymphatic System Disorders (75.4%) in subjects treated with DL2S v4.

In Study BMC-001, in Cohort 1, TEAEs were generally similar to those reported in the 017001 DLBCL Treated Set and the Pooled 3L+ DLBCL Set.

In Study 017007 and in Study BCM-002, the results for TEAEs were generally similar to those in the Pooled 3L+ DLBCL Set.

Table 62. Treatment-emergent Adverse Events by System Organ Class and Preferred Term with Preferred Term Reported in ≥ 10% of Total Subjects – Pooled 3L+ DLBCL Set

System Organ Class Preferred Term	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Subjects with any TEAE	**267 (99.3)**	**126 (100)**	**27 (100)**	**10 (100)**	**17 (100)**	**26 (100)**	**347 (99.4)**
Blood and lymphatic system disorders	**209 (77.7)**	**95 (75.4)**	**26 (96.3)**	**10 (100)**	**15 (88.2)**	**18 (69.2)**	**278 (79.7)**
Neutropenia	169 (62.8)	77 (61.1)	20 (74.1)	9 (90.0)	11 (64.7)	12 (46.2)	221 (63.3)
Anaemia	129 (48.0)	52 (41.3)	15 (55.6)	8 (80.0)	7 (41.2)	12 (46.2)	171 (49.0)
Thrombocytopenia	84 (31.2)	37 (29.4)	7 (25.9)	9 (90.0)	8 (47.1)	11 (42.3)	119 (34.1)
Leukopenia	44 (16.4)	18 (14.3)	6 (22.2)	9 (90.0)	8 (47.1)	9 (34.6)	76 (21.8)
Gastrointestinal disorders	**195 (72.5)**	**94 (74.6)**	**13 (48.1)**	**3 (30.0)**	**11 (64.7)**	**17 (65.4)**	**239 (68.5)**
Nausea	90 (33.5)	45 (35.7)	4 (14.8)	1 (10.0)	4 (23.5)	8 (30.8)	107 (30.7)
Diarrhoea	71 (26.4)	36 (28.6)	4 (14.8)	1 (10.0)	2 (11.8)	1 (3.8)	79 (22.6)
Constipation	62 (23.0)	28 (22.2)	3 (11.1)	1 (10.0)	7 (41.2)	4 (15.4)	77 (22.1)
Vomiting	56 (20.8)	22 (17.5)	2 (7.4)	1 (10.0)	2 (11.8)	4 (15.4)	65 (18.6)
Abdominal pain	44 (16.4)	24 (19.0)	3 (11.1)	0	1 (5.9)	1 (3.8)	49 (14.0)
General disorders and administration site conditions	**197 (73.2)**	**99 (78.6)**	**15 (55.6)**	**6 (60.0)**	**10 (58.8)**	**9 (34.6)**	**237 (67.9)**
Fatigue	119 (44.2)	55 (43.7)	0	4 (40.0)	4 (23.5)	7 (26.9)	134 (38.4)
Pyrexia	45 (16.7)	24 (19.0)	14 (51.9)	1 (10.0)	0	2 (7.7)	62 (17.8)
Oedema peripheral	42 (15.6)	22 (17.5)	1 (3.7)	1 (10.0)	2 (11.8)	1 (3.8)	47 (13.5)
Nervous system disorders	**179 (66.5)**	**87 (69.0)**	**15 (55.6)**	**1 (10.0)**	**11 (64.7)**	**17 (65.4)**	**223 (63.9)**
Headache	80 (29.7)	41 (32.5)	6 (22.2)	0	4 (23.5)	4 (15.4)	94 (26.9)
Dizziness	60 (22.3)	27 (21.4)	1 (3.7)	0	2 (11.8)	3 (11.5)	66 (18.9)
Tremor	41 (15.2)	20 (15.9)	3 (11.1)	0	5 (29.4)	5 (19.2)	54 (15.5)
Metabolism and nutrition disorders	**170 (63.2)**	**81 (64.3)**	**9 (33.3)**	**2 (20.0)**	**7 (41.2)**	**13 (50.0)**	**201 (57.6)**
Decreased appetite	76 (28.3)	35 (27.8)	1 (3.7)	1 (10.0)	3 (17.6)	4 (15.4)	85 (24.4)
Hypomagnesaemia	50 (18.6)	21 (16.7)	5 (18.5)	1 (10.0)	0	6 (23.1)	62 (17.8)
Hypokalaemia	52 (19.3)	32 (25.4)	3 (11.1)	1 (10.0)	0	5 (19.2)	61 (17.5)
Hypophosphataemia	27 (10.0)	14 (11.1)	3 (11.1)	0	3 (17.6)	7 (26.9)	40 (11.5)
Immune system disorders	**127 (47.2)**	**56 (44.4)**	**13 (48.1)**	**5 (50.0)**	**6 (35.3)**	**10 (38.5)**	**161 (46.1)**
Cytokine release syndrome	113 (42.0)	48 (38.1)	11 (40.7)	5 (50.0)	6 (35.3)	10 (38.5)	145 (41.5)
Hypogammaglobulinaemia	37 (13.8)	21 (16.7)	4 (14.8)	1 (10.0)	0	0	42 (12.0)
Respiratory, thoracic and mediastinal disorders	**134 (49.8)**	**67 (53.2)**	**7 (25.9)**	**1 (10.0)**	**7 (41.2)**	**10 (38.5)**	**159 (45.6)**
Cough	57 (21.2)	24 (19.0)	4 (14.8)	0	3 (17.6)	3 (11.5)	67 (19.2)
Dyspnoea	36 (13.4)	16 (12.7)	0	0	2 (11.8)	0	38 (10.9)
Musculoskeletal and connective tissue disorders	**129 (48.0)**	**61 (48.4)**	**9 (33.3)**	**0**	**6 (35.3)**	**12 (46.2)**	**156 (44.7)**
Back pain	33 (12.3)	13 (10.3)	1 (3.7)	0	3 (17.6)	6 (23.1)	43 (12.3)
Psychiatric disorders	**105 (39.0)**	**53 (42.1)**	**4 (14.8)**	**1 (10.0)**	**2 (11.8)**	**8 (30.8)**	**120 (34.4)**
Confusional state	39 (14.5)	20 (15.9)	3 (11.1)	1 (10.0)	0	2 (7.7)	45 (12.9)
Insomnia	36 (13.4)	18 (14.3)	0	0	2 (11.8)	1 (3.8)	39 (11.2)
Vascular disorders	**109 (40.5)**	**51 (40.5)**	**1 (3.7)**	**0**	**1 (5.9)**	**7 (26.9)**	**118 (33.8)**
Hypotension	60 (22.3)	25 (19.8)	0	0	1 (5.9)	4 (15.4)	65 (18.6)
Hypertension	37 (13.8)	15 (11.9)	0	0	0	1 (3.8)	38 (10.9)
Cardiac disorders	**85 (31.6)**	**37 (29.4)**	**5 (18.5)**	**0**	**2 (11.8)**	**3 (11.5)**	**95 (27.2)**
Sinus tachycardia	42 (15.6)	18 (14.3)	0	0	0	1 (3.8)	43 (12.3)

3L+ = third-line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Adverse events were coded using MedDRA version 21.0. A TEAE was defined as an adverse event that started any time from initiation of JCAR017 administration through and including 90 days following the final cycle of JCAR017. Any adverse event occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (Study BCM-002) was not considered a TEAE. Table is sorted by descending frequency on the Total column.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 3.2.1.1 and SCS Table3.2.2.1.b.

Table 63. Treatment-emergent Adverse Events by Preferred Terms Reported in ≥ 10% of Total Subjects-Pooled 3L+ DLBCL Set

System Organ Class Preferred Term	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Subjects with any TEAE	**267 (99.3)**	**126 (100)**	**27 (100)**	**10 (100)**	**17 (100)**	**26 (100)**	**347 (99.4)**
Neutropenia	169 (62.8)	77 (61.1)	20 (74.1)	9 (90.0)	11 (64.7)	12 (46.2)	221 (63.3)
Anaemia	129 (48.0)	52 (41.3)	15 (55.6)	8 (80.0)	7 (41.2)	12 (46.2)	171 (49.0)
Cytokine release syndrome	113 (42.0)	48 (38.1)	11 (40.7)	5 (50.0)	6 (35.3)	10 (38.5)	145 (41.5)
Fatigue	119 (44.2)	55 (43.7)	0	4 (40.0)	4 (23.5)	7 (26.9)	134 (38.4)
Thrombocytopenia	84 (31.2)	37 (29.4)	7 (25.9)	9 (90.0)	8 (47.1)	11 (42.3)	119 (34.1)
Nausea	90 (33.5)	45 (35.7)	4 (14.8)	1 (10.0)	4 (23.5)	8 (30.8)	107 (30.7)
Headache	80 (29.7)	41 (32.5)	6 (22.2)	0	4 (23.5)	4 (15.4)	94 (26.9)
Decreased appetite	76 (28.3)	35 (27.8)	1 (3.7)	1 (10.0)	3 (17.6)	4 (15.4)	85 (24.4)
Diarrhoea	71 (26.4)	36 (28.6)	4 (14.8)	1 (10.0)	2 (11.8)	1 (3.8)	79 (22.6)
Constipation	62 (23.0)	28 (22.2)	3 (11.1)	1 (10.0)	7 (41.2)	4 (15.4)	77 (22.1)
Leukopenia	44 (16.4)	18 (14.3)	6 (22.2)	9 (90.0)	8 (47.1)	9 (34.6)	76 (21.8)
Cough	57 (21.2)	24 (19.0)	4 (14.8)	0	3 (17.6)	3 (11.5)	67 (19.2)
Dizziness	60 (22.3)	27 (21.4)	1 (3.7)	0	2 (11.8)	3 (11.5)	66 (18.9)
Hypotension	60 (22.3)	25 (19.8)	0	0	1 (5.9)	4 (15.4)	65 (18.6)
Vomiting	56 (20.8)	22 (17.5)	2 (7.4)	1 (10.0)	2 (11.8)	4 (15.4)	65 (18.6)
Hypomagnesaemia	50 (18.6)	21 (16.7)	5 (18.5)	1 (10.0)	0	6 (23.1)	62 (17.8)
Pyrexia	45 (16.7)	24 (19.0)	14 (51.9)	1 (10.0)	0	2 (7.7)	62 (17.8)
Hypokalaemia	52 (19.3)	32 (25.4)	3 (11.1)	1 (10.0)	0	5 (19.2)	61 (17.5)
Tremor	41 (15.2)	20 (15.9)	3 (11.1)	0	5 (29.4)	5 (19.2)	54 (15.5)
Abdominal pain	44 (16.4)	24 (19.0)	3 (11.1)	0	1 (5.9)	1 (3.8)	49 (14.0)
Oedema peripheral	42 (15.6)	22 (17.5)	1 (3.7)	1 (10.0)	2 (11.8)	1 (3.8)	47 (13.5)
Confusional state	39 (14.5)	20 (15.9)	3 (11.1)	1 (10.0)	0	2 (7.7)	45 (12.9)
Back pain	33 (12.3)	13 (10.3)	1 (3.7)	0	3 (17.6)	6 (23.1)	43 (12.3)
Sinus tachycardia	42 (15.6)	18 (14.3)	0	0	0	1 (3.8)	43 (12.3)
Hypogammaglobulinaemia	37 (13.8)	21 (16.7)	4 (14.8)	1 (10.0)	0	0	42 (12.0)
Hypophosphataemia	27 (10.0)	14 (11.1)	3 (11.1)	0	3 (17.6)	7 (26.9)	40 (11.5)
Insomnia	36 (13.4)	18 (14.3)	0	0	2 (11.8)	1 (3.8)	39 (11.2)
Dyspnoea	36 (13.4)	16 (12.7)	0	0	2 (11.8)	0	38 (10.9)
Hypertension	37 (13.8)	15 (11.9)	0	0	0	1 (3.8)	38 (10.9)

3L+ = third-line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Adverse events were coded using MedDRA version 21.0. A TEAE was defined as an adverse event that started any time from initiation of JCAR017 administration through and including 90 days following the final cycle of JCAR017. Any adverse event occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (Study BCM-002) was not considered a TEAE. Table is sorted by descending frequency on the Total column.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 3.3.1.1 and SCS Table 3.3.2.1.b.

Grade ≥ 3 Treatment-emergent Adverse Events

The findings in the 017001 DLBCL Treated Set were similar to those of the Pooled 3L+ DLBCL Set.

In the Study BCM-001 Cohort 1, Grade ≥ 3 TEAEs in the Blood and Lymphatic System Disorders SOC were reported in a higher percentage of subjects compared to the Pooled 3L+DLBCL Set (92.6% versus 74.5%).

In Studies 017007 and BCM-002, the results for Grade ≥ 3 TEAEs were generally similar to those in the Pooled 3L+ DLBCL Set, most frequently in the Blood and Lymphatic System Disorders SOC (70.6% and 61.5%, respectively).

Table 64. Grade ≥ 3 Treatment-emergent Adverse Events by System Organ Class and Preferred Term with Preferred Terms Reported in ≥ 2% of Total Subjects – Pooled 3L+ DLBCL Set

System Organ Class Preferred Term	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Subjects with any Grade ≥ 3 TEAE	**213 (79.2)**	**102 (81.0)**	**25 (92.6)**	**9 (90.0)**	**15 (88.2)**	**19 (73.1)**	**281 (80.5)**
Blood and lymphatic system disorders	**198 (73.6)**	**91 (72.2)**	**25 (92.6)**	**9 (90.0)**	**12 (70.6)**	**16 (61.5)**	**260 (74.5)**
Neutropenia	161 (59.9)	74 (58.7)	18 (66.7)	9 (90.0)	11 (64.7)	11 (42.3)	210 (60.2)
Anaemia	101 (37.5)	42 (33.3)	9 (33.3)	7 (70.0)	3 (17.6)	6 (23.1)	126 (36.1)
Thrombocytopenia	72 (26.8)	33 (26.2)	4 (14.8)	7 (70.0)	2 (11.8)	8 (30.8)	93 (26.6)
Leukopenia	39 (14.5)	16 (12.7)	6 (22.2)	8 (80.0)	6 (35.3)	8 (30.8)	67 (19.2)
Febrile neutropenia	24 (8.9)	12 (9.5)	3 (11.1)	0	1 (5.9)	0	28 (8.0)
Lymphopenia	7 (2.6)	5 (4.0)	5 (18.5)	0	2 (11.8)	4 (15.4)	18 (5.2)
Metabolism and nutrition disorders	**47 (17.5)**	**26 (20.6)**	**1 (3.7)**	**0**	**0**	**4 (15.4)**	**52 (14.9)**
Hypophosphataemia	16 (5.9)	9 (7.1)	1 (3.7)	0	0	3 (11.5)	20 (5.7)
Hyponatraemia	9 (3.3)	4 (3.2)	0	0	0	0	9 (2.6)
Hypokalaemia	6 (2.2)	3 (2.4)	0	0	0	2 (7.7)	8 (2.3)
Decreased appetite	7 (2.6)	4 (3.2)	0	0	0	0	7 (2.0)
Infections and infestations	**33 (12.3)**	**15 (11.9)**	**4 (14.8)**	**0**	**2 (11.8)**	**5 (19.2)**	**44 (12.6)**
Pneumonia	8 (3.0)	4 (3.2)	2 (7.4)	0	0	3 (11.5)	13 (3.7)
Nervous system disorders	**31 (11.5)**	**13 (10.3)**	**4 (14.8)**	**0**	**1 (5.9)**	**3 (11.5)**	**39 (11.2)**
Encephalopathy	12 (4.5)	1 (0.8)	0	0	0	2 (7.7)	14 (4.0)
Syncope	6 (2.2)	4 (3.2)	0	0	1 (5.9)	1 (3.8)	8 (2.3)
Vascular disorders	**22 (8.2)**	**9 (7.1)**	**1 (3.7)**	**0**	**0**	**2 (7.7)**	**25 (7.2)**
Hypertension	12 (4.5)	4 (3.2)	0	0	0	1 (3.8)	13 (3.7)
Hypotension	8 (3.0)	3 (2.4)	0	0	0	1 (3.8)	9 (2.6)
Immune system disorders	**6 (2.2)**	**4 (3.2)**	**2 (7.4)**	**0**	**0**	**0**	**8 (2.3)**
Cytokine release syndrome	6 (2.2)	4 (3.2)	2 (7.4)	0	0	0	8 (2.3)

Grade ≥ 3 TEAEs in the DLBCL histology subgroup were very similar to those of the total 017001 DLBCL Treated Set. (Table 65).

In subjects with PMBCL, Grade ≥ 3 TEAEs were reported in 66.7% (10/15) of subjects. The most frequently reported Grade ≥ 3 TEAEs were neutropenia (6 subjects, 40.0%) and anaemia (5 subjects, 33.3%); all other PTs were reported in 1 subject (6.7%) each.

All 3 subjects with FL3B (100%) had Grade ≥ 3 TEAEs reported; the PTs were neutropenia, leukopenia (2 subjects each, 66.7%), and anaemia.

Table 65. Grade ≥ 3 Treatment-emergent Adverse Events by System Organ Class and Preferred Term with Preferred Terms Reported in ≥ 2% of Total Subjects in Study 017001, by NHL Subtype in the DLBCL Cohort-JCAR017-treated Set

System Organ Class Preferred Term	DLBCL Cohort Total (N = 269) n (%)	DLBCL Histology Subgroup						
		DLBCL Subgroup Total (NOS, HGL, tFL, tiNHL) (N = 251) n (%)	DLBCL NOS (N = 137) n (%)	HGL (N = 36) n (%)	tFL (N = 60) n (%)	tiNHL (N = 18) n (%)	PMBCL (N = 15) n (%)	FL3B (N = 3) n (%)
Subjects with any Grade ≥ 3 TEAE	**213 (79.2)**	**200 (79.7)**	**108 (78.8)**	**30 (83.3)**	**48 (80.0)**	**14 (77.8)**	**10 (66.7)**	**3 (100)**
Blood and lymphatic system disorders	**198 (73.6)**	**186 (74.1)**	**101 (73.7)**	**28 (77.8)**	**44 (73.3)**	**13 (72.2)**	**9 (60.0)**	**3 (100)**
Neutropenia	161 (59.9)	153 (61.0)	83 (60.6)	23 (63.9)	35 (58.3)	12 (66.7)	6 (40.0)	2 (66.7)
Anaemia	101 (37.5)	95 (37.8)	56 (40.9)	14 (38.9)	19 (31.7)	6 (33.3)	5 (33.3)	1 (33.3)
Thrombocytopenia	72 (26.8)	72 (28.7)	41 (29.9)	8 (22.2)	15 (25.0)	8 (44.4)	0	0
Leukopenia	39 (14.5)	37 (14.7)	21 (15.3)	5 (13.9)	9 (15.0)	2 (11.1)	0	2 (66.7)
Febrile neutropenia	24 (8.9)	23 (9.2)	15 (10.9)	0	8 (13.3)	0	1 (6.7)	0
Lymphopenia	7 (2.6)	7 (2.8)	6 (4.4)	0	1 (1.7)	0	0	0
Metabolism and nutrition disorders	**47 (17.5)**	**46 (18.3)**	**28 (20.4)**	**5 (13.9)**	**9 (15.0)**	**4 (22.2)**	**1 (6.7)**	**0**
Hypophosphataemia	16 (5.9)	16 (6.4)	11 (8.0)	0	4 (6.7)	1 (5.6)	0	0
Hyponatraemia	9 (3.3)	9 (3.6)	5 (3.6)	1 (2.8)	1 (1.7)	2 (11.1)	0	0
Decreased appetite	7 (2.6)	6 (2.4)	3 (2.2)	1 (2.8)	1 (1.7)	1 (5.6)	1 (6.7)	0
Hypokalaemia	6 (2.2)	6 (2.4)	5 (3.6)	0	1 (1.7)	0	0	0
Infections and infestations	**33 (12.3)**	**31 (12.4)**	**17 (12.4)**	**6 (16.7)**	**6 (10.0)**	**2 (11.1)**	**2 (13.3)**	**0**
Pneumonia	8 (3.0)	7 (2.8)	2 (1.5)	4 (11.1)	1 (1.7)	0	1 (6.7)	0
Nervous system disorders	**31 (11.5)**	**30 (12.0)**	**16 (11.7)**	**5 (13.9)**	**6 (10.0)**	**3 (16.7)**	**1 (6.7)**	**0**
Encephalopathy	12 (4.5)	12 (4.8)	6 (4.4)	1 (2.8)	3 (5.0)	2 (11.1)	0	0
Syncope	6 (2.2)	6 (2.4)	4 (2.9)	0	1 (1.7)	1 (5.6)	0	0
Vascular disorders	**22 (8.2)**	**22 (8.8)**	**13 (9.5)**	**1 (2.8)**	**6 (10.0)**	**2 (11.1)**	**0**	**0**
Hypertension	12 (4.5)	12 (4.8)	7 (5.1)	0	5 (8.3)	0	0	0
Hypotension	8 (3.0)	8 (3.2)	4 (2.9)	1 (2.8)	1 (1.7)	2 (11.1)	0	0
Renal and urinary disorders	**10 (3.7)**	**10 (4.0)**	**6 (4.4)**	**3 (8.3)**	**1 (1.7)**	**0**	**0**	**0**
Acute kidney injury	6 (2.2)	6 (2.4)	3 (2.2)	2 (5.6)	1 (1.7)	0	0	0
Immune system disorders	**6 (2.2)**	**5 (2.0)**	**3 (2.2)**	**2 (5.6)**	**0**	**0**	**1 (6.7)**	**0**
Cytokine release syndrome	6 (2.2)	5 (2.0)	3 (2.2)	2 (5.6)	0	0	1 (6.7)	0

DLBCL = diffuse large B-cell lymphoma; FL3B = follicular lymphoma Grade 3B; HGL = high-grade lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal B-cell lymphoma; tCLL/SLL = DLBCL transformed from chronic lymphocytic leukemia/small lymphocytic lymphoma; TEAE = treatment-emergent adverse event; tFL = DLBCL transformed from follicular lymphoma; tiNHL = DLBCL transformed from indolent non-Hodgkin lymphoma (tMZL + tCLL/SLL + tOther); tMZL = DLBCL transformed from marginal zone lymphoma; tOther = DLBCL transformed from other indolent lymphomas, including Waldenstrom macroglobulinemia.

Adverse events were coded using MedDRA version 21.0. A TEAE was defined as an adverse event that started any time from initiation of JCAR017 administration through and including 90 days following the final cycle of JCAR017. Any adverse event occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment was not considered a TEAE. Adverse event toxicity was graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03, except for cytokine release syndrome, which was graded according to the Lee criteria (Lee, 2014). Table is sorted by descending frequency on the DLBCL Cohort Total column.

Data cutoff date: 12 Aug 2019.

Source: SCS Table 3.4.2.1.

Post-treatment-emergent Adverse Events

The post-treatment-emergent period started from 91 days after the final cycle of JCAR017, or from initiation of another anticancer therapy or JCAR017 retreatment if subjects initiated another anticancer therapy or JCAR017 retreatment prior to 91 days after the final cycle of JCAR017, or in Study BCM-002, from the start of combination therapy. Thus, analyses of AEs occurring in the post-treatment-emergent period included AEs reported following JCAR017 retreatment, as well as those following post-JCAR017 anticancer therapy. (Table 66). Post-treatment-emergent AEs reported in > 5% subjects were anaemia (11.3%), neutropenia (10.9%), thrombocytopenia (9.3%), fatigue (8.3%), and nausea (6.6%).

Table 66. Adverse Events in the Post Treatment-emergent Period by System Organ Class and Preferred Term (Pooled 3L + DLBCL Treated Set)

System Organ Class Preferred Term	017001 DLBCL Cohort N=247 n (%)	BCM-001 Cohort 1 N=15 n (%)	BCM-001 Cohort 3 N=10 n (%)	BCM-001 Cohorts 1+3 N=25 n (%)	Total 017001 DLBCL Cohort + BCM-001 Cohorts 1+3 N=272 n (%)	017007 N=8 n (%)	BCM-002 N=22 n (%)	Total N=302 n (%)
Subjects with any AEs post treatment-emergent period	100 (40.5)	9 (60.0)	7 (70.0)	16 (64.0)	116 (42.6)	0	21 (95.5)	137 (45.4)
Blood and lymphatic system disorders	43 (17.4)	5 (33.3)	6 (60.0)	11 (44.0)	54 (19.9)	0	15 (68.2)	69 (22.8)
Anaemia	19 (7.7)	2 (13.3)	3 (30.0)	5 (20.0)	24 (8.8)	0	10 (45.5)	34 (11.3)
Neutropenia	20 (8.1)	2 (13.3)	3 (30.0)	5 (20.0)	25 (9.2)	0	8 (36.4)	33 (10.9)
Thrombocytopenia	14 (5.7)	1 (6.7)	5 (50.0)	6 (24.0)	20 (7.4)	0	8 (36.4)	28 (9.3)
Leukopenia	4 (1.6)	0	4 (40.0)	4 (16.0)	8 (2.9)	0	6 (27.3)	14 (4.6)
Febrile neutropenia	10 (4.0)	1 (6.7)	0	1 (4.0)	11 (4.0)	0	2 (9.1)	13 (4.3)
Lymphopenia	3 (1.2)	1 (6.7)	0	1 (4.0)	4 (1.5)	0	3 (13.6)	7 (2.3)
Hypofibrinogenaemia	0	0	2 (20.0)	2 (8.0)	2 (0.7)	0	0	2 (0.7)
Haemolytic anaemia	0	0	0	0	0	0	1 (4.5)	1 (0.3)
Splenic haematoma	0	1 (6.7)	0	1 (4.0)	1 (0.4)	0	0	1 (0.3)
General disorders and administration site conditions	28 (11.3)	3 (20.0)	1 (10.0)	4 (16.0)	32 (11.8)	0	8 (36.4)	40 (13.2)

MedDRA version 21.0 is used for coding.
Include adverse event (AE) records with onset date from 91 days post the final cycle of JCAR017, or initiation of another anticancer therapy or JCAR017 retreatment if subjects initiated another anticancer therapy or JCAR017 retreatment prior to 91 days post the final cycle of JCAR017.
Source: iss_nhl3l\..\maa\..\maascs\..\t_ae_socpt_post.sas; Snapshot: 2019-09-26 for 017001, 2019-11-08 for BCM001, 2019-09-25 for BCM002 and 017007; Data cutoff: 2019-08-12 for 017001, 2019-09-13 for BCM001, 2019-08-01 for BCM002 and 017007; Output: Version1; Run: 2020-02-27T11:44:41

Grade ≥ 3 AEs are reported in Table 67. Grade ≥ 3 AEs reported in > 2% of subjects were anaemia, neutropenia (8.9% each), thrombocytopenia (5.6%), febrile neutropenia (4.0%), and leukopenia (2.6%).

In the 017001 DLBCL Treated Set, and in the subset of subjects in the 017001 DLBCL Treated Set who were treated with DL2S v4, AEs reported during the post-treatment-emergent period were similar to those reported in the Pooled 3L+ DLBCL Set during this time period.

In Study BCM-001 Cohort 1, AEs reported in the post treatment emergent period were generally similar to those in the Pooled 3L+ DLBCL Set.

In Study BCM-002, the percentages of subjects with AEs reported in the post-treatment-emergent period (21 of 22 subjects, 95.5%) were generally higher compared with the Pooled 3L+ DLBCL Set (45.4%). Adverse events were most frequently reported in the SOC of Blood and Lymphatic System Disorders (68.2%), and the most frequent AEs were anaemia (45.5%), neutropenia, thrombocytopenia, fatigue (36.4% each), leukopenia, and nausea (27.3% each). Similarly, the percentages of subjects with Grade ≥ 3 AEs in the post-treatment-emergent period (16 out of 22 subjects, 72.7%) were generally higher compared with the Pooled 3L+ DLBCL Set (25.2%). Grade ≥ 3 AEs were most frequently reported in the SOC of Blood and Lymphatic System Disorders (59.1%).

Table 67. Grade 3 or Higher Adverse Events in the Post Treatment-emergent Period by System Organ Class and Preferred Term (Pooled 3L + DLBCL Treated Set)

System Organ Class Preferred Term	017001 DLBCL Cohort N=247 n (%)	BCM-001 Cohort 1 N=15 n (%)	BCM-001 Cohort 3 N=10 n (%)	BCM-001 Cohorts 1+3 N=25 n (%)	Total 017001 DLBCL Cohort + BCM-001 Cohorts 1+3 N=272 n (%)	017007 N=8 n (%)	BCM-002 N=22 n (%)	Total N=302 n (%)
Subjects with any grade >= 3 AEs post treatment-emergent period	52 (21.1)	3 (20.0)	5 (50.0)	8 (32.0)	60 (22.1)	0	16 (72.7)	76 (25.2)
Blood and lymphatic system disorders	33 (13.4)	3 (20.0)	5 (50.0)	8 (32.0)	41 (15.1)	0	13 (59.1)	54 (17.9)
Anaemia	16 (6.5)	1 (6.7)	3 (30.0)	4 (16.0)	20 (7.4)	0	7 (31.8)	27 (8.9)
Neutropenia	16 (6.5)	2 (13.3)	3 (30.0)	5 (20.0)	21 (7.7)	0	6 (27.3)	27 (8.9)
Thrombocytopenia	9 (3.6)	1 (6.7)	3 (30.0)	4 (16.0)	13 (4.8)	0	4 (18.2)	17 (5.6)
Febrile neutropenia	9 (3.6)	1 (6.7)	0	1 (4.0)	10 (3.7)	0	2 (9.1)	12 (4.0)
Leukopenia	2 (0.8)	0	2 (20.0)	2 (8.0)	4 (1.5)	0	4 (18.2)	8 (2.6)
Lymphopenia	2 (0.8)	0	0	0	2 (0.7)	0	3 (13.6)	5 (1.7)
Hypofibrinogenaemia	0	0	1 (10.0)	1 (4.0)	1 (0.4)	0	0	1 (0.3)
Infections and infestations	12 (4.9)	0	0	0	12 (4.4)	0	2 (9.1)	14 (4.6)

MedDRA version 21.0 is used for coding.
Include adverse event (AE) records with onset date from 91 days post the final cycle of JCAR017, or initiation of another anticancer therapy or JCAR017 retreatment if subjects initiated another anticancer therapy or JCAR017 retreatment prior to 91 days post the final cycle of JCAR017.
Adverse event toxicity is graded using NCI CTCAE v4.03, except CRS, which is graded according to the Lee criteria (Lee 2014).
Table is sorted by SOC and PT in descending order of incidence in the 'Total' column.
Source: iss_nhl3l\..\maa\..\maascs\..\t_ae_socpt_post.sas; Snapshot: 2019-09-26 for 017001, 2019-11-08 for BCM001, 2019-09-25 for BCM002 and 017007; Data cutoff: 2019-08-12 for 017001, 2019-09-13 for BCM001, 2019-08-01 for BCM002 and 017007; Output: Version1; Run: 2020-02-27T11:44:47

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Deaths after JCAR017 treatment were primarily due to disease progression.

In the Pooled 3L+ DLBCL Set, 119 out of 143 deaths reported after the first JCAR017 treatment were due to disease progression, 16 were due to AEs, 5 were due to unknown causes, and 3 were due to other causes (stroke unrelated to study, pneumonia, and diffuse intra-abdominal ischemia, all of which were subjects in the 017001 DLBCL Treated Set) (Table 68). Of the 143 deaths after the first JCAR017 treatment, 101 deaths occurred more than 90 days after the last JCAR017 treatment. Eleven of the 143 deaths occurred within 30 days after the first JCAR017 treatment, with 6 deaths due to disease progression and 5 deaths due to AEs (diffuse alveolar damage, septic shock, cardiomyopathy, respiratory failure, and staphylococcal sepsis). Thirty-one of the 143 deaths occurred between 30 and 90 days after the last JCAR017 infusion, of which 21 were due to disease progression, 8 were due to AEs, and 2 were due to unknown causes.

The percentages of subjects who died and the primary causes of death were generally similar in the 017001 DLBCL Treated Set (39%), in the subset of subjects in the 017001 DLBCL Treated Set who were treated with DL2S v4 (39.7%), and in Cohorts 1 of BCM-001 (33%).

Table 68. Summary of Deaths After the First JCAR017 Infusion – Pooled 3L+ DLBCL Set

System Organ Class Preferred Term	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Death occurred any time after the first JCAR017 infusion	**122 (45.4)**	**58 (46.0)**	**11 (40.7)**	**2 (20.0)**	**0**	**8 (30.8)**	**143 (41.0)**
Primary cause of death:							
Disease progression	105 (39.0)	50 (39.7)	9 (33.3)	0	0	5 (19.2)	119 (34.1)
Adverse event	10 (3.7)	5 (4.0)	2 (7.4)	1 (10.0)	0	3 (11.5)	16 (4.6)
Unknown	4 (1.5)	0	0	1 (10.0)	0	0	5 (1.4)
Other[a]	3 (1.1)	3 (2.4)	0	0	0	0	3 (0.9)
Death occurred within 30 days after the last JCAR017 infusion[b]	**9 (3.3)**	**4 (3.2)**	**1 (3.7)**	**0**	**0**	**1 (3.8)**	**11 (3.2)**
Primary cause of death:							
Disease progression	6 (2.2)	3 (2.4)	0	0	0	0	6 (1.7)
Adverse event	3 (1.1)	1 (0.8)	1 (3.7)	0	0	1 (3.8)	5 (1.4)
Death occurred after 30 days and within 90 days after the last JCAR017 infusion[b]	**24 (8.9)**	**11 (8.7)**	**3 (11.1)**	**2 (20.0)**	**0**	**2 (7.7)**	**31 (8.9)**
Primary cause of death:							
Disease progression	18 (6.7)	7 (5.6)	2 (7.4)	0	0	1 (3.8)	21 (6.0)
Adverse event	5 (1.9)	4 (3.2)	1 (3.7)	1 (10.0)[c]	0	1 (3.8)	8 (2.3)
Unknown	1 (0.4)	0	0	1 (10.0)	0	0	2 (0.6)
Death occurred after 90 days after the last JCAR017 infusion[b]	**89 (33.1)**	**43 (34.1)**	**7 (25.9)**	**0**	**0**	**5 (19.2)**	**101 (28.9)**
Primary cause of death:							
Disease progression	81 (30.1)	40 (31.7)	7 (25.9)	0	0	4 (15.4)	92 (26.4)
Adverse event	2 (0.7)	0	0	0	0	1 (3.8)	3 (0.9)
Unknown	3 (1.1)	0	0	0	0	0	3 (0.9)
Other[a]	3 (1.1)	3 (2.4)	0	0	0	0	3 (0.9)

3L+ = third-line or later; AE = adverse event; DL1D = Dose Level 1, 2 Doses; DL1S = Dose Level 1, Single Dose; DL2S = Dose Level 2, Single Dose; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DL3S = Dose Level 3, Single Dose; DLBCL = diffuse large B-cell lymphoma.; SCS = Summary of Clinical Safety; TEAE = treatment-emergent adverse event.

Note: In Study BCM-002, after the start of combination therapy, 4 deaths occurred due to disease progression, and no deaths due to adverse event, other or unknown cause.

[a] Three subject deaths in Study 017001 from other causes occurred post-JCAR017 treatment in the JCAR017-treated Set: stroke unrelated to study, pneumonia, and diffuse intra-abdominal ischemia. Refer to CSR 017001 Listing 16.2.7.5 for details.

Deaths Due to AEs (Grade 5 AEs)

Sixteen of 349 subjects (4.6%) in the Pooled 3L+ DLBCL Set died due to Grade 5 AEs after the first JCAR017 treatment. Grade 5 TEAEs were reported in 11 out of 349 subjects (3.2%).

Grade 5 TEAEs (Table 69).

In the 017001 DLBCL Treated Set, Grade 5 TEAEs (n=7 of 269, 2.6%) were PML (*related to multiple prior courses of rituximab),* septic shock (*related to LDC, ongoing CRS event at time of death*), diffuse alveolar damage (*related to JCAR017 and LDC*), pulmonary haemorrhage (*ongoing CRS event at time of death, related to JCAR017 and LDC*), cardiomyopathy (*related to JCAR017 and LDC*), multiple organ dysfunction syndrome (*related to JCAR017 and LDC*), and leukoencephalopathy (*related to LDC – prior fludarabine exposure)*.

In Study BCM-001, Grade 5 TEAEs (n=2 of 37, 5.4%) were candida sepsis (*related to LDC and JCAR017)* and respiratory failure (*related to JCAR017 and unrelated to LDC, ongoing CRS event at time of death*).

In Study BCM-002, 2 out of 26 subjects (7.7%) had Grade 5 TEAEs. One subject died due to staphylococcal sepsis on Study Day 25, which was considered not related to JCAR017 but related to LDC (*ongoing CRS event at time of death).* One subject died due to pneumonia on Study Day 45, which was considered not related to both JCAR017 and LDC.

Table 69. Grade 5 Treatment-emergent Adverse Events by System Organ Class and Preferred Term – Pooled 3L+DLBCL Set

System Organ Class Preferred Term	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Subjects with any Grade 5 TEAE	**7 (2.6)**	**4 (3.2)**	**2 (7.4)**	**0**	**0**	**2 (7.7)**	**11 (3.2)**
Infections and infestations	**2 (0.7)**	**0**	**1 (3.7)**	**0**	**0**	**2 (7.7)**	**5 (1.4)**
Candida sepsis	0	0	1 (3.7)	0	0	0	1 (0.3)
Pneumonia	0	0	0	0	0	1 (3.8)	1 (0.3)
Progressive multifocal leukoencephalopathy	1 (0.4)	0	0	0	0	0	1 (0.3)
Septic shock	1 (0.4)	0	0	0	0	0	1 (0.3)
Staphylococcal sepsis	0	0	0	0	0	1 (3.8)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**2 (0.7)**	**1 (0.8)**	**1 (3.7)**	**0**	**0**	**0**	**3 (0.9)**
Diffuse alveolar damage	1 (0.4)	0	0	0	0	0	1 (0.3)
Pulmonary haemorrhage	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
Respiratory failure	0	0	1 (3.7)	0	0	0	1 (0.3)
Cardiac disorders	**1 (0.4)**	**1 (0.8)**	**0**	**0**	**0**	**0**	**1 (0.3)**
Cardiomyopathy	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
General disorders and administration site conditions	**1 (0.4)**	**1 (0.8)**	**0**	**0**	**0**	**0**	**1 (0.3)**
Multiple organ dysfunction syndrome	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
Nervous system disorders	**1 (0.4)**	**1 (0.8)**	**0**	**0**	**0**	**0**	**1 (0.3)**
Leukoencephalopathy	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)

3L+ = third-line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Adverse events were coded using MedDRA version 21.0. A TEAE was defined as an adverse event that started any time from initiation of JCAR017 administration through and including 90 days following the final cycle of JCAR017. Any adverse event occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (Study BCM-002) was not considered a TEAE. Adverse event toxicity was graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03, except for cytokine release syndrome, which was graded according to the Lee criteria (Lee, 2014). Table is sorted by descending frequency on the Total column.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 3.5.1.1 and SCS Table 3.5.2.1.b.

Grade 5 AEs Occurring in the Post-treatment-emergent Period

Grade 5 AEs were reported for 5 out of 349 subjects (1.4%) during the post-treatment-emergent period. Three subjects in Study 017001 had Grade 5 AEs during the post-treatment-emergent period: one subject with myelodysplastic syndrome (MDS) (occurred > 670 days after last dose of JCAR017), one with PML (the event began as a Grade 3 event on Day 710 and the subject died from the event after completing the study with no intervening anticancer therapy), and one with septic shock (occurred after starting subsequent anticancer therapy). Of these 3 Grade 5 events, only PML was considered related to JCAR017. One subject in Cohort 3 of Study BCM-001 died on Day 52 due to multiple organ dysfunction syndrome and one subject in Study BCM-002 died on Day 95 due to an AE of sepsis; neither of these events was considered related to JCAR017.

Serious Adverse Events

In the Pooled 3L+ DLBCL Set, treatment-emergent SAEs were reported in 154 out of 349 subjects (44.1%) and occurred most frequently in the SOCs of Immune System Disorders (17.5%), Nervous System Disorders (15.5%), and Infections and Infestations (10.3%) (Table 70).

Treatment-emergent SAEs were generally similar in the 017001 DLBCL Treated Set and in the subset of subjects in the 017001 DLBCL Treated Set treated with DL2S v4.

In Cohort 1 of Study BCM-001, the results for treatment-emergent SAEs were generally similar to those in the 017001 DLBCL Treated Set and the Pooled 3L+ DLBCL Set.

Table 70. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term with Preferred Terms Reported in ≥ 2% of Total Subjects – Pooled 3L+ DLBCL Set

System Organ Class Preferred Term	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Subjects with any treatment-emergent SAE	**122 (45.4)**	**60 (47.6)**	**11 (40.7)**	**1 (10.0)**	**8 (47.1)**	**12 (46.2)**	**154 (44.1)**
Immune system disorders	**44 (16.4)**	**19 (15.1)**	**6 (22.2)**	**0**	**6 (35.3)**	**5 (19.2)**	**61 (17.5)**
Cytokine release syndrome	44 (16.4)	19 (15.1)	6 (22.2)	0	6 (35.3)	5 (19.2)	61 (17.5)
Nervous system disorders	**41 (15.2)**	**19 (15.1)**	**5 (18.5)**	**0**	**3 (17.6)**	**5 (19.2)**	**54 (15.5)**
Encephalopathy	14 (5.2)	2 (1.6)	0	0	0	1 (3.8)	15 (4.3)
Aphasia	9 (3.3)	7 (5.6)	3 (11.1)	0	0	0	12 (3.4)
Tremor	3 (1.1)	1 (0.8)	2 (7.4)	0	3 (17.6)	1 (3.8)	9 (2.6)
Infections and infestations	**28 (10.4)**	**16 (12.7)**	**4 (14.8)**	**0**	**0**	**4 (15.4)**	**36 (10.3)**
Pneumonia	8 (3.0)	5 (4.0)	1 (3.7)	0	0	2 (7.7)	11 (3.2)
Blood and lymphatic system disorders	**25 (9.3)**	**8 (6.3)**	**3 (11.1)**	**0**	**2 (11.8)**	**2 (7.7)**	**32 (9.2)**
Neutropenia	11 (4.1)	3 (2.4)	1 (3.7)	0	1 (5.9)	0	13 (3.7)
Thrombocytopenia	10 (3.7)	4 (3.2)	0	0	0	2 (7.7)	12 (3.4)
Febrile neutropenia	10 (3.7)	4 (3.2)	0	0	1 (5.9)	0	11 (3.2)
Psychiatric disorders	**20 (7.4)**	**13 (10.3)**	**4 (14.8)**	**0**	**0**	**2 (7.7)**	**26 (7.4)**
Confusional state	8 (3.0)	6 (4.8)	3 (11.1)	0	0	0	11 (3.2)
Mental status changes	7 (2.6)	3 (2.4)	0	0	0	1 (3.8)	8 (2.3)
General disorders and administration site conditions	**17 (6.3)**	**9 (7.1)**	**1 (3.7)**	**0**	**1 (5.9)**	**1 (3.8)**	**20 (5.7)**
Pyrexia	10 (3.7)	5 (4.0)	1 (3.7)	0	0	1 (3.8)	12 (3.4)
Vascular disorders	**11 (4.1)**	**5 (4.0)**	**1 (3.7)**	**0**	**0**	**0**	**12 (3.4)**
Hypotension	8 (3.0)	2 (1.6)	0	0	0	0	8 (2.3)

3L+ = third-line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Adverse events were coded using MedDRA version 21.0. A TEAE was defined as an adverse event that started any time from initiation of JCAR017 administration through and including 90 days following the final cycle of JCAR017. Any adverse event occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (Study BCM-002) was not considered a TEAE. Table is sorted by descending frequency on the Total column.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 3.6.1.1 and SCS Table 3.6.2.1.b.

In the total 017001 DLBCL Treated Set, treatment-emergent SAEs were reported in 122 out of 269 subjects (45.4%) and occurred most frequently in the SOCs of Immune System Disorders (16.4%), Nervous System Disorders (15.2%), and Infections and Infestations (10.4%). The most frequently reported treatment-emergent SAEs were CRS (16.4%) and encephalopathy (5.2%). Treatment-emergent SAEs in the DLBCL histology subgroup were very similar to those of the total 017001 DLBCL Treated Set. However, serious pneumonia was reported more frequently in subjects with HGL (13.9%) compared to the other subtypes (0% to 1.7%). In subjects with PMBCL, treatment-emergent SAEs were reported in 10 out of 15 subjects (66.7%) and the most frequently reported treatment-emergent SAEs were CRS (4 subjects, 26.7%) and Clostridium difficile infection (2 subjects, 13.3%). In subjects with FL3B, no treatment-emergent SAEs were reported, yet limited sample size hampers proper safety assessments. No clear differences were noted in the frequencies or types of treatment-emergent SAEs in the subset of subjects treated with DL2S v4 compared with those of the total 017001 DLBCL Treated Set (Table 71).

Table 71. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term with Preferred Terms Reported in ≥ 2% of Total Subjects in Study 017001, by NHL Subtype in the DLBCL Cohort-JCAR017-treated Set

System Organ Class Preferred Term	DLBCL Cohort Total (N = 269) n (%)	DLBCL Histology Subgroup						
		DLBCL Subgroup Total (NOS, HGL, tFL, tiNHL) (N = 251) n (%)	DLBCL NOS (N = 137) n (%)	HGL (N = 36) n (%)	tFL (N = 60) n (%)	tiNHL (N = 18) n (%)	PMBCL (N = 15) n (%)	FL3B (N = 3) n (%)
Subjects with any treatment-emergent SAE	**122 (45.4)**	**112 (44.6)**	**65 (47.4)**	**14 (38.9)**	**24 (40.0)**	**9 (50.0)**	**10 (66.7)**	**0**
Immune system disorders	**44 (16.4)**	**40 (15.9)**	**26 (19.0)**	**5 (13.9)**	**6 (10.0)**	**3 (16.7)**	**4 (26.7)**	**0**
Cytokine release syndrome	44 (16.4)	40 (15.9)	26 (19.0)	5 (13.9)	6 (10.0)	3 (16.7)	4 (26.7)	0
Nervous system disorders	**41 (15.2)**	**38 (15.1)**	**21 (15.3)**	**5 (13.9)**	**10 (16.7)**	**2 (11.1)**	**3 (20.0)**	**0**
Encephalopathy	14 (5.2)	14 (5.6)	7 (5.1)	1 (2.8)	4 (6.7)	2 (11.1)	0	0
Aphasia	9 (3.3)	8 (3.2)	6 (4.4)	1 (2.8)	1 (1.7)	0	1 (6.7)	0
Infections and infestations	**28 (10.4)**	**25 (10.0)**	**13 (9.5)**	**7 (19.4)**	**3 (5.0)**	**2 (11.1)**	**3 (20.0)**	**0**
Pneumonia	8 (3.0)	7 (2.8)	1 (0.7)	5 (13.9)	1 (1.7)	0	1 (6.7)	0
Blood and lymphatic system disorders	**25 (9.3)**	**25 (10.0)**	**17 (12.4)**	**2 (5.6)**	**4 (6.7)**	**2 (11.1)**	**0**	**0**
Neutropenia	11 (4.1)	11 (4.4)	7 (5.1)	2 (5.6)	1 (1.7)	1 (5.6)	0	0
Febrile neutropenia	10 (3.7)	10 (4.0)	9 (6.6)	0	1 (1.7)	0	0	0
Thrombocytopenia	10 (3.7)	10 (4.0)	6 (4.4)	1 (2.8)	2 (3.3)	1 (5.6)	0	0
Psychiatric disorders	**20 (7.4)**	**17 (6.8)**	**8 (5.8)**	**4 (11.1)**	**5 (8.3)**	**0**	**3 (20.0)**	**0**
Confusional state	8 (3.0)	7 (2.8)	4 (2.9)	1 (2.8)	2 (3.3)	0	1 (6.7)	0
Mental status changes	7 (2.6)	6 (2.4)	2 (1.5)	1 (2.8)	3 (5.0)	0	1 (6.7)	0
General disorders and administration site conditions	**17 (6.3)**	**16 (6.4)**	**11 (8.0)**	**3 (8.3)**	**1 (1.7)**	**1 (5.6)**	**1 (6.7)**	**0**
Pyrexia	10 (3.7)	10 (4.0)	8 (5.8)	1 (2.8)	0	1 (5.6)	0	0
Vascular disorders	**11 (4.1)**	**11 (4.4)**	**7 (5.1)**	**0**	**3 (5.0)**	**1 (5.6)**	**0**	**0**
Hypotension	8 (3.0)	8 (3.2)	5 (3.6)	0	2 (3.3)	1 (5.6)	0	0

DLBCL = diffuse large B-cell lymphoma; FL3B = follicular lymphoma Grade 3B; HGL = high-grade lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal B-cell lymphoma; SAE = serious adverse event; tCLL/SLL = DLBCL transformed from chronic lymphocytic leukemia/small lymphocytic lymphoma; TEAE = treatment-emergent adverse event; tFL = DLBCL transformed from follicular

Adverse Events of Special Interest (AESI)

Summary of Adverse Events of Special Interest

Overviews of treatment-emergent AESI by category and grade are presented for the Pooled 3L+ DLBCL Set in Table 72. AESIs of hypogammaglobulinaemia, second primary malignancies (SPMs), and autoimmune disorders were analysed for the entire study period (both during and after the treatment-emergent AE period), given their potential for late onset (Table 73).

During the treatment-emergent period, CRS, prolonged cytopenia, and iiNT were the most frequently reported AESIs in the Pooled 3L+ DLBCL Set.

Treatment-emergent AESIs were similar for subjects in the 017001 DLBCL Treated Set, in the subset of subjects in the 017001 DLBCL Treated Set who were treated at DL2S v4, and for subjects in Cohort 1 of Study BCM-001.

Table 72. Treatment-emergent AESIs by Category and Grade – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort (N = 269) n (%)	BCM-001		017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
		Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)			
CRS or iiNT	127 (47.2)	12 (44.4)	5 (50.0)	7 (41.2)	11 (42.3)	162 (46.4)
Grade 3-4	29 (10.8)	4 (14.8)	0	0	3 (11.5)	36 (10.3)
Grade 5	0	0	0	0	0	0
CRS	113 (42.0)	11 (40.7)	5 (50.0)	6 (35.3)	10 (38.5)	145 (41.5)
Grade 3-4	6 (2.2)	2 (7.4)	0	0	0	8 (2.3)
Grade 5	0	0	0	0	0	0
iiNT	80 (29.7)	5 (18.5)	1 (10.0)	4 (23.5)	6 (23.1)	96 (27.5)
Grade 3-4	27 (10.0)	4 (14.8)	0	0	3 (11.5)	34 (9.7)
Grade 5	0	0	0	0	0	0
IRR	3 (1.1)	0	0	0	1 (3.8)	4 (1.1)
Grade 3-4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
MAS	0	2 (7.4)	0	0	0	2 (0.6)
Grade 3-4	0	2 (7.4)	0	0	0	2 (0.6)
Grade 5	0	0	0	0	0	0
TLS	2 (0.7)	0	0	0	0	2 (0.6)
Grade 3-4	2 (0.7)	0	0	0	0	2 (0.6)
Grade 5	0	0	0	0	0	0
Infections, Grade ≥ 3	33 (12.3)	4 (14.8)	0	2 (11.8)	5 (19.2)	44 (12.6)
Grade 3-4	31 (11.5)	3 (11.1)	0	2 (11.8)	3 (11.5)	39 (11.2)
Grade 5	2 (0.7)	1 (3.7)	0	0	2 (7.7)	5 (1.4)
Grade ≥ 3 Cytopenia[a] at Day 29 Visit[b]	100 (37.2)	9 (33.3)	4 (40.0)	3 (17.6)	8 (30.8)	124 (35.5)

Table 73. Second Primary Malignancies, Hypogammaglobulinaemia, and Autoimmune Disorders in Treatment-emergent and Posttreatment-emergent Periods – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	n (%)	DL2S v4 n (%)	BCM-001 Cohort 1 n (%)	BCM-001 Cohort 3 n (%)	017007 n (%)	BCM-002 n (%)	Total n (%)
Treatment-emergent period							
N	269	126	27	10	17	26	349
Second primary malignancy	5 (1.9)	5 (4.0)	0	0	0	1 (3.8)	6 (1.7)
Grade ≥ 3	2 (0.7)	2 (1.6)	0	0	0	1 (3.8)	3 (0.9)
Hypogammaglobulinaemia	37 (13.8)	21 (16.7)	5 (18.5)	1 (10.0)	0	0	43 (12.3)
Grade ≥ 3	0	0	0	0	0	0	0
Autoimmune disorders	0	0	0	0	0	0	0
Grade ≥ 3	0	0	0	0	0	0	0
Posttreatment-emergent period							
N	247	117	15	10	8	22	302
Second primary malignancy	15 (6.1)	7 (6.0)	0	0	0	2 (9.1)	17 (5.6)
Grade ≥ 3	8 (3.2)	4 (3.4)	0	0	0	2 (9.1)	10 (3.3)
Hypogammaglobulinaemia	12 (4.9)	8 (6.8)	0	0	0	2 (9.1)	14 (4.6)
Grade ≥ 3	0	0	0	0	0	0	0
Autoimmune disorders	0	0	0	0	0	0	0
Grade ≥ 3	0	0	0	0	0	0	0

3L+ = third line or later; AE = adverse event; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; HLGT = high-level group term; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardized MedDRA query.
Treatment-emergent period starts any time from initiation of JCAR017 administration through and including 90 days following the final dose of JCAR017, or the initiation of another anticancer therapy or JCAR017 retreatment or combination therapy (for Study BCM-002), whichever comes first.
Posttreatment-emergent period starts from 91 days post the final cycle of JCAR017, or initiation of another anticancer therapy or JCAR017 retreatment if subjects initiated another anticancer therapy or JCAR017 retreatment prior to 91 days post the final cycle of JCAR017.
Second primary malignancy includes post-JCAR017 AEs in Malignancy SMQ and Premalignancy conditions SMQ. Events identified by consensus of an adjudication committee.
Hypogammaglobulinaemia includes post-JCAR017 AEs with the following MedDRA preferred terms: Blood immunoglobulin A decreased, Blood immunoglobulin D decreased, Blood immunoglobulin E decreased, Blood immunoglobulin G decreased, hypogammaglobulinaemia, immunoglobulins (IgM) decreased, selective IgA immunodeficiency, selective IgG subclass deficiency and selective IgM immunodeficiency.
Autoimmune disorders include post-JCAR017 AEs with HLGT 'Autoimmune disorders' plus the additional preferred terms: temporal arteritis, granulomatosis with polyangiitis, Behcet's syndrome, and Basedow's disease, vasculitis, and erythema nodosum. Events identified by consensus of an adjudication committee.
Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: SCS Table 4.2.1.1, SCS Table 4.3.1.1, SCS Table 4.2.1.1.b, and SCS Table 4.3.1.1.b.

Cytokine Release Syndrome

Table 74. Treatment-emergent Cytokine Release Syndrome by Category and Grade-Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
CRS	113 (42.0)	48 (38.1)	11 (40.7)	5 (50.0)	6 (35.3)	10 (38.5)	145 (41.5)
Grade 1-2	107 (39.8)	44 (34.9)	9 (33.3)	5 (50.0)	6 (35.3)	10 (38.5)	137 (39.3)
Grade 3-4	6 (2.2)	4 (3.2)	2 (7.4)	0	0	0	8 (2.3)
Grade 5	0	0	0	0	0	0	0
SAE	44 (16.4)	19 (15.1)	6 (22.2)	0	6 (35.3)	5 (19.2)	61 (17.5)

3L+ = third-line or later; AE = adverse event; CRS = cytokine release syndrome; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
CRS includes TEAEs with MedDRA PT = Cytokine release syndrome. CRS is graded based on the Lee grading criteria (Lee, 2014).
A TEAE is defined as an AE that starts any time from initiation of JCAR017 administration through and including 90 days following the final dose of JCAR017. Any AE occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (BCM-002) will not be considered as a TEAE.
Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: SCS Table 4.1.1.1 and SCS Table 4.1.1.1.b.

Cytokine release syndrome was ongoing at the time of death for the 4 subjects who did not have resolution of CRS. However, CRS was not the cause of death for any of these subjects. Cytokine release syndrome was an SAE in 61 out of 349 subjects (17.5%), which was similar to the incidence reported in the 017001 DLBCL Treated Set (16.4%).

Time to Onset and Duration of Cytokine Release Syndrome

Table 75. Time to Onset and Time to Resolution of Treatment-emergent CRS – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001		017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)			
Time to onset of first CRS (days)[a]							
n	113	48	11	5	6	10	145
Median	5.0	4.0	4.0	3.0	4.5	6.0	5.0
Q1, Q3	3.0, 7.0	3.0, 6.5	3.0, 6.0	2.0, 4.0	3.0, 7.0	4.0, 8.0	3.0, 7.0
Min, Max	1, 14	1, 11	3, 12	2, 9	2, 9	3, 14	1, 14
Time to resolution of first CRS (days)[b]							
n	111	47	10	5	6	9	141
Median	5.0	5.0	7.5	4.0	4.5	4.0	5.0
Q1, Q3	3.0, 8.0	2.0, 7.0	3.0, 9.0	3.0, 5.0	2.0, 6.0	4.0, 5.0	3.0, 7.0
Min, Max	1, 17	1, 15	1, 16	1, 5	1, 9	2, 9	1, 17
Time to onset of first Grade ≥ 3 CRS (days)[a]							
n	6	4	2	0	0	0	8
Median	6.5	4.5	6.0	–	–	–	6.0
Q1, Q3	4.0, 9.0	3.5, 8.5	5.0, 7.0	–	–	–	4.5, 8.5
Min, Max	3, 12	3, 12	5, 7	–	–	–	3, 12
Time to resolution of first Grade ≥ 3 CRS (days)[b]							
n	5	3	1	0	0	0	6
Median	6.0	5.0	7.0	–	–	–	6.5
Q1, Q3	5.0, 9.0	5.0, 6.0	7.0, 7.0	–	–	–	5.0, 9.0
Min, Max	5, 15	5, 6	7, 7	–	–	–	5, 15

3L+ = third-line or later; CRS = cytokine release syndrome; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; Max = maximum; Min = minimum; Q = quartile.

[a] Time to onset is calculated from the latest JCAR017 infusion to the first onset of a CRS event.

[b] Any CRS events stop/start within 7 days (start date-stop date ≤7) were considered in a single episode. Time to resolution of CRS is defined when the last CRS event of the first episode end. Subjects with an unresolved event in the episode are excluded from the summary.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 4.6.1.1 and SCS Table 4.6.1.1.b.

Cytokine Release Syndrome Symptoms

The 3 most frequently occurring symptoms of CRS in the Pooled 3L+ DLBCL Set were pyrexia, occurring in 135 out of 145 subjects with CRS (93.1%), hypotension in 64 out of 145 subjects with CRS (44.1%), and tachycardia in 52 out of 145 subjects with CRS (35.9%) (Table 76).

Table 76. Treatment-emergent CRS Symptoms Occurring in ≥ 2% of Subjects by Grade – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Subjects with Treatment-emergent CRS Symptoms							
Any grade	113 (42.0)	48 (38.1)	11 (40.7)	5 (50.0)	6 (35.3)	10 (38.5)	145 (41.5)
Grade ≥ 3	20 (7.4)	8 (6.3)	4 (14.8)	1 (10.0)	0	1 (3.8)	26 (7.4)
Pyrexia	107 (39.8)	46 (36.5)	10 (37.0)	5 (50.0)	4 (23.5)	9 (34.6)	135 (38.7)
Grade 1-2	101 (37.5)	43 (34.1)	10 (37.0)	4 (40.0)	4 (23.5)	9 (34.6)	128 (36.7)
Grade 3-4	6 (2.2)	3 (2.4)	0	1 (10.0)	0	0	7 (2.0)
Grade 5	0	0	0	0	0	0	0
Hypotension	55 (20.4)	25 (19.8)	5 (18.5)[a]	1 (10.0)	0	3 (11.5)	64 (18.3)
Grade 1-2	48 (17.8)	21 (16.7)	1 (3.7)	1 (10.0)	0	3 (11.5)	53 (15.2)
Grade 3-4	7 (2.6)	4 (3.2)	3 (11.1)	0	0	0	10 (2.9)
Grade 5	0	0	0	0	0	0	0
Tachycardia	47 (17.5)	20 (15.9)	2 (7.4)	0	2 (11.8)	1 (3.8)	52 (14.9)
Grade 1-2	47 (17.5)	20 (15.9)	1 (3.7)	0	2 (11.8)	1 (3.8)	51 (14.6)
Grade 3-4	0	0	1 (3.7)	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0
Chills	34 (12.6)	16 (12.7)	1 (3.7)	0	0	3 (11.5)	38 (10.9)
Grade 1-2	34 (12.6)	16 (12.7)	1 (3.7)	0	0	3 (11.5)	38 (10.9)
Grade 3-4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
Hypoxia	26 (9.7)	14 (11.1)	3 (11.1)	2 (20.0)	1 (5.9)	1 (3.8)	33 (9.5)
Grade 1-2	17 (6.3)	11 (8.7)	2 (7.4)	2 (20.0)	1 (5.9)	1 (3.8)	23 (6.6)
Grade 3-4	9 (3.3)	3 (2.4)	1 (3.7)	0	0	0	10 (2.9)
Grade 5	0	0	0	0	0	0	0
Headache	17 (6.3)	5 (4.0)	0	0	0	2 (7.7)	19 (5.4)
Grade 1-2	14 (5.2)	5 (4.0)	0	0	0	2 (7.7)	16 (4.6)
Grade 3-4	3 (1.1)	0	0	0	0	0	3 (0.9)
Grade 5	0	0	0	0	0	0	0
Fatigue	17 (6.3)	6 (4.8)	0	0	0	0	17 (4.9)
Grade 1-2	17 (6.3)	6 (4.8)	0	0	0	0	17 (4.9)
Grade 3-4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
Nausea	8 (3.0)	2 (1.6)	1 (3.7)	1 (10.0)	0	0	10 (2.9)
Grade 1-2	8 (3.0)	2 (1.6)	1 (3.7)	1 (10.0)	0	0	10 (2.9)
Grade 3-4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0

	017001 DLBCL Cohort		BCM-001				
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Tachypnoea	7 (2.6)	4 (3.2)	0	0	0	0	7 (2.0)
Grade 1-2	6 (2.2)	4 (3.2)	0	0	0	0	6 (1.7)
Grade 3-4	1 (0.4)	0	0	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0

3L+ = third-line or later; CRF = case report form; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma.

[a] 1 subject had hypotension with missing grade (CSR BCM-001 Listing 16.2.7.11.4).

A treatment-emergent CRS symptom is defined as a CRS symptom that starts any time from initiation of JCAR017 administration through and including 90 days following the final cycle of JCAR017. Any CRS symptoms occurring after the start of combination therapy (for Study BCM-002) or the initiation of another anticancer therapy or JCAR017 retreatment will not be considered as treatment-emergent.

Includes data collected on the CRS Symptoms CRF (017001, 017007) or the Clinical Events - CRS Details CRF (BCM-001, BCM-002).

CRS symptoms are graded per CTCAE version 4.03. The maximum CTCAE grade of a CRS symptom for a subject is summarized.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 4.4.1.1 and SCS Table 4.4.1.1.b.

Use of Concomitant Medications to Treat Cytokine Release Syndrome

Table 77. Concomitant Medication Use for Treatment of CRS – Pooled 3L+ DLBCL Set

Number of Subjects Administered	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Tocilizumab and/or Corticosteroid	53 (19.7)	27 (21.4)	6 (22.2)	3 (30.0)	3 (17.6)	4 (15.4)	69 (19.8)
Tocilizumab only	27 (10.0)	15 (11.9)	4 (14.8)	3 (30.0)	1 (5.9)	4 (15.4)	39 (11.2)
Corticosteroid only[a]	5 (1.9)	0	0	0	0	0	5 (1.4)
Both Tocilizumab and Corticosteroid	21 (7.8)	12 (9.5)	2 (7.4)	0	2 (11.8)	0	25 (7.2)
Vasopressor	7 (2.6)	5 (4.0)	3 (11.1)	0	1 (5.9)	0	11 (3.2)
Other immunosuppressive therapy[b]	1 (0.4)	1 (0.8)	1 (3.7)	0	0	1 (3.8)	3 (0.9)

3L+ = third line or later; CRS = cytokine release syndrome; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma.

[a] If a subject receives multiple corticosteroids, the subject will only be counted once in the subcategories in the order of dexamethasone, prednisone and/or methylprednisolone, and hydrocortisone.

[b] Other immunosuppressive agents given include siltuximab, anakinra, and etanercept.

Medications with start date after first JCAR017 infusion and up to 90 days post final JCAR017 infusion are included except medications with start dates after the start of combination therapy (for Study BCM-002) or the initiation of another anticancer treatment or after retreatment.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 4.10.1.1 and SCS Table 4.10.1.1.b.

Neurologic Toxicity (NT)

The AEs reported are referred to as investigator-identified neurologic toxicity (iiNT). AEs report rates were similar in the 017001 DLBCL Treated Set (29.7% iiNT, 14.5% SAE iiNT), in Study 017007 (23.5% iiNT, 17.6% SAE iiNT) and in Study BCM-002 (23.1% iiNT, 11.5% SAE iiNT). No clear differences in the severity or frequency of iiNT were noted in the subset of subjects treated with DL2S v4 (31.7% iiNT, 15.1% SAE iiNT) compared with the total 017001 DLBCL Treated Set. In Study BCM-001, the proportion of subjects who experienced iiNT of any grade (18.5%) was lower than that reported for the 017001 DLBCL Treated Set (29.7%) and the Pooled 3L+ DLBCL Set (27.5%). There were no Grade 5 events attributed to iiNT (Table 78).

Table 78. Treatment-emergent iiNT by Grade – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
iiNT	80 (29.7)	40 (31.7)	5 (18.5)	1 (10.0)	4 (23.5)	6 (23.1)	96 (27.5)
Grade 1-2	53 (19.7)	28 (22.2)	1 (3.7)	1 (10.0)	4 (23.5)	3 (11.5)	62 (17.8)
Grade 3-4	27 (10.0)	12 (9.5)	4 (14.8)	0	0	3 (11.5)	34 (9.7)
Grade 5	0	0	0	0	0	0	0
SAE	39 (14.5)	19 (15.1)	5 (18.5)	0	3 (17.6)	3 (11.5)	50 (14.3)

3L+ = third-line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; iiNT = investigator-identified neurologic toxicity; SAE = serious adverse event.
iiNT is defined as a central nervous system adverse event that is reported by investigator as related to JCAR017.
Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: SCS Table 4.1.1.1 and SCS Table 4.1.1.1.b.

Time to Onset and Resolution of Neurologic Toxicity

Table 79. Time to Onset and Time to Resolution of Treatment-emergent iiNT-Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Time to onset of first iiNT (days)[a]							
n	80	40	5	1	4	6	96
Median	9.0	8.5	6.0	4.0	9.5	9.0	8.5
Q1, Q3	6.0, 13.0	5.0, 12.5	6.0, 7.0	4.0, 4.0	8.5, 13.0	8.0, 15.0	6.0, 13.0
Min, Max	1, 66	1, 46	6, 9	4, 4	8, 16	6, 22	1, 66
Time to resolution of first iiNT (days)[b]							
n	72	37	4	1	4	6	87
Median	11.0	14.0	7.5	3.0	3.0	6.5	9.0
Q1, Q3	4.0, 18.5	3.0, 25.0	5.0, 11.0	3.0, 3.0	2.0, 7.0	5.0, 11.0	4.0, 17.0
Min, Max	1, 86	1, 84	4, 13	3, 3	1, 11	3, 42	1, 86
Time to onset of first Grade ≥ 3 iiNT (days)[a]							
n	27	12	4	0	0	3	34
Median	9.0	9.5	7.5	-	-	9.0	9.0
Q1, Q3	6.0, 14.0	4.5, 13.0	6.5, 8.5	-		8.0, 22.0	7.0, 14.0
Min, Max	2, 44	2, 34	6, 9	-	-	8, 22	2, 44
Time to resolution of first Grade ≥ 3iiNT (days)[b]							
n	21	10	3	0	0	3	27
Median	12.0	11.5	9.0	-	-	4.0	11.0
Q1, Q3	9.0, 26.0	3.0, 28.0	4.0, 13.0	-	-	3.0, 42.0	5.0, 26.0
Min, Max	3, 83	3, 78	4, 13	-	-	3, 42	3, 83

3L+ = third-line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; iiNT = investigator-identified neurologic toxicity; Max = maximum; Min = minimum; NT = neurologic toxicity; Q = quartile.
[a] Time to onset is calculated from the latest JCAR017 infusion to the first onset of a NT event.
[b] Any NT events stop/start within 7 days (start date-stop date ≤ 7) were considered in a single episode. Time to resolution of iiNT is defined when the last NT event of the first episode end. Subjects with an unresolved event in the episode are excluded from the summary.
Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: SCS Table 4.7.1.1 and SCS Table 4.7.1.1.b.

Neurotoxicity events of special interest (NESI)

iiNT events were evaluated by grouping them into categories of NESI that are defined as clusters of neurological symptoms or signs that are associated with immunotherapies based on literature review.

The 8 main NESIs were encephalopathy, aphasia, tremor, delirium, dizziness, headache, anxiety, and insomnia. Investigator-identified NT AEs that did not fall into one of the 8 main NESI categories were grouped into 12 additional categories, based on medical review by an adjudication panel. This adjudication process consisted of review of PTs reported within the ND/PD SOC.

The additional 12 NESI categories were ataxia/gait disturbance, brain edema, seizure, cerebellar syndrome, cerebrovascular, mood disorder, motor dysfunction, visual disturbance, peripheral neuropathy, cognitive disorder, incontinence, and NOS (includes all other PTs from ND or PD SOC not specified in the above categories).

Treatment-emergent iiNT by NESI Category in Studies in the Pooled 3L+DLBCL Set

The 3 most frequent NESI categories for iiNT reported as SAE were encephalopathy (31 out of 349 subjects; 8.9%), aphasia (12 out of 349 subjects; 3.4%), and tremor (10 out of 349 subjects; 2.9%).

Table 80. Treatment-emergent iiNT by NESI Category, Preferred Term, and Grade occurring in ≥ 2% of Subjects-Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
NESI Category Preferred Term	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Encephalopathy - Any Event	57 (21.2)	26 (20.6)	3 (11.1)	1 (10.0)	1 (5.9)	3 (11.5)	65 (18.6)
Grade 1-2	39 (14.5)	20 (15.9)	1 (3.7)	1 (10.0)	1 (5.9)	2 (7.7)	44 (12.6)
Grade 3-4	18 (6.7)	6 (4.8)	2 (7.4)	0	0	1 (3.8)	21 (6.0)
Grade 5	0	0	0	0	0	0	0
Confusional state	30 (11.2)	15 (11.9)	3 (11.1)	1 (10.0)	0	0	34 (9.7)
Grade 1-2	28 (10.4)	14 (11.1)	1 (3.7)	1 (10.0)	0	0	30 (8.6)
Grade 3-4	2 (0.7)	1 (0.8)	2 (7.4)	0	0	0	4 (1.1)
Grade 5	0	0	0	0	0	0	0
Encephalopathy	17 (6.3)	3 (2.4)	0	0	0	1 (3.8)	18 (5.2)
Grade 1-2	6 (2.2)	2 (1.6)	0	0	0	0	6 (1.7)
Grade 3-4	11 (4.1)	1 (0.8)	0	0	0	1 (3.8)	12 (3.4)
Grade 5	0	0	0	0	0	0	0
Mental status changes	10 (3.7)	6 (4.8)	0	0	0	0	10 (2.9)
Grade 1-2	6 (2.2)	3 (2.4)	0	0	0	0	6 (1.7)
Grade 3-4	4 (1.5)	3 (2.4)	0	0	0	0	4 (1.1)
Grade 5	0	0	0	0	0	0	0
Somnolence	6 (2.2)	4 (3.2)	1 (3.7)	0	0	1 (3.8)	8 (2.3)
Grade 1-2	5 (1.9)	3 (2.4)	1 (3.7)	0	0	1 (3.8)	7 (2.0)
Grade 3-4	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0

NESI Category Preferred Term	017001 DLBCL Cohort (N = 269) n (%)	017001 DLBCL Cohort DL2S v4 (N = 126) n (%)	BCM-001 Cohort 1 (N = 27) n (%)	BCM-001 Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Memory impairment	4 (1.5)	0	1 (3.7)	0	0	2 (7.7)	7 (2.0)
Grade 1-2	4 (1.5)	0	1 (3.7)	0	0	2 (7.7)	7 (2.0)
Grade 3-4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
Tremor - Any Event	26 (9.7)	15 (11.9)	2 (7.4)	0	3 (17.6)	2 (7.7)	33 (9.5)
Grade 1-2	26 (9.7)	15 (11.9)	1 (3.7)	0	3 (17.6)	2 (7.7)	32 (9.2)
Grade 3-4	0	0	1 (3.7)	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0
Tremor	25 (9.3)	14 (11.1)	2 (7.4)	0	3 (17.6)	2 (7.7)	32 (9.2)
Grade 1-2	25 (9.3)	14 (11.1)	1 (3.7)	0	3 (17.6)	2 (7.7)	31 (8.9)
Grade 3-4	0	0	1 (3.7)	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0
Aphasia - Any Event	26 (9.7)	15 (11.9)	3 (11.1)	0	1 (5.9)	1 (3.8)	31 (8.9)
Grade 1-2	21 (7.8)	13 (10.3)	0	0	1 (5.9)	1 (3.8)	23 (6.6)
Grade 3-4	5 (1.9)	2 (1.6)	3 (11.1)	0	0	0	8 (2.3)
Grade 5	0	0	0	0	0	0	0
Aphasia	22 (8.2)	14 (11.1)	3 (11.1)	0	0	1 (3.8)	26 (7.4)
Grade 1-2	19 (7.1)	12 (9.5)	0	0	0	1 (3.8)	20 (5.7)
Grade 3-4	3 (1.1)	2 (1.6)	3 (11.1)	0	0	0	6 (1.7)
Grade 5	0	0	0	0	0	0	0
Delirium - Any Event	16 (5.9)	11 (8.7)	2 (7.4)	0	0	1 (3.8)	19 (5.4)
Grade 1-2	12 (4.5)	8 (6.3)	1 (3.7)	0	0	0	13 (3.7)
Grade 3-4	4 (1.5)	3 (2.4)	1 (3.7)	0	0	1 (3.8)	6 (1.7)
Grade 5	0	0	0	0	0	0	0
Agitation	9 (3.3)	5 (4.0)	0	0	0	1 (3.8)	10 (2.9)
Grade 1-2	6 (2.2)	3 (2.4)	0	0	0	0	6 (1.7)
Grade 3-4	3 (1.1)	2 (1.6)	0	0	0	1 (3.8)	4 (1.1)
Grade 5	0	0	0	0	0	0	0
Dizziness - Any Event	11 (4.1)	6 (4.8)	0	0	0	2 (7.7)	13 (3.7)
Grade 1-2	9 (3.3)	4 (3.2)	0	0	0	1 (3.8)	10 (2.9)
Grade 3-4	2 (0.7)	2 (1.6)	0	0	0	1 (3.8)	3 (0.9)
Grade 5	0	0	0	0	0	0	0
Dizziness	11 (4.1)	6 (4.8)	0	0	0	1 (3.8)	12 (3.4)
Grade 1-2	10 (3.7)	5 (4.0)	0	0	0	1 (3.8)	11 (3.2)
Grade 3-4	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0
Headache - Any Event	9 (3.3)	7 (5.6)	0	0	0	2 (7.7)	11 (3.2)
Grade 1-2	7 (2.6)	5 (4.0)	0	0	0	2 (7.7)	9 (2.6)
Grade 3-4	2 (0.7)	2 (1.6)	0	0	0	0	2 (0.6)
Grade 5	0	0	0	0	0	0	0
Headache	9 (3.3)	7 (5.6)	0	0	0	2 (7.7)	11 (3.2)
Grade 1-2	7 (2.6)	5 (4.0)	0	0	0	2 (7.7)	9 (2.6)
Grade 3-4	2 (0.7)	2 (1.6)	0	0	0	0	2 (0.6)
Grade 5	0	0	0	0	0	0	0
Anxiety - Any Event	0	0	0	0	0	0	0
Insomnia - Any Event	0	0	0	0	0	0	0

3L+ = third-line or later; 3L+ = third line or later; AE = adverse event; DL2S v4 = dose level 2, single dose, manufacturing version 4; DL2S v4 = dose level 2, single dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; iiNT = investigator-identified neurologic toxicity; NESI = neurotoxicity events of special interest; NT = neurologic toxicity; PT = preferred term.

Investigated-identified NT is defined as a central nervous system AE that is reported by investigator as related to JCAR017.

Table shows only those preferred terms within the 8 NESI categories shown and occurring in ≥ 2% of subjects.

Table is sorted by NESI category and preferred term in descending order of frequency in the "Total" column.

The grade of a group term is the maximum grade of all the individual PTs that constitute the group term. For this reason, the number of subjects of a certain grade in the individual PTs may not add up to the total for the same grade in the NESI category.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Table 4.12.1.1 and SCS Table 4.12.1.1.b.

Neurologic Toxicity by ND/PD SOC TEAEs

For Study 017001, Study BCM-001, and the Pooled 3L+ DLBCL Set, in addition to the analyses of iiNT, all TEAEs coding to MedDRA preferred terms within the Nervous System Disorders and Psychiatric Disorders (ND/PD) system organ classes (SOCs) were also evaluated. As with other CAR T-cell products, ND/PD SOC events were evaluated by grouping them into categories of NESI. The 8 main NESIs were encephalopathy, aphasia, tremor, delirium, dizziness, headache, anxiety, and insomnia.

The incidence of TEAEs from the ND/PD SOC in Study BCM-001 Cohort 1 (55.6%) was lower than that observed for the 017001 DLBCL Treated Set (74.3%) and the Pooled 3L+ DLBCL Set (71.1%). The incidences of TEAEs from the ND/PD SOC in Studies 017007 and BCM-002 were generally similar to that observed for the Pooled 3L+ DLBCL Set (Table 81).

Table 81. Treatment-emergent Adverse Events in the ND/PD SOC by NESI Category, Preferred Term, and Grade Occurring in ≥ 2% of Subjects – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
NESI Category Preferred Term	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Subjects with Any ND/PD SOC TEAEs	200 (74.3)	93 (73.8)	15 (55.6)	2 (20.0)	11 (64.7)	20 (76.9)	248 (71.1)
Grade 1-2	160 (59.5)	74 (58.7)	11 (40.7)	2 (20.0)	10 (58.8)	15 (57.7)	198 (56.7)
Grade 3-4	39 (14.5)	18 (14.3)	4 (14.8)	0	1 (5.9)	5 (19.2)	49 (14.0)
Grade 5	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
Headache - Any Event	81 (30.1)	41 (32.5)	6 (22.2)	0	4 (23.5)	4 (15.4)	95 (27.2)
Grade 1-2	78 (29.0)	38 (30.2)	6 (22.2)	0	4 (23.5)	4 (15.4)	92 (26.4)
Grade 3-4	3 (1.1)	3 (2.4)	0	0	0	0	3 (0.9)
Grade 5	0	0	0	0	0	0	0
Headache	80 (29.7)	41 (32.5)	6 (22.2)	0	4 (23.5)	4 (15.4)	94 (26.9)
Grade 1-2	77 (28.6)	38 (30.2)	6 (22.2)	0	4 (23.5)	4 (15.4)	91 (26.1)
Grade 3-4	3 (1.1)	3 (2.4)	0	0	0	0	3 (0.9)
Grade 5	0	0	0	0	0	0	0

NESI Category Preferred Term	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Encephalopathy – Any Event	77 (28.6)	37 (29.4)	3 (11.1)	1 (10.0)	2 (11.8)	8 (30.8)	91 (26.1)
Grade 1-2	55 (20.4)	30 (23.8)	1 (3.7)	1 (10.0)	2 (11.8)	5 (19.2)	64 (18.3)
Grade 3-4	21 (7.8)	6 (4.8)	2 (7.4)	0	0	3 (11.5)	26 (7.4)
Grade 5	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
Confusional state	39 (14.5)	20 (15.9)	3 (11.1)	1 (10.0)	0	2 (7.7)	45 (12.9)
Grade 1-2	37 (13.8)	19 (15.1)	1 (3.7)	1 (10.0)	0	2 (7.7)	41 (11.7)
Grade 3-4	2 (0.7)	1 (0.8)	2 (7.4)	0	0	0	4 (1.1)
Grade 5	0	0	0	0	0	0	0
Encephalopathy	19 (7.1)	3 (2.4)	0	0	0	2 (7.7)	21 (6.0)
Grade 1-2	7 (2.6)	2 (1.6)	0	0	0	0	7 (2.0)
Grade 3-4	12 (4.5)	1 (0.8)	0	0	0	2 (7.7)	14 (4.0)
Grade 5	0	0	0	0	0	0	0
Lethargy	15 (5.6)	9 (7.1)	0	0	1 (5.9)	0	16 (4.6)
Grade 1-2	15 (5.6)	9 (7.1)	0	0	1 (5.9)	0	16 (4.6)
Grade 3-4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
Mental status changes	13 (4.8)	6 (4.8)	0	0	0	2 (7.7)	15 (4.3)
Grade 1-2	8 (3.0)	3 (2.4)	0	0	0	1 (3.8)	9 (2.6)
Grade 3-4	5 (1.9)	3 (2.4)	0	0	0	1 (3.8)	6 (1.7)
Grade 5	0	0	0	0	0	0	0
Somnolence	13 (4.8)	6 (4.8)	1 (3.7)	0	0	1 (3.8)	15 (4.3)
Grade 1-2	11 (4.1)	5 (4.0)	1 (3.7)	0	0	1 (3.8)	13 (3.7)
Grade 3-4	2 (0.7)	1 (0.8)	0	0	0	0	2 (0.6)
Grade 5	0	0	0	0	0	0	0
Memory impairment	5 (1.9)	0	1 (3.7)	0	0	3 (11.5)	9 (2.6)
Grade 1-2	5 (1.9)	0	1 (3.7)	0	0	3 (11.5)	9 (2.6)
Grade 3-4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
Dizziness - Any Event	64 (23.8)	29 (23.0)	1 (3.7)	0	3 (17.6)	4 (15.4)	72 (20.6)
Grade 1-2	57 (21.2)	24 (19.0)	1 (3.7)	0	2 (11.8)	3 (11.5)	63 (18.1)
Grade 3-4	7 (2.6)	5 (4.0)	0	0	1 (5.9)	1 (3.8)	9 (2.6)
Grade 5	0	0	0	0	0	0	0
Dizziness	60 (22.3)	27 (21.4)	1 (3.7)	0	2 (11.8)	3 (11.5)	66 (18.9)
Grade 1-2	59 (21.9)	26 (20.6)	1 (3.7)	0	2 (11.8)	3 (11.5)	65 (18.6)
Grade 3-4	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0

NESI Category Preferred Term	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Syncope	6 (2.2)	4 (3.2)	0	0	1 (5.9)	1 (3.8)	8 (2.3)
Grade 1-2	0	0	0	0	0	0	0
Grade 3-4	6 (2.2)	4 (3.2)	0	0	1 (5.9)	1 (3.8)	8 (2.3)
Grade 5	0	0	0	0	0	0	0
Tremor - Any Event	43 (16.0)	21 (16.7)	3 (11.1)	0	5 (29.4)	6 (23.1)	57 (16.3)
Grade 1-2	43 (16.0)	21 (16.7)	2 (7.4)	0	5 (29.4)	6 (23.1)	56 (16.0)
Grade 3-4	0	0	1 (3.7)	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0
Tremor	41 (15.2)	20 (15.9)	3 (11.1)	0	5 (29.4)	5 (19.2)	54 (15.5)
Grade 1-2	41 (15.2)	20 (15.9)	2 (7.4)	0	5 (29.4)	5 (19.2)	53 (15.2)
Grade 3-4	0	0	1 (3.7)	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0
Insomnia - Any Event	37 (13.8)	18 (14.3)	0	0	2 (11.8)	1 (3.8)	40 (11.5)
Grade 1-2	36 (13.4)	17 (13.5)	0	0	2 (11.8)	1 (3.8)	39 (11.2)
Grade 3-4	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0
Insomnia	36 (13.4)	18 (14.3)	0	0	2 (11.8)	1 (3.8)	39 (11.2)
Grade 1-2	35 (13.0)	17 (13.5)	0	0	2 (11.8)	1 (3.8)	38 (10.9)
Grade 3-4	1 (0.4)	1 (0.8)	0	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0
Delirium - Any Event	28 (10.4)	15 (11.9)	2 (7.4)	0	0	4 (15.4)	34 (9.7)
Grade 1-2	22 (8.2)	11 (8.7)	1 (3.7)	0	0	3 (11.5)	26 (7.4)
Grade 3-4	6 (2.2)	4 (3.2)	1 (3.7)	0	0	1 (3.8)	8 (2.3)
Grade 5	0	0	0	0	0	0	0
Agitation	13 (4.8)	6 (4.8)	0	0	0	4 (15.4)	17 (4.9)
Grade 1-2	9 (3.3)	4 (3.2)	0	0	0	3 (11.5)	12 (3.4)
Grade 3-4	4 (1.5)	2 (1.6)	0	0	0	1 (3.8)	5 (1.4)
Grade 5	0	0	0	0	0	0	0
Aphasia - Any Event	27 (10.0)	15 (11.9)	3 (11.1)	0	1 (5.9)	2 (7.7)	33 (9.5)
Grade 1-2	21 (7.8)	13 (10.3)	0	0	1 (5.9)	2 (7.7)	24 (6.9)
Grade 3-4	6 (2.2)	2 (1.6)	3 (11.1)	0	0	0	9 (2.6)
Grade 5	0	0	0	0	0	0	0
Aphasia	22 (8.2)	14 (11.1)	3 (11.1)	0	0	1 (3.8)	26 (7.4)
Grade 1-2	19 (7.1)	12 (9.5)	0	0	0	1 (3.8)	20 (5.7)
Grade 3-4	3 (1.1)	2 (1.6)	3 (11.1)	0	0	0	6 (1.7)
Grade 5	0	0	0	0	0	0	0

NESI Category Preferred Term	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Dysarthria	6 (2.2)	2 (1.6)	0	0	1 (5.9)	1 (3.8)	8 (2.3)
Grade 1-2	3 (1.1)	2 (1.6)	0	0	1 (5.9)	1 (3.8)	5 (1.4)
Grade 3-4	3 (1.1)	0	0	0	0	0	3 (0.9)
Grade 5	0	0	0	0	0	0	0
Anxiety - Any Event	28 (10.4)	9 (7.1)	1 (3.7)	0	1 (5.9)	0	30 (8.6)
Grade 1-2	28 (10.4)	9 (7.1)	1 (3.7)	0	1 (5.9)	0	30 (8.6)
Grade 3-4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
Anxiety	27 (10.0)	9 (7.1)	1 (3.7)	0	1 (5.9)	0	29 (8.3)
Grade 1-2	27 (10.0)	9 (7.1)	1 (3.7)	0	1 (5.9)	0	29 (8.3)
Grade 3-4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0

3L+ = third line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; ND/PD = Nervous System Disorders/Psychiatric Disorders; NESI = neurotoxicity events of special interest; NOS = not otherwise specified; SOC = system organ class; TEAE = treatment-emergent adverse event.
Table shows only those preferred terms within the 8 NESI categories shown and occurring in ≥ 2% of subjects.
Table is sorted by NESI category and preferred term in descending order of incidence in the "Total" column.
Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: SCS Table 4.13.1.1 and SCS Table 4.13.1.1.b.

Use of Concomitant Medications to Treat Investigator-identified Neurologic Toxicity

Because some concomitant medications (e.g., tocilizumab and/or corticosteroids) were given for both CRS and iiNT, some subjects received tocilizumab or corticosteroids for a concurrent CRS event (Table 82).

Table 82. Concomitant Medication Use for Treatment of iiNT – Pooled 3L+ DLBCL Set

Number of Subjects Administered	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	(N = 17) n (%)	(N = 26) n (%)	(N = 349) n (%)
Tocilizumab and/or Corticosteroid	45 (16.7)	20 (15.9)	4 (14.8)	0	1 (5.9)	4 (15.4)	54 (15.5)
Tocilizumab only	1 (0.4)	0	0	0	0	0	1 (0.3)
Corticosteroid only[a]	36 (13.4)	14 (11.1)	4 (14.8)	0	1 (5.9)	4 (15.4)	45 (12.9)
Both Tocilizumab and Corticosteroid	8 (3.0)	6 (4.8)	0	0	0	0	8 (2.3)
Vasopressor	1 (0.4)	0	0	0	0	0	1 (0.3)
Other immunosuppressive therapy[b]	2 (0.7)	2 (1.6)	0	0	0	0	2 (0.6)

3L+ = third-line or later; AE = adverse event; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; iiNT = investigator-identified neurologic toxicity; NT = neurologic toxicity.
Medications with start date after first JCAR017 infusion and up to 90 days post final JCAR017 infusion are included except medications with start dates after the start of combination therapy (for Study BCM-002) or the initiation of another anticancer treatment or after retreatment.
Investigated-identified NT is defined as a central nervous system AE that is reported by investigator as related to JCAR017.
[a] If a subject receives multiple corticosteroids, the subject will only be counted once in the subcategories, in the order of (dexamethasone, prednisone and/or methylprednisolone, and hydrocortisone).
[b] Other immunosuppressive agents given include siltuximab, anakinra, and etanercept.
Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: SCS Table 4.11.1.1 and SCS Table 4.11.1.1.b.

Correlations of Pharmacokinetic Parameters and Biomarkers with iiNT and ND/PD SOC Events

In order to explore whether there were biologic correlations differentiating subjects with iiNT events versus subjects with ND/PD SOC events that were not iiNT, PK parameters and inflammatory biomarkers were compared in these 2 populations.

Of the total number of subjects in the DLBCL Treated Set (N = 269) as of 12 Aug 2019, 3 subpopulations were further defined and evaluated:

- **iiNT**: subjects who had ND/PD SOC events that were identified as iiNT (n = 80)
- **not iiNT**: subjects who had ND/PD SOC events that were not identified as iiNT (n = 120)
- **no ND/PD SOC**: subjects who did not have any ND/PD SOC events (n = 69)

Subjects with all-grade iiNT had higher JCAR017 median maximum observed concentration (Cmax) and area under the concentration-time curve through 28 days after the first infusion (AUC0-28) than subjects with "not iiNT" (Figure 31). Similar to PK, the median values of CRP at baseline were significantly higher for subjects with iiNT as compared to those with "not iiNT" or "no ND/PD SOC" events (p = 0.0027 and p = 0.0001, respectively) (Figure 32). A similar relationship was observed for median peak values of CRP (Figure 33). No statistical difference was observed in the CRP median baseline between subjects with "not iiNT" events and those with "no ND/PD SOC events", although the CRP peak median was 1.80-fold greater in "not iiNT" than "no ND/PD SOC" (p = 0.0283).

Figure 31. Box Plot of Cmax in Subjects With iiNT, not iiNT or No ND/PD SOC Events in the Study 017001 DLBCL Cohort, Single Dose Schedule – JCAR017-treated Set

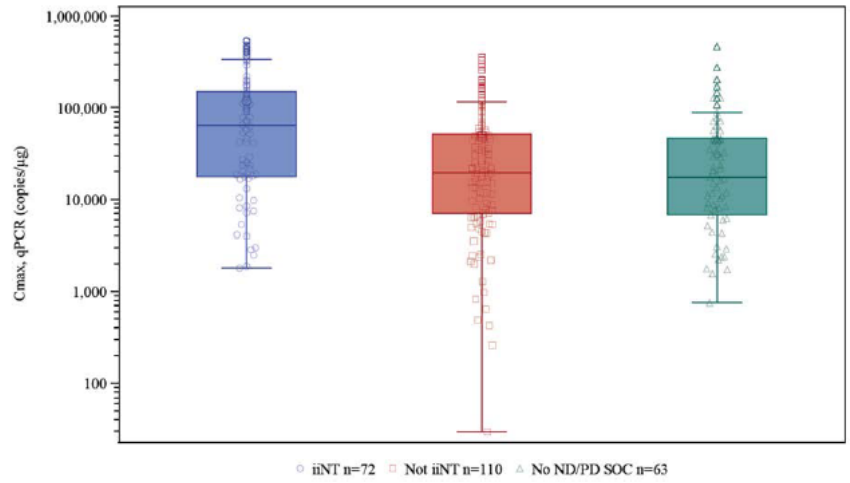


Figure 32. Box Plot of Baseline C-Reactive Protein in Subjects with iiNT, not iiNT or No ND/PD SOC Events in the Study 017001 DLBCL Cohort – JCAR017-Treated Set

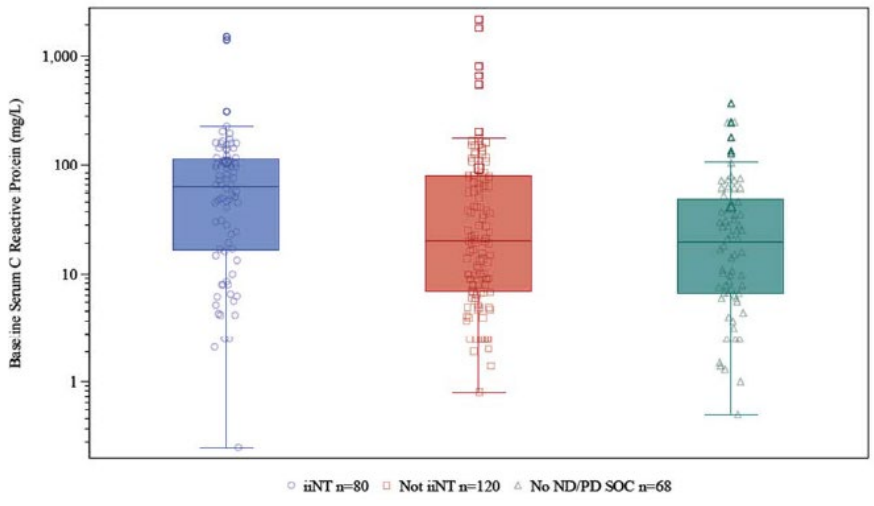
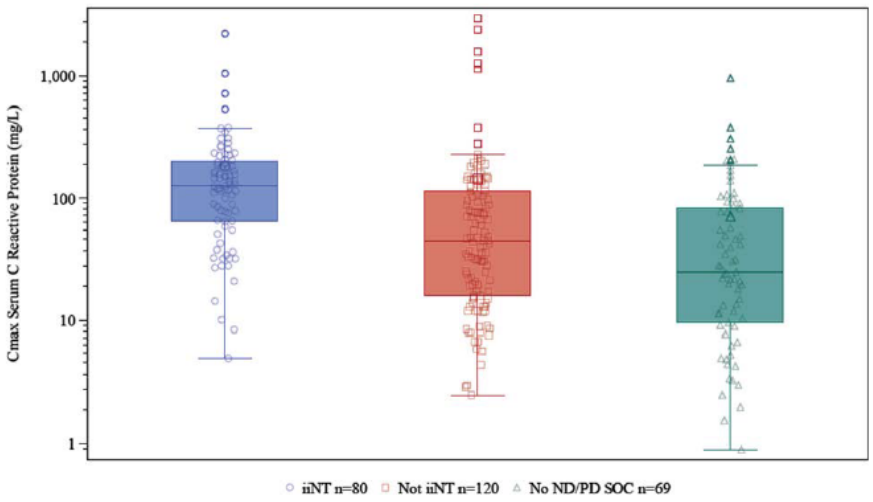


Figure 33. Box Plot of Peak C-Reactive Protein in Subjects with iiNT, not iiNT or No ND/PD SOC Events in Study 017001 DLBCL Cohort – JCAR017-Treated Set



Cytopenia and Prolonged cytopenia

Prolonged cytopenia is defined as Grade ≥ 3 cytopenias of neutropenia, thrombocytopenia, or anaemia that was not resolved at the time of the Day 29 visit. Haematology laboratory data were collected systematically through the Day 29 visit for Study 017001, and up to 2 years for the other studies. For Study 017001, laboratory information past Day 29 was not required as per the protocol. However, sites were retrospectively asked to enter into the eCRF the date that prolonged cytopenias resolved to Grade 2 or better and the result on that date (Table 83 and 84).

Table 83. Grade ≥ 3 Cytopenias and Prolonged Cytopenias – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Grade ≥ 3 Cytopenia from Day 1 through Day 29 Visit	249 (92.6)	117 (92.9)	23 (85.2)	9 (90.0)	15 (88.2)	20 (76.9)	316 (90.5)
Grade ≥ 3 at Day 29 Visit[a]	100 (37.2)	52 (41.3)	9 (33.3)	4 (40.0)	3 (17.6)	8 (30.8)	124 (35.5)
Grade ≤ 2 at Day 29 Visit	128 (47.6)	54 (42.9)	8 (29.6)	3 (30.0)	9 (52.9)	10 (38.5)	158 (45.3)
Unknown at Day 29 Visit	21 (7.8)	11 (8.7)	6 (22.2)	2 (20.0)	3 (17.6)	2 (7.7)	34 (9.7)
Grade >= 3 decreased Hemoglobin from Day 1 through Day 29 Visit	101 (37.5)	41 (32.5)	4 (14.8)	5 (50.0)	3 (17.6)	5 (19.2)	118 (33.8)
Grade ≥ 3 at Day 29 Visit	17 (6.3)	7 (5.6)	1 (3.7)	1 (10.0)	0	0	19 (5.4)
Grade ≤ 2 at Day 29 Visit	73 (27.1)	30 (23.8)	3 (11.1)	3 (30.0)	2 (11.8)	5 (19.2)	86 (24.6)
Unknown at Day 29 Visit	11 (4.1)	4 (3.2)	0	1 (10.0)	1 (5.9)	0	13 (3.7)
Grade >= 3 decreased Neutrophil count from Day 1 through Day 29 Visit	242 (90.0)	112 (88.9)	23 (85.2)	8 (80.0)	15 (88.2)	20 (76.9)	308 (88.3)
Grade ≥ 3 at Day 29 Visit	52 (19.3)	26 (20.6)	7 (25.9)	2 (20.0)	1 (5.9)	3 (11.5)	65 (18.6)
Grade ≤ 2 at Day 29 Visit	165 (61.3)	73 (57.9)	10 (37.0)	4 (40.0)	11 (64.7)	15 (57.7)	205 (58.7)
Unknown at Day 29 Visit	25 (9.3)	13 (10.3)	6 (22.2)	2 (20.0)	3 (17.6)	2 (7.7)	38 (10.9)
Grade >= 3 decreased Platelet count from Day 1 through Day 29 Visit	115 (42.8)	53 (42.1)	9 (33.3)	6 (60.0)	3 (17.6)	10 (38.5)	143 (41.0)
Grade ≥ 3 at Day 29 Visit	80 (29.7)	42 (33.3)	7 (25.9)	4 (40.0)	2 (11.8)	8 (30.8)	101 (28.9)
Grade ≤ 2 at Day 29 Visit	25 (9.3)	6 (4.8)	0	1 (10.0)	0	1 (3.8)	27 (7.7)
Unknown at Day 29 Visit	10 (3.7)	5 (4.0)	2 (7.4)	1 (10.0)	1 (5.9)	1 (3.8)	15 (4.3)

3L+ third line or later; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma.
[a] Prolonged cytopenia is defined as any grade ≥ 3 laboratory result of decreased hemoglobin, decreased neutrophil count, or decreased platelet count at the Study Day 29 visit.
The protocol defined window for the Day 29 Visit is 29 ± 2 days after JCAR017 administration. If multiple test results are available in the window, the maximum grade is selected.
Results after the initiation of subsequent anticancer therapy or JCAR017 retreatment or combination therapy (Study BCM-002) are not considered.
Segmented neutrophils is used for Study BCM-001.
Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: SCS Table 4.8.1.1 and SCS Table 4.8.1.1.b.

Table 84. Recovery from Laboratory-based Grade ≥ 3 Prolonged Cytopenias in the Study 017001 DLBCL Cohort –JCAR017-treated Set

	DLBCL Cohort Total (N = 269) n (%)	DLBCL Subgroup Total (NOS, HGL, tFL, tiNHL) (N = 251) n (%)	DLBCL Histology Subgroup				PMBCL (N = 15) n (%)	FL3B (N = 3) n (%)
			DLBCL NOS (N = 137) n (%)	HGL (N = 36) n (%)	tFL (N = 60) n (%)	tiNHL (N = 18) n (%)		
Grade ≥3 decreased Hemoglobin at Day 29 visit	17 (6.3)	17 (6.8)	9 (6.6)	5 (13.9)	2 (3.3)	1 (5.6)	0	0
Had hemoglobin lab results post Day 29 visit	11 (4.1)	11 (4.4)	5 (3.6)	3 (8.3)	2 (3.3)	1 (5.6)	0	0
Recovered to Grade ≤ 2 by Day 60	8 (3.0)	8 (3.2)	4 (2.9)	1 (2.8)	2 (3.3)	1 (5.6)	0	0
Recovered to Grade ≤ 2 by Day 90	9 (3.3)	9 (3.6)	4 (2.9)	2 (5.6)	2 (3.3)	1 (5.6)	0	0
Recovered to Grade ≤ 2 by EOS	10 (3.7)	10 (4.0)	5 (3.6)	2 (5.6)	2 (3.3)	1 (5.6)	0	0
Grade ≥3 decreased ANC at Day 29 visit	52 (19.3)	51 (20.3)	29 (21.2)	12 (33.3)	9 (15.0)	1 (5.6)	1 (6.7)	0
Had ANC lab results post Day 29 visit	43 (16.0)	42 (16.7)	23 (16.8)	11 (30.6)	7 (11.7)	1 (5.6)	1 (6.7)	0
Recovered to Grade ≤ 2 by Day 60	27 (10.0)	27 (10.8)	18 (13.1)	4 (11.1)	5 (8.3)	0	0	0
Recovered to Grade ≤ 2 by Day 90	36 (13.4)	35 (13.9)	21 (15.3)	9 (25.0)	5 (8.3)	0	1 (6.7)	0
Recovered to Grade ≤ 2 by EOS	41 (15.2)	40 (15.9)	23 (16.8)	11 (30.6)	6 (10.0)	0	1 (6.7)	0
Grade ≥3 decreased Platelet Count at Day 29 visit	80 (29.7)	80 (31.9)	48 (35.0)	14 (38.9)	13 (21.7)	5 (27.8)	0	0
Had platelet lab results post Day 29 visit	58 (21.6)	58 (23.1)	33 (24.1)	9 (25.0)	11 (18.3)	5 (27.8)	0	0
Recovered to Grade ≤ 2 by Day 60	26 (9.7)	26 (10.4)	16 (11.7)	2 (5.6)	6 (10.0)	2 (11.1)	0	0
Recovered to Grade ≤ 2 by Day 90	36 (13.4)	36 (14.3)	21 (15.3)	5 (13.9)	8 (13.3)	2 (11.1)	0	0
Recovered to Grade ≤ 2 by EOS	47 (17.5)	47 (18.7)	27 (19.7)	7 (19.4)	10 (16.7)	3 (16.7)	0	0

ANC = absolute neutrophil count; DLBCL = diffuse large B-cell lymphoma; D = day; EOS = end of study; FL3B = follicular lymphoma Grade 3B; HGL = high-grade lymphoma; LDC = lymphodepleting chemotherapy; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal B-cell lymphoma; tCLL/SLL = DLBCL transformed from chronic lymphocytic leukemia/small lymphocytic lymphoma; tFL = DLBCL transformed from follicular lymphoma; tiNHL = DLBCL transformed from indolent non-Hodgkin lymphoma (tMZL + tCLL/SLL + tOther); tMZL = DLBCL transformed from marginal zone lymphoma; tOther = DLBCL transformed from other indolent lymphomas, including Waldenstrom macroglobulinemia.
Results after the initiation of subsequent anticancer therapy or JCAR017 retreatment were not considered.
EOS was the data cut-off date for those subjects who did not have their EOS visit yet.
Source: SCS Table 4.15.2.1.

Infusion reactions

Infusion-related reaction related to JCAR017 was reported in 4 out of 349 subjects (1.1%) in the Pooled 3L+ DLBCL Set. These events occurred on the day of infusion and were Grade 1 or 2.

Macrophage Activation Syndrome

MAS is a potentially life-threatening adverse event that has been observed in association with approved anti-CD19 CAR T-cell therapeutics and has been attributed to excess activation of CD8 T lymphocytes.

Among the 349 subjects treated in the Pooled 3L+ DLBCL Set, 2 subjects (0.6%) in Study BCM-001 developed Grade 4 MAS. Both subjects had postmortem findings consistent with MAS, but deaths were suspected of being for other causes (the first due to respiratory failure and the second from candida sepsis).

Tumour Lysis Syndrome

Tumour lysis syndrome was reported in 2 out of 349 subjects (0.6%) in the Pooled 3L+ DLBCL Set (both in subjects in the 017001 DLBCL Treated Set). Both events were Grade 3, and neither was reported as an SAE. Allopurinol was reported as a concomitant medication in 186 out of 269 subjects (69.1%) and rasburicase in 9 out of 269 subjects (3.3%), generally for prophylaxis of TLS or hyperuricemia.

There were no reports of TLS in Study BCM-001. Allopurinol and rasburicase were reported as a concomitant medication in 13 out of 27 subjects (48.1%) and 7 out of 27 subjects (25.9%), respectively, in Cohort 1.

Infections (Grade ≥ 3)

In the Pooled 3L+ DLBCL Set, all-grade TEAEs in the SOC of Infections and Infestations were reported in 133 out of 349 subjects (38.1%) (Table 85). The most frequent types of infections were pneumonia (22 out of 349 subjects, 6.3%), upper respiratory tract infection (15 subjects; 4.3%), candida infection (13 subjects; 3.7%), urinary tract infection (12 subjects; 3.4%), and sinusitis (11 subjects; 3.2%). All

other PTs were reported in ≤ 3% of subjects. These findings were similar to the rates of all-grade infections in the 017001 DLBCL Treated Set.

In Study BCM-001, all-grade infections occurred in 11 out of 37 subjects (29.7%).

Treatment-emergent AEs of infection considered Grade ≥ 3 in severity were reported in 44 out of 349 subjects (12.6%) with pathogen unspecified reported in 30 subjects (8.6%), bacterial in 14 subjects (4.0%), and viral and fungal in 4 subjects each (1.1%). These results were similar to the rates of Grade ≥ 3 infections in the 017001 DLBCL Treated Set.

In addition to the three Grade 5 events previously described (2 in Study 017001 and 1 in Study BCM-001), there were 2 additional events in Study BCM-002, 1 each of pneumonia and Staphylococcal sepsis.

Table 85. Adverse Events of Infection in the Treatment-emergent Period - Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	(N = 269) n (%)	DL2S v4 (N = 126) n (%)	Cohort 1 (N = 27) n (%)	Cohort 3 (N = 10) n (%)	017007 (N = 17) n (%)	BCM-002 (N = 26) n (%)	Total (N = 349) n (%)
Infections, Any Grade	110 (40.9)	53 (42.1)	10 (37.0)	1 (10.0)	3 (17.6)	9 (34.6)	133 (38.1)
Grade ≥ 3 infections	33 (12.3)	15 (11.9)	4 (14.8)	0	2 (11.8)	5 (19.2)	44 (12.6)
Grade 3-4	31 (11.5)	15 (11.9)	3 (11.1)	0	2 (11.8)	3 (11.5)	39 (11.2)
Grade 5	2 (0.7)	0	1 (3.7)	0	0	2 (7.7)	5 (1.4)
Grade ≥ 3 bacterial infections	11 (4.1)	4 (3.2)	1 (3.7)	0	1 (5.9)	1 (3.8)	14 (4.0)
Grade 3-4	11 (4.1)	4 (3.2)	1 (3.7)	0	1 (5.9)	0	13 (3.7)
Grade 5	0	0	0	0	0	1 (3.8)	1 (0.3)
Grade ≥ 3 fungal infections	2 (0.7)	2 (1.6)	2 (7.4)	0	0	0	4 (1.1)
Grade 3-4	2 (0.7)	2 (1.6)	1 (3.7)	0	0	0	3 (0.9)
Grade 5	0	0	1 (3.7)	0	0	0	1 (0.3)
Grade ≥ 3 viral infections	4 (1.5)	1 (0.8)	0	0	0	0	4 (1.1)
Grade 3-4	3 (1.1)	1 (0.8)	0	0	0	0	3 (0.9)
Grade 5	1 (0.4)	0	0	0	0	0	1 (0.3)
Grade ≥ 3 infections - pathogen unspecified	22 (8.2)	11 (8.7)	2 (7.4)	0	1 (5.9)	5 (19.2)	30 (8.6)
Grade 3-4	21 (7.8)	11 (8.7)	2 (7.4)	0	1 (5.9)	4 (15.4)	28 (8.0)
Grade 5	1 (0.4)	0	0	0	0	1 (3.8)	2 (0.6)

3L+ = third line or later; AE = adverse event; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; SOC = system organ class.
Treatment-emergent period is defined as any time from initiation of JCAR017 administration through 90 days post the final cycle of JCAR017, or the initiation of another anticancer therapy or JCAR017 retreatment, whichever comes first.
Infection includes post-JCAR017 Grade ≥ 3 AEs from Infections and infestations SOC, by AE high level group term.
Source: SCS Table 3.2.1.1, SCS Table 3.2.1.1b, SCS Table 4.1.1.1, and SCS Table 4.1.1.1 b.

During the post-treatment-emergent period, Grade ≥ 3 infections were reported for 14 out of 302 subjects (4.6%). The most frequent was unspecified pathogen, reported in 9 subjects (3.0%) (Table 86).

Table 86. Adverse Events of Infection in the Post-treatment-emergent Period-Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001		017007 (N = 8) n (%)	BCM-002 (N = 22) n (%)	Total (N = 302) n (%)
	(N = 247) n (%)	DL2S v4 (N = 117) n (%)	Cohort 1 (N = 15) n (%)	Cohort 3 (N = 10) n (%)			
Infections, Any Grade	23 (9.3)	11 (9.4)	2 (13.3)	1 (10.0)	0	7 (31.8)	33 (10.9)
Grade ≥ 3 infections	12 (4.9)	5 (4.3)	0	0	0	2 (9.1)	14 (4.6)
Grade 3-4	10 (4.0)	4 (3.4)	0	0	0	2 (9.1)	12 (4.0)
Grade 5	2 (0.8)	1 (0.9)	0	0	0	0	2 (0.7)
Grade ≥ 3 bacterial infections	4 (1.6)	2 (1.7)	0	0	0	1 (4.5)	5 (1.7)
Grade 3-4	4 (1.6)	2 (1.7)	0	0	0	1 (4.5)	5 (1.7)
Grade 5	0	0	0	0	0	0	0
Grade ≥ 3 fungal infections	1 (0.4)	0	0	0	0	0	1 (0.3)
Grade 3-4	1 (0.4)	0	0	0	0	0	1 (0.3)
Grade 5	0	0	0	0	0	0	0
Grade ≥ 3 viral infections	3 (1.2)	0	0	0	0	1 (4.5)	4 (1.3)
Grade 3-4	2 (0.8)	0	0	0	0	1 (4.5)	3 (1.0)
Grade 5	1 (0.4)	0	0	0	0	0	1 (0.3)
Grade ≥ 3 infections - pathogen unspecified	8 (3.2)	4 (3.4)	0	0	0	1 (4.5)	9 (3.0)
Grade 3-4	7 (2.8)	3 (2.6)	0	0	0	1 (4.5)	8 (2.6)
Grade 5	1 (0.4)	1 (0.9)	0	0	0	0	1 (0.3)

3L+ = third line or later; AE = adverse event; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; SOC = system organ class.
Posttreatment-emergent period starts from 91 days post the final cycle of JCAR017, or initiation of another anticancer therapy or JCAR017 retreatment if subjects initiated another anticancer therapy or JCAR017 retreatment prior to 91 days post the final cycle of JCAR017.
Infection includes post-JCAR017 Grade ≥ 3 AEs from Infections and infestations SOC, by AE high level group term.
Sources: SCS Table 3.7.1.1, SCS Table 3.7.1.1.b, SCS Table 4.19.1.1, and SCS Table 4.19.1.1.b.

Infection prophylaxis

In the 017001 DLBCL Treated Set, sulfamethoxazole trimethoprim use was reported in 141 of 269 subjects (52.4%), generally for infection prophylaxis.

Antivirals were reported as concomitant medications, generally for viral infection prophylaxis. These include acyclovir in 237 of 269 subjects (88.1%), valacidovir in 26 of 269 subjects (9.7%), and ribavirin, ganciclovir, and valganciclovir in lower numbers of subjects.

Antifungals for systemic use, which were reported as concomitant medications generally indicated for fungal infection prophylaxis, included fluconazole in 111 of 269 subjects (41.3%), micafungin in 35 of 269 subjects (13.0%), micafungin sodium in 15 of 269 subjects (5.6%), posaconazole in 14 of 269 subjects (5.2%), amphotericin B in 12 of 269 subjects (4.5%), voriconazole in 11 of 269 subjects (4.1%), and isavuconazonium (sulfate), caspofungin (acetate), and itraconazole in lower numbers of subjects.

In the Study BCM-001, sulfamethoxazole trimethoprim was used in 20 (74.1%) subjects in Cohort 1 (N = 27). Acyclovir was used in 15 (55.6%) subjects, valacyclovir hydrochloride was used in 5 (18.5%) subjects, and valacyclovir was used in 4 (14.8%) subjects.

Fluconazole was used in 9 (33.3%) subjects and amphotericin B was used in 4 (14.8%) subjects. Other antifungals were used in fewer than 20% of subjects.

Hepatitis B and C. Subjects with a history of hepatitis B without active infection were eligible to screen for Studies 017001 and 017007, whereas subjects with previous history of hepatitis B were not eligible to screen for Studies BCM-001 or BCM-002. Eleven subjects (4.1%) in the 017001 DLBCL Treated Set had pre-treatment evidence of latent or suppressed hepatitis B virus (HBV) infection. Ten subjects were on one or more suppressive antiviral medications at the time of study enrollment and thereafter, and one has a hepatitis B surface antigen positive medical history and was never treated with a hepatitis B antiviral medication after JCAR017 treatment. None of the 11 subjects developed AEs or laboratory values suggestive of HBV reactivation following JCAR017 therapy. Additionally, a total of 2 subjects had

a history of hepatitis C in the Study 017001 DLBCL Treated Set and neither was associated with reports of worsening infection.

Hypogammaglobulinaemia/B-cell Aplasia

In the Pooled 3L+ DLBCL Set, TEAEs of hypogammaglobulinaemia were noted in 43 out of 349 subjects (12.3%) and were reported in 14 out of 302 subjects (4.6%) in the post-treatment emergent period. All events were Grade 1 or 2. The occurrence of treatment emergent hypogammaglobulinaemia in the 017001 DLBCL Treated Set (13.8%) and in the BCM-001 (16.2%) was similar to that in the Pooled 3L+ DLBCL Set (12.3%) (Table 87).

In the 017001 DLBCL Treated Set on the single-dose schedule, IgG < 500 mg/dL was observed in 123 out of 253 subjects (49%) at baseline. On Days 29 and 365, 136 out of 236 subjects (58%) and 68 out of 112 subjects (61%) had IgG < 500 mg/dL.

B-cell aplasia was evident at baseline in 92% (241 out of 262 subjects) of the 017001 DLBCL Treated Set. Consistent with transgene persistence, B-cell aplasia was observed in 98% of subjects (240 out of 244 subjects) on Day 29, 93% (153 out of 165 subjects) on Day 90, 86% (100 out of 116 subjects) on Day 180, and 73% (51 out of 70 subjects) on Day 365.

Subjects in Study BCM-001 (Cohort 1) exhibited a similar high rate of B-cell aplasia ranging from 100% on Day 29 (N = 23) and Day 90 (N = 10), 86% (6 of 7 subjects) on Day 180, and 75% (3 out of 4 subjects) on Day 270.

These patients were treated with intravenous immunoglobulin replacement therapy following the institutional guidelines.

Table 87. Adverse Events of Hypogammaglobulinaemia in Treatment-emergent and Post-treatment-emergent Periods – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001				
	n (%)	DL2S v4 n (%)	Cohort 1 n (%)	Cohort 3 n (%)	017007 n (%)	BCM-002 n (%)	Total n (%)
Treatment-emergent Period							
N	269	126	27	10	17	26	349
Hypogammaglobulinaemia[a]	37 (13.8)	21 (16.7)	5 (18.5)	1 (10.0)	0	0	43 (12.3)
Grade ≥ 3	0	0	0	0	0	0	0
Posttreatment-emergent Period							
N	247	117	15	10	8	22	302
Hypogammaglobulinaemia[a]	12 (4.9)	8 (6.8)	0	0	0	2 (9.1)	14 (4.6)
Grade ≥ 3	0	0	0	0	0	0	0

3L+ = third line or later; AE = adverse event; DL2S v4 = Dose Level 2, Single Dose, manufacturing version 4; DLBCL = diffuse large B-cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.

[a] Hypogammaglobulinaemia includes post-JCAR017 AEs with the following MedDRA preferred terms: Blood immunoglobulin A decreased, Blood immunoglobulin D decreased, Blood immunoglobulin E decreased, Blood immunoglobulin G decreased, Blood immunoglobulin M decreased, Hypogammaglobulinaemia, Immunoglobulins decreased, Selective IgA immunodeficiency, Selective IgG subclass deficiency, and Selective IgM immunodeficiency.

Treatment-emergent period is defined as any time from initiation of JCAR017 administration through 90 days after the final dose of JCAR017, or the initiation of another anticancer therapy or JCAR017 retreatment or combination therapy (for Study BCM-002), whichever comes first. Any adverse event occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment was not considered a TEAE.

Post treatment-emergent period starts from 91 days after the final cycle of JCAR017, or initiation of another anticancer therapy or JCAR017 retreatment if subjects initiated another anticancer therapy or JCAR017 retreatment prior to 91 days post the final cycle of JCAR017.

Source: SCS Table 4.2.1.1, SCS Table 4.2.1.1.b, SCS Table 4.3.1.1, and SCS Table 4.3.1.1.b.

Second Primary Malignancies (SPMs)

Second primary malignancies were defined as newly diagnosed reports of cancer not representing relapse of the underlying disease.

In the Pooled 3L+ DLBCL Set, across both the treatment-emergent and posttreatment-emergent periods, 23 subjects (6.6%) had 1 or more SPMs. In Study 017001, 20 subjects had a total of 29 events and in Study BCM-002, 3 subjects had a total of 3 events. There were no reported SPMs from Studies BCM-001 or 17007. A total of 6 out of 349 subjects (1.7%) had SPMs reported during the treatment-emergent period, including five subjects from Study 017001 (3 solid tumours [cutaneous basal cell carcinoma, endometrial adenocarcinoma, and cutaneous squamous cell carcinoma *in situ*] and 2 haematopoietic malignancies [peripheral T-cell lymphoma and MDS]), whereas one subject with Grade 3 colon carcinoma *in situ* was reported from Study BCM-002. During the posttreatment-emergent period, a total of 17 out of 302 subjects (5.6%) had SPMs: fifteen of these were in Study 017001 which included events of MDS, acute myelogenous leukaemia, basal cell carcinoma, cutaneous squamous cell carcinoma, squamous cell carcinoma of the lung, papillary urothelial carcinoma of the bladder, and neoplasm of the appendix, whereas two subjects developed cutaneous squamous cell carcinoma (both Grade 3) in Study BCM-002 (Table 88).

Table 88. Adverse Events of Second Primary Malignancy in Treatment-emergent and Post-treatment-emergent Periods – Pooled 3L+ DLBCL Set

	017001 DLBCL Cohort		BCM-001		017007	BCM-002	Total
	n (%)	DL2S v4 n (%)	Cohort 1 n (%)	Cohort 3 n (%)	n (%)	n (%)	n (%)
Treatment-emergent period							
N	269	126	27	10	17	26	349
Second Primary Malignancy	5 (1.9)	5 (4.0)	0	0	0	1 (3.8)	6 (1.7)
Grade ≥ 3	2 (0.7)	2 (1.6)	0	0	0	1 (3.8)	3 (0.9)
Posttreatment-emergent period							
N	247	117	15	10	8	22	302
Second Primary Malignancy	15 (6.1)	7 (6.0)	0	0	0	2 (9.1)	17 (5.6)
Grade ≥ 3	8 (3.2)	4 (3.4)	0	0	0	2 (9.1)	10 (3.3)

3L+ = third line or later; AE = adverse event; DL2S = dose level 2, single dose; DLBCL = diffuse large B-cell lymphoma; MedDRA = medical dictionary of regulatory activities; SMQ = standardized MedDRA query.

Treatment-emergent period is defined as any time from initiation of JCAR017 administration through 90 days following the final dose of JCAR017, or the initiation of another anticancer therapy or JCAR017 retreatment or combination therapy (for Study BCM-002), whichever comes first.

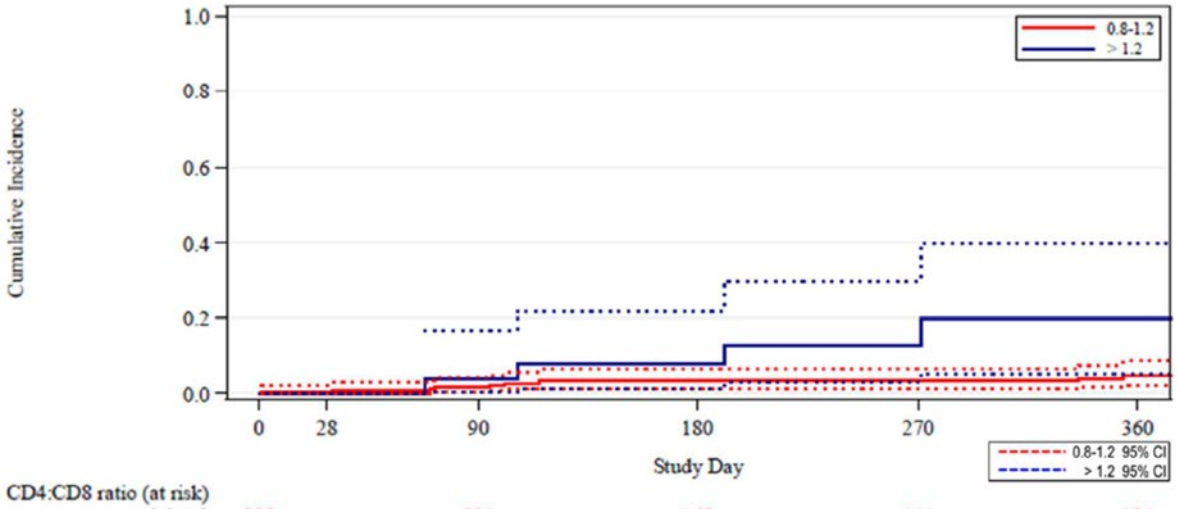
Post treatment-emergent period starts from 91 days post the final cycle of JCAR017, or initiation of another anticancer therapy or JCAR017 retreatment if subjects initiated another anticancer therapy or JCAR017 retreatment prior to 91 days post the final cycle of JCAR017.

Second primary malignancy includes post-JCAR017 AEs in Malignancies SMQ and Pre-malignant conditions SMQ. Events identified by consensus of an adjudication committee.

Source: SCS Table 4.2.1.1, SCS Table 4.2.1.1.b, SCS Table 4.3.1.1, and SCS Table 4.3.1.1.b.

Notably, the cumulative incidence for SPM continues to increase throughout the 360 days of follow-up for subgroup of patients with CD4+:CD8+ cell components ratio > 1.2, although the numbers of patients at risk are low.

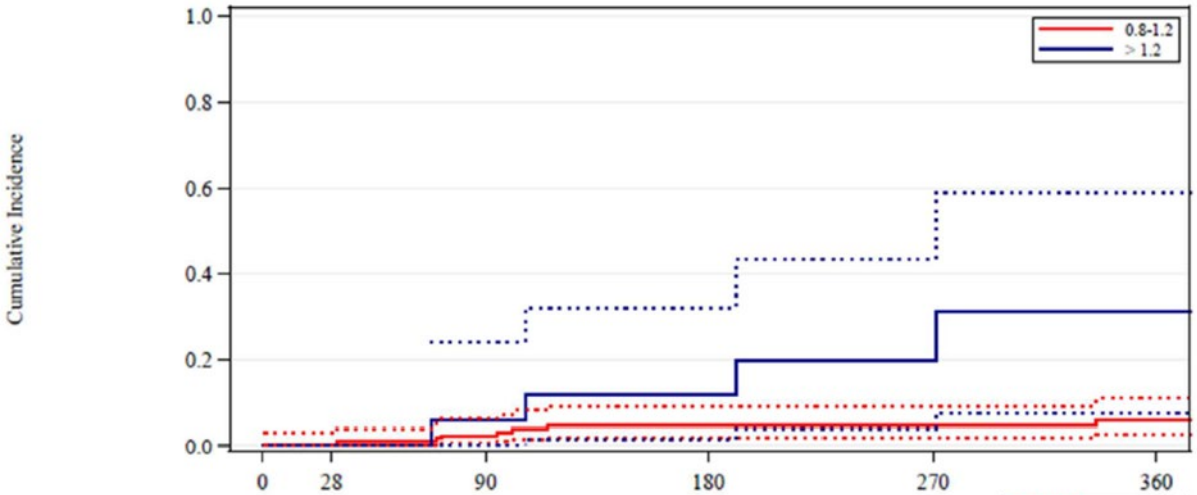
Panel A: Second Primary Malignancy in the Study 017001 JCAR017-treated Set DLBCL Cohort



CD4:CD8 ratio (at risk)					
0.8-1.2	235	201	165	144	124
> 1.2	28	26	20	14	11
CIF 0.8-1.2	0	0.0181	0.0332	0.0332	0.0484
CIF > 1.2	0	0.0385	0.0769	0.1282	0.1953

DL1D subjects are excluded.

Panel B: Second Primary Malignancy in the Study 017001 DLBCL Cohort JCAR017-treated Set DL2



CD4:CD8 ratio (at risk)					
0.8-1.2	159	134	111	94	80
> 1.2	18	17	13	8	7
CIF 0.8-1.2	0	0.0267	0.0493	0.0493	0.0607
CIF > 1.2	0	0.0588	0.1176	0.1979	0.3125

Autoimmune Disorders

No subject in the Pooled 3L+ DLBCL Set developed autoimmune disorders.

Hospitalisations

Analyses were performed for subjects who received JCAR017 in an inpatient setting (244 out of 269 subjects, 90.7%) and for those treated in an outpatient setting (25 out of 269 subjects, 9.3%) in Study 017001. Among 244 subjects who received JCAR017 in the inpatient setting, 18 subjects (7.4%) were admitted to the intensive care unit (ICU); the median number of ICU days was 7.5 (range 1 to 56 days;

Q1, Q3 = 3.0, 18.0 days). Among the 25 subjects who received JCAR017 in the outpatient setting, 18 (72.0%) were admitted to hospital, with a median of 5.0 days after JCAR017 administration (range 3 to 22 days) and 1 subject (5.6%) was admitted to the ICU for 3 days.

Considering all hospitalisations up to the end of the study, 33 out of 269 subjects (12.3%) in the 017001 DLBCL Treated Set were admitted to the ICU; the median number of ICU days was 8.0 (range 1 to 56 days).

As of the 19 Jun 2020 data cutoff date, out of 38 third-line or later (3L+) diffuse large B-cell lymphoma (DLBCL) subjects with intensive care unit (ICU) admissions from studies 017001 and BCM-001, 37 subjects were monitored as inpatients and 1 subject was monitored as an outpatient following liso-cel infusion. Ten out of the 37 subjects admitted to ICU after liso-cel had concurrent CRS, 11 had neurological events, 4 had infection, and 4 had hypotension. The only (1) outpatient subject admitted to the ICU had CRS.

Long-term Follow-up – Study GC-LTFU-001

Study GC-LTFU-001 is an ongoing, prospective, observational study evaluating the long-term safety and efficacy of JCAR017 and other effector T-cell therapeutics in consenting subjects previously treated in completed clinical trials. Subjects will be followed for 15 years from the last genetically modified (GM) T-cell infusion, withdrawal of consent, lost to follow-up, or death, whichever occurs first.

All 29 subjects enrolled in the LTFU study at the time of the first data cut-off were from Study 017001: 26 of the subjects were from the DLBCL Treated Set (i.e., in the DLBCL Cohort and received JCAR017); 2 subjects were from the DLBCL Cohort and received non-conforming product; and 1 subject was from the MCL Cohort and received non-conforming product.

Total on-study follow-up time while enrolled in Study GC-LTFU-001 for the 26 subjects from the 017001 DLBCL Treated Set was 13.71 patient-years. Median age in the 29 subjects was 64 years (range 39 to 79 years) at enrollment, 19 (65.5%) subjects were male, and most subjects were white (93.1%).

There were no AEs reported in the clinical trial database as of the 12 Aug 2019 data cut-off date, but there was 1 SAE report in the Safety database. A single AE of basal cell carcinoma was reported from a 55-year-old woman with HGL from the DLBCL Treated Set who enrolled in Study GC-LTFU-001. The investigator considered the tumour unrelated to prior JCAR017 treatment, but transgene assay was not performed from tumour tissue excised for cure.

The data of the last cut-off date (19 Jun 2020) are reported in Day 120 Safety Update section.

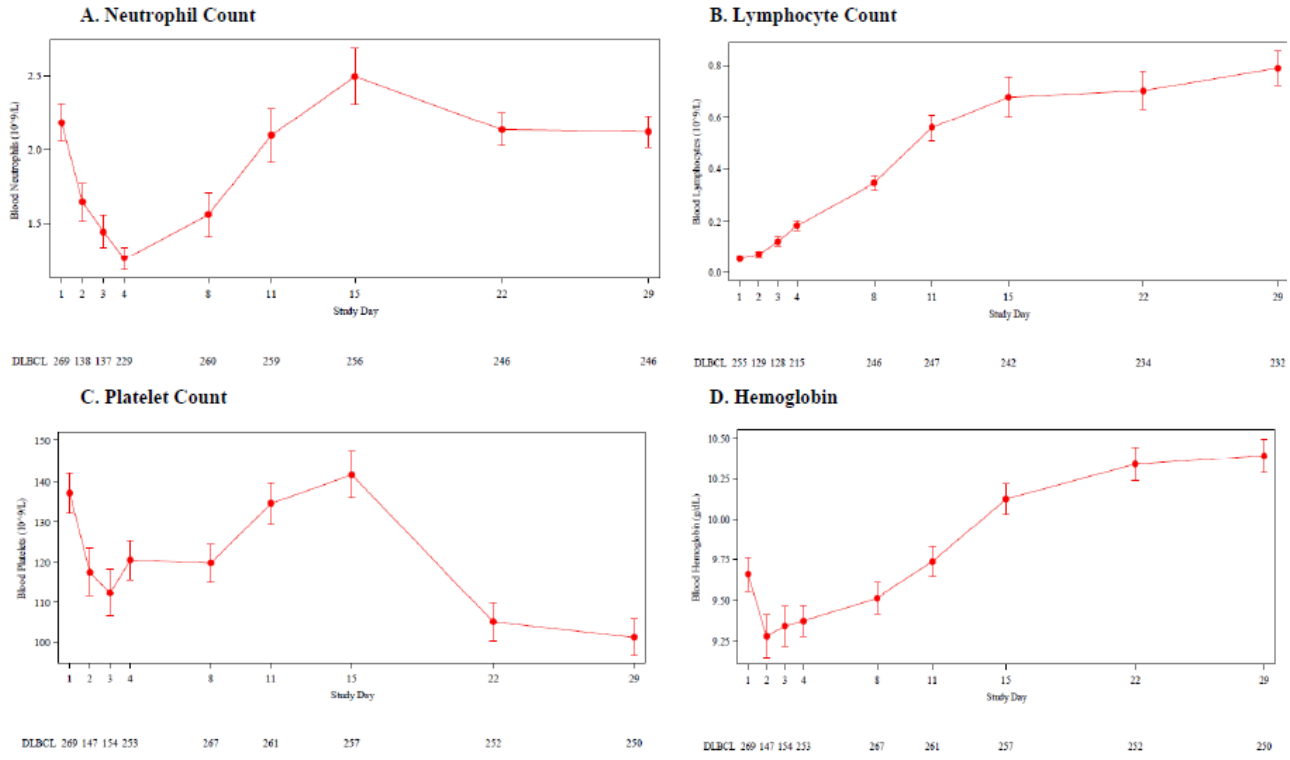
2.6.8.4. Laboratory findings

Haematology

Graphs of mean haematology values over time (from day of JCAR017 administration through Day 29) in the 017001 DLBCL Treated Set are shown in Figure 34.

In the 017001 DLBCL Treated Set, neutrophils showed a decline through Day 4, followed by recovery. This pattern was consistent with the receipt of LDC administration prior to JCAR017 Treatment. Lymphocyte counts were low at Day 1, followed by an increase over the first 2 weeks, concurrent with JCAR017 expansion. Platelet counts appeared relatively stable from Day 1 through Day 15, then a progressively decrease was observed. Haemoglobin levels generally increased from Day 8 through Day 29.

Figure 34. Haematology Parameters (Mean and SE) Over Time in Study 017001 (DLBCL Cohort)-JCAR017-treated Set



DLBCL = diffuse large B-cell lymphoma; SE = standard error.
Data cutoff date: 12 Aug 2019.
Source: CSR 017001 Figure 14.3.4.1.a.1.

In the study BCM-001 (Cohort 1), neutrophil count showed a decline from screening through Day 8, with a fluctuation of the mean between 1.5 and 2.0 × 10^9/L neutrophil counts through Day 29 followed by a slow recovery. This pattern was consistent with the general receipt of bridging therapy during JCAR017 manufacturing followed by LDC administration prior to JCAR017 infusion. Lymphocyte count decreased from time of LDC, likely reflecting the effects of anticancer therapy for disease control and LDC, followed by an increase over the first 2 weeks from JCAR017 infusion, concurrent with JCAR017 expansion. Platelet counts appeared relatively stable from screening to Day 15 and then decreased through Day 29 followed by an increase at Day 90. Haemoglobin levels appeared relatively stable through Day 90.

Shifts from pre-JCAR017 to maximum post-JCAR017 NCI CTCAE grade during treatment for haematologic laboratory abnormalities in the Pooled 3L+ DLBCL Set are presented in Table 89. In detail:

i) Pre-JCAR017, 331 (94.8%) subjects had Grade 3 or 4 lymphocyte count decreased, and post-JCAR017, 325 (93.1%) subjects had maximum Grade 3 or 4 lymphocyte count decreased;

ii) Pre-JCAR017, 95 (27.2%) subjects had Grade 3 or 4 neutrophil count decreased, and post-JCAR017, 306 (87.7%) subjects had maximum Grade 3 or 4 neutrophil count decreased;

iii) Pre-JCAR017, 34 (9.7%) subjects had Grade 3 or 4 platelet count decreased, and post-JCAR017, 143 (41.0%) subjects had maximum Grade 3 or 4 platelet count decreased;

iv) Pre-JCAR017, 45 (12.9%) subjects had Grade 3 anaemia, and post-JCAR017, 112 (32.1%) subjects had maximum Grade 3 anaemia.

Table 89. Shift from Pre-JCAR017 to Maximum Post-JCAR017 Haematology Laboratory Abnormalities – Pooled 3L+ DLBCL Set

Lab test CTCAE Grade	Pre-JCAR017 n	Maximum Post-JCAR017 Results					
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)
Anemia[a]							
Grade 0	21	3 (14.3)	13 (61.9)	5 (23.8)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 1	136	0 (0.0)	58 (42.6)	71 (52.2)	7 (5.1)	0 (0.0)	0 (0.0)
Grade 2	147	0 (0.0)	2 (1.4)	79 (53.7)	66 (44.9)	0 (0.0)	0 (0.0)
Grade 3	45	0 (0.0)	0 (0.0)	6 (13.3)	39 (86.7)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte Count Decreased							
Grade 0	2	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)
Grade 1	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	2	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
Grade 3	27	1 (3.7)	0 (0.0)	2 (7.4)	18 (66.7)	6 (22.2)	0 (0.0)
Grade 4	304	2 (0.7)	1 (0.3)	3 (1.0)	34 (11.2)	264 (86.8)	0 (0.0)
Missing	14	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (100.0)
Platelet Count Decreased							
Grade 0	142	43 (30.3)	58 (40.8)	7 (4.9)	21 (14.8)	13 (9.2)	0 (0.0)
Grade 1	124	0 (0.0)	53 (42.7)	33 (26.6)	23 (18.5)	15 (12.1)	0 (0.0)
Grade 2	49	0 (0.0)	3 (6.1)	9 (18.4)	20 (40.8)	17 (34.7)	0 (0.0)
Grade 3	23	0 (0.0)	0 (0.0)	0 (0.0)	6 (26.1)	17 (73.9)	0 (0.0)
Grade 4	11	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	10 (90.9)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil Count Decreased							
Grade 0	155	14 (9.0)	4 (2.6)	14 (9.0)	54 (34.8)	69 (44.5)	0 (0.0)
Grade 1	30	0 (0.0)	0 (0.0)	2 (6.7)	7 (23.3)	21 (70.0)	0 (0.0)
Grade 2	69	2 (2.9)	3 (4.3)	1 (1.4)	25 (36.2)	38 (55.1)	0 (0.0)
Grade 3	50	1 (2.0)	0 (0.0)	0 (0.0)	9 (18.0)	40 (80.0)	0 (0.0)
Grade 4	45	1 (2.2)	0 (0.0)	1 (2.2)	5 (11.1)	38 (84.4)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

3L+ = third line or later; DLBCL = diffuse large B-cell lymphoma; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
[a] Grade 3 and 4 anemia cannot be differentiated programmatically.
Pre-JCAR017 is the latest measurement taken prior to the date of the JCAR017 infusion or on the date of the JCAR017 infusion but prior to JCAR017 administration.
Post-JCAR017 includes lab results collected after the first JCAR017 infusion and up to Day 29 visit (+2 days). Any lab results after the start of combination therapy (for Study BCM-002) or the initiation of subsequent anticancer therapy or JCAR017 retreatment were not included.
Toxicity grade is programmatically determined based on laboratory results according to the NCI CTCAE v4.03.
Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: SCS Table 5.1.1.1.

Chemistry

Shifts from pre-JCAR017 to maximum post-JCAR017 NCI CTCAE grade for chemistry laboratory abnormalities in the Pooled 3L+ DLBCL Set are presented in Table 90.

In the total Pooled 3L+ DLBCL Set, mean CRP and ferritin values were elevated on Day 1. Mean CRP levels decreased through Day 29 while ferritin values were relatively stable.

Table 90. Shift from Pre-JCAR017 to Maximum Post-JCAR017 Chemistry Laboratory Abnormalities – Pooled 3L+ DLBCL Set

Lab test CTCAE Grade	Pre-JCAR017 n	Maximum Post-JCAR017 Results Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)
Alanine Aminotransferase Increased							
Grade 0	326	248 (76.1)	72 (22.1)	4 (1.2)	2 (0.6)	0 (0.0)	0 (0.0)
Grade 1	22	6 (27.3)	14 (63.6)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate Aminotransferase Increased							
Grade 0	307	240 (78.2)	57 (18.6)	8 (2.6)	2 (0.7)	0 (0.0)	0 (0.0)
Grade 1	40	7 (17.5)	25 (62.5)	5 (12.5)	3 (7.5)	0 (0.0)	0 (0.0)
Grade 2	2	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood Bilirubin Increased							
Grade 0	325	301 (92.6)	14 (4.3)	7 (2.2)	3 (0.9)	0 (0.0)	0 (0.0)
Grade 1	17	4 (23.5)	7 (41.2)	4 (23.5)	2 (11.8)	0 (0.0)	0 (0.0)
Grade 2	5	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	2	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine Increased							
Grade 0	319	265 (83.1)	46 (14.4)	7 (2.2)	1 (0.3)	0 (0.0)	0 (0.0)
Grade 1	27	1 (3.7)	20 (74.1)	6 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	3	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Lab test CTCAE Grade	Pre-JCAR017 n	Maximum Post-JCAR017 Results Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)
Hyperkalemia							
Grade 0	349	342 (98.0)	6 (1.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Grade 1	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalemia							
Grade 0	324	249 (76.9)	5 (1.5)	64 (19.8)	6 (1.9)	0 (0.0)	0 (0.0)
Grade 1	1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	23	8 (34.8)	0 (0.0)	14 (60.9)	1 (4.3)	0 (0.0)	0 (0.0)
Grade 3	1	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypermagnesemia							
Grade 0	342	316 (92.4)	23 (6.7)	0 (0.0)	3 (0.9)	0 (0.0)	0 (0.0)
Grade 1	7	3 (42.9)	3 (42.9)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)
Grade 2	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypomagnesemia							
Grade 0	297	215 (72.4)	82 (27.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 1	51	4 (7.8)	47 (92.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypernatremia							
Grade 0	341	326 (95.6)	13 (3.8)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 1	4	0 (0.0)	3 (75.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia							
Grade 0	311	216 (69.5)	88 (28.3)	0 (0.0)	7 (2.3)	0 (0.0)	0 (0.0)
Grade 1	38	4 (10.5)	26 (68.4)	0 (0.0)	8 (21.1)	0 (0.0)	0 (0.0)
Grade 2	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Lab test CTCAE Grade	Pre-JCAR017 n	Maximum Post-JCAR017 Results Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)
Hypophosphatemia							
Grade 0	305	207 (67.9)	11 (3.6)	58 (19.0)	28 (9.2)	1 (0.3)	0 (0.0)
Grade 1	12	0 (0.0)	4 (33.3)	3 (25.0)	5 (41.7)	0 (0.0)	0 (0.0)
Grade 2	28	6 (21.4)	0 (0.0)	12 (42.9)	10 (35.7)	0 (0.0)	0 (0.0)
Grade 3	4	0 (0.0)	0 (0.0)	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)
Grade 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperuricemia							
Grade 0	342	333 (97.4)	0 (0.0)	0 (0.0)	9 (2.6)	0 (0.0)	0 (0.0)
Grade 1	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	6	5 (83.3)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Grade 4	1	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Missing	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

3L+ = third line or later; DLBCL = diffuse large B-cell lymphoma; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Pre-JCAR017 is the latest measurement taken prior to the date of the JCAR017 infusion or on the date of the JCAR017 infusion but prior to JCAR017 administration.

Post-JCAR017 includes lab results collected after the first JCAR017 infusion and up to Day 29 visit (+2 days). Any lab results after the start of combination therapy (for Study BCM-002) or the initiation of subsequent anticancer therapy or JCAR017 retreatment were not included.

Toxicity grade is programmatically determined based on laboratory results according to the NCI CTCAE v4.03.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007

Source: SCS Table 5.2.1.1.

Coagulation

In the total Pooled 3L+ DLBCL Set, mean aPTT, INR, and D-dimer were stable from pre-treatment evaluation through Day 29 and mean fibrinogen decreased from Day 4 through Day 29.

Vital Signs

There were no notable abnormalities in vital signs aside from those findings associated with CRS and iiNT.

2.6.8.5. Safety in special populations

Analysis of Adverse Events by Age

In the Pooled 3L+ DLBCL Set, safety was generally similar between subjects < 65 years (n= 198) and ≥ 65 years of age (n= 151) and between subjects < 75 years (n= 311) and ≥ 75 years of age (n= 38) (Table 91). However, a numerical increase in the proportion of subjects ≥ 75 years with iiNT compared with those < 75 years of age (36.8% versus 26.4%, respectively) was noted.

Table 91. Treatment-emergent Adverse Events and Adverse Events of Special Interest by Age Group - Pooled 3L+ DLBCL Set

	Age < 65 years (N = 198) n (%)	Age ≥ 65 years (N = 151) n (%)	Age < 75 years (N = 311) n (%)	Age ≥ 75 years (N = 38) n (%)
Subjects with any TEAE	198 (100)	149 (98.7)	309 (99.4)	38 (100)
Grade ≥ 3 TEAE	157 (79.3)	124 (82.1)	247 (79.4)	34 (89.5)
Grade 5 TEAE	5 (2.5)	6 (4.0)	10 (3.2)	1 (2.6)
Treatment-emergent SAE	89 (44.9)	65 (43.0)	135 (43.4)	19 (50.0)
AESI category				
CRS or iiNT[a,b]	102 (51.5)	60 (39.7)	144 (46.3)	18 (47.4)
Grade 3-4	23 (11.6)	13 (8.6)	30 (9.6)	6 (15.8)
Grade 5	0	0	0	0
SAE	62 (31.3)	30 (19.9)	80 (25.7)	12 (31.6)

	Age < 65 years (N = 198) n (%)	Age ≥ 65 years (N = 151) n (%)	Age < 75 years (N = 311) n (%)	Age ≥ 75 years (N = 38) n (%)
AESI category (continued)				
CRS[a]	94 (47.5)	51 (33.8)	130 (41.8)	15 (39.5)
Grade 3-4	7 (3.5)	1 (0.7)	7 (2.3)	1 (2.6)
Grade 5	0	0	0	0
SAE	43 (21.7)	18 (11.9)	55 (17.7)	6 (15.8)
iiNT[b]	58 (29.3)	38 (25.2)	82 (26.4)	14 (36.8)
Grade 3-4	22 (11.1)	12 (7.9)	29 (9.3)	5 (13.2)
Grade 5	0	0	0	0
SAE	35 (17.7)	15 (9.9)	43 (13.8)	7 (18.4)

3L+ = third line or later; AE = adverse event; AESI = adverse event of special interest; CNS = central nervous system; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; iiNT = investigator-identified neurologic toxicity; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] CRS includes TEAE with MedDRA PT = Cytokine release syndrome. CRS is graded based on the Lee criteria (Lee, 2014).

[b] iiNT is defined as a CNS AE that is reported by investigator as related to JCAR017.

Note: Adverse events are coded using MedDRA version 21.0. A TEAE is defined as an AE that starts any time from initiation of JCAR017 administration through and including 90 days following the final dose of JCAR017. Any AE occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (BCM-002) was not considered as a TEAE.

Data cutoff dates: 12 Aug 2019 for Study 017001; 13 Sep 2019 for Study BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: SCS Tables 3.1.1.2 and 4.1.1.2.

At the most recent data cut-off date of 19 Jun 2020, although the poor representation of the older population (n=38/359, 10.6% ≥ 75 years old), the proportions of TEAE types observed in subjects ≥ 75 years old were generally similar to those observed in subjects < 65 years old. No pattern of unexpected events or safety signals was observed in the eldest subjects. For all of the specified adverse event (AE)

categories, there was no clinically meaningful increase in frequency with increasing age. No clear differences (i.e., ≥ 20% absolute difference) were noted between any of the 3 age subgroups for any of the requested AE categories, or for any other system organ classes (SOCs) or individual preferred terms (PTs). An exception was the SOC of nervous system disorders with a numerical difference (> 10% but < 20%) in subjects 65 to < 75 years old (56.3%) compared with those 75 to < 85 years old (73.0%) and the SOC of vascular disorders, with a numerical difference in subjects < 65 years old (30.7%) compared with those 75 to < 85 years old (43.2%) (Table 92).

Table 92. Summary of Treatment-emergent Adverse Events by Criteria or MedDRA Terms and Age Subgroups – Pooled 3L+ DLBCL Set

Criteria or MedDRA Terms	< 65 years (N = 202) n (%)	65 to < 75 years (N = 119) n (%)	75 to < 85 years (N = 37) n (%)	≥ 85 years (N = 1) n (%)
Total TEAEs[a]	202 (100)	117 (98.3)	37 (100)	1 (100)
Serious TEAEs – Total[a,b]	92 (45.5)	49 (41.2)	19 (51.4)	0
Resulted in death	6 (3.0)	5 (4.2)	1 (2.7)	0
Inpatient hospitalization or prolongation of existing hospitalization	82 (40.6)	41 (34.5)	16 (43.2)	0
Life threatening	9 (4.5)	3 (2.5)	1 (2.7)	0
Persistent or significant disability/incapacity	0	1 (0.8)	0	0
Other medically important event	23 (11.4)	12 (10.1)	3 (8.1)	0
TEAE leading to treatment discontinuation[c]	NA	NA	NA	NA
Psychiatric disorders (SOC)	72 (35.6)	38 (31.9)	13 (35.1)	1 (100)
Nervous system disorders (SOC)	133 (65.8)	67 (56.3)	27 (73.0)	1 (100)
Accidents and injuries[d]	15 (7.4)	6 (5.0)	3 (8.1)	0
Cardiac disorders (SOC)	62 (30.7)	23 (19.3)	10 (27.0)	0
Vascular disorders (SOC)	62 (30.7)	41 (34.5)	16 (43.2)	0
Cerebrovascular disorders[e]	4 (2.0)	5 (4.2)	1 (2.7)	0
Infections and infestations (SOC)	77 (38.1)	45 (37.8)	15 (40.5)	1 (100)
Anticholinergic syndrome (PT)	0	0	0	0
Quality of life decreased[f]	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, and fractures[g]	57 (28.2)	35 (29.4)	14 (37.8)	1 (100)

3L + = third-line or later; AE = adverse event; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; HLGT = high-level group term; HLT = high-level term; JCAR017 = lisocabtagene maraleucel (liso-cel); MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; PT = preferred term; SAE = serious adverse event; SMQ = standardized MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] Subjects with ≥ 1 event. Subjects are counted only once in the Total row.

[b] Subjects may have met more than 1 SAE criterion, ie, for subjects with different SAE criteria for different SAE events, the subject is counted for all criteria. For subjects with multiple criteria present for a single SAE, a hierarchy is used to classify the SAE criteria: Death > Life Threatening > Hospitalization Required > Disability > Other Medically Important Condition.

[c] As JCAR017 was intended for administration as a single dose for most subjects in the 4 studies in the Pooled 3L+ DLBCL Set (Studies 017001, BCM-001, BCM-002, and 017007), and follow-up continued for subjects for survival and long-term safety regardless of AEs, an analysis of TEAEs leading to treatment discontinuation is not applicable.

[d] Narrow scope of SMQ Accidents and injuries.

[e] Narrow scope of Central nervous system vascular disorders; Narrow scope of Sub-SMQ CNS vascular disorders, not specified as hemorrhagic or ischemic; Narrow scope of Sub-SMQ Conditions associated with central nervous system hemorrhages and cerebrovascular accidents, Narrow scope of Sub-SMQ Hemorrhagic central nervous system vascular conditions; and Narrow scope of Sub-SMQ Ischemic central nervous system vascular conditions.

[f] Search includes PTs of impaired quality of life and quality of life decreased.

[g] Search includes PTs of blood pressure orthostatic decreased, dizziness, dizziness exertional, dizziness postural, fall, loss of consciousness, orthostatic hypotension, persistent-postural perceptual dizziness, presyncope, procedural dizziness, and syncope; HLT Gait disturbances and HLT Coordination and balance disturbances; and HLGT Fractures.

Notes: A treatment-emergent AE is defined as an AE that starts any time from initiation of JCAR017 administration through and including 90 days following the final dose of JCAR017. Any AE occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (BCM-002) will not be considered as a TEAE. MedDRA v21.0 is used for coding.

Data cutoff dates: 19 Jun 2020 for Studies 017001, BCM-001, and Long-term Follow-up Study GC-LTFU-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Sources: D120 SCS Table 3.3.1.1.1, D120 SCS Table Q242.1.1, D120 SCS Table Q242.1.2, D120 SCS Table Q242.1.3, D120 SCS Table Q242.1.4, D120 SCS Table Q242.1.5; D120 BCM-001 Table 2.1, D120 BCM-001 Table 2.2; D120 BCM-002 Table 1.1, D120 BCM-002 Table 1.2; D120 017001 Table 3.1; D120 017007 Table 4.1.

Analysis of Adverse Events by Sex, Ethnicity, and Race

No clinically relevant differences were noted between sex, race, or ethnicity subgroups for subjects treated with JCAR017 in the Pooled 3L+ DLBCL Set.

Analysis of Adverse Events by Baseline Disease Characteristic

SPD Prior to LDC

In the Pooled 3L+ DLBCL Set, the overall rate of TEAEs was similar between subjects with SPD ≥ 50 cm2 (n= 114) and those with SPD < 50 cm2 (n= 231). Numerically larger proportions (≥ 15% difference) of subjects with SPD ≥ 50 cm2 had treatment-emergent SAEs (57.0% versus 38.1%, respectively), all-grade CRS (53.5% versus 35.5%, respectively), and all grade iiNT (38.6% versus 22.5%, respectively) (Table 93).

Table 93. Treatment-emergent Adverse Events and Adverse Events of Special Interest by SPD Prior to LDC - Pooled 3L+ DLBCL Set

	SPD < 50 cm^2 (N = 231) n (%)	SPD ≥ 50 cm^2 (N = 114) n (%)
Subjects with any TEAE	230 (99.6)	113 (99.1)
Grade ≥ 3 TEAE	177 (76.6)	102 (89.5)
Grade 5 TEAE	6 (2.6)	5 (4.4)
Treatment-emergent SAE	88 (38.1)	65 (57.0)
AESI Category		
CRS or iiNT[a,b]	94 (40.7)	66 (57.9)
Grade 3-4	16 (6.9)	20 (17.5)
Grade 5	0	0
SAE	51 (22.1)	41 (36.0)
CRS[a]	82 (35.5)	61 (53.5)
Grade 3-4	2 (0.9)	6 (5.3)
Grade 5	0	0
SAE	35 (15.2)	26 (22.8)
iiNT[b]	52 (22.5)	44 (38.6)
Grade 3-4	14 (6.1)	20 (17.5)
Grade 5	0	0
SAE	22 (9.5)	28 (24.6)

LDH Prior to LDC

In the Pooled 3L+ DLBCL Set, while the overall rate of TEAEs was similar in subjects with LDH ≥ 500 U/L (n= 78) and those with LDH < 500 U/L (n= 271), the incidences of Grade ≥ 3 TEAEs, treatment-emergent SAEs, all-grade CRS or iiNT events, and all-grade CRS events were higher in subjects with LDH ≥ 500 U/L (Table 94).

Table 94. Treatment-emergent Adverse Events and Adverse Events of Special Interest by LDH Prior to LDC - Pooled 3L+ DLBCL Set

	LDH < 500 U/L (N = 271) n (%)	LDH ≥ 500 U/L (N = 78) n (%)
Subjects with any TEAE	269 (99.3)	78 (100)
Grade ≥ 3 TEAE	206 (76.0)	75 (96.2)
Grade 5 TEAE	6 (2.2)	5 (6.4)
Treatment-emergent SAE	104 (38.4)	50 (64.1)
AESI Category		
CRS or iiNT[a,b]	109 (40.2)	53 (67.9)
Grade 3-4	21 (7.7)	15 (19.2)
Grade 5	0	0
SAE	57 (21.0)	35 (44.9)
CRS[a]	94 (34.7)	51 (65.4)
Grade 3-4	4 (1.5)	4 (5.1)
Grade 5	0	0
SAE	36 (13.3)	25 (32.1)
iiNT[b]	63 (23.2)	33 (42.3)
Grade 3-4	19 (7.0)	15 (19.2)
Grade 5	0	0
SAE	28 (10.3)	22 (28.2)

Baseline CRP

In the Pooled 3L+ DLBCL Set, while the overall rate of across TEAE categories was similar in subjects with baseline CRP < 20 mg/L (n= 172) and those with baseline CRP ≥ 20 mg/L (n= 176), the incidences of JCAR017-related TEAEs, JCAR017-related SAEs, and all-grade CRS or iiNT events were higher in subjects with CRP ≥ 20 mg/L (Table 95).

Table 95. Treatment-emergent Adverse Events and Adverse Events of Special Interest by Baseline CRP - Pooled 3L+ DLBCL Set

	Baseline CRP < 20 mg/L (N = 172) n (%)	Baseline CRP ≥ 20 mg/L (N = 176) n (%)
Subjects with any TEAE	171 (99.4)	175 (99.4)
Grade ≥ 3 TEAE	133 (77.3)	147 (83.5)
Grade 5 TEAE	2 (1.2)	9 (5.1)
Treatment-emergent SAE	59 (34.3)	95 (54.0)
AESI Category		
CRS or iiNT[a,b]	61 (35.5)	101 (57.4)
Grade 3-4	9 (5.2)	27 (15.3)
Grade 5	0	0
SAE	29 (16.9)	63 (35.8)
CRS[a]	56 (32.6)	89 (50.6)
Grade 3-4	1 (0.6)	7 (4.0)
Grade 5	0	0
SAE	20 (11.6)	41 (23.3)
iiNT[b]	32 (18.6)	64 (36.4)
Grade 3-4	9 (5.2)	25 (14.2)
Grade 5	0	0
SAE	14 (8.1)	36 (20.5)

Use of Anticancer Therapy for Disease Control

The incidences of Grade ≥ 3 TEAEs and all-grade CRS or iiNT were higher in subjects who received anticancer therapy for disease control (Table 96).

Table 96. Treatment-emergent Adverse Events and Adverse Events of Special Interest by Use of Anticancer Therapy for Disease Control in Study 017001 (DLBCL Cohort) - JCAR017-treated Set

	Anticancer Therapy for Disease Control	
	Yes (N = 159) n (%)	No (N = 110) n (%)
Subjects with any TEAE	158 (99.4)	109 (99.1)
Grade ≥ 3 TEAE	137 (86.2)	76 (69.1)
AESI Category		
CRS or iiNT[a,b]	88 (55.3)	39 (35.5)
Grade 3-4	22 (13.8)	7 (6.4)
Grade 5	0	0
SAE	52 (32.7)	19 (17.3)
CRS[a]	81 (50.9)	32 (29.1)
Grade 3-4	5 (3.1)	1 (0.9)
Grade 5	0	0
SAE	30 (18.9)	14 (12.7)
iiNT[b]	53 (33.3)	27 (24.5)
Grade 3-4	21 (13.2)	6 (5.5)
Grade 5	0	0
SAE	31 (19.5)	8 (7.3)

Pre-existing secondary CNS lymphoma

The rates of overall TEAEs were similar between subjects with and without secondary CNS involvement by lymphoma at the time of JCAR017 treatment. However, the rate of Grade ≥ 3 TEAEs was higher in subjects with secondary CNS involvement compared to those without (100% versus 78.6%) (Table 97). Adverse events of special interest were relatively similar between these groups. Notably, similar rates of iiNT were observed between both groups (78 of 262 subjects [29.8%] without secondary CNS involvement versus 2 of 7 subjects [28.6%] with secondary CNS involvement).

Table 97. Treatment-emergent Adverse Events and Adverse Events of Special Interest by Active CNS Disease at Time of JCAR017 Administration in Study 017001 (DLBCL Cohort) - JCAR017-treated Set

	Active CNS Disease at Time of JCAR017 Infusion	
	Yes (N = 7) n (%)	No (N = 262) n (%)
Subjects with any TEAE	7 (100)	260 (99.2)
Grade ≥ 3 TEAE	7 (100)	206 (78.6)
Grade 5 TEAE	1 (14.3)	6 (2.3)
Treatment-emergent SAE	4 (57.1)	118 (45.0)
AESI Category		
CRS or iiNT[a,b]	2 (28.6)	125 (47.7)
Grade 3-4	2 (28.6)	27 (10.3)
Grade 5	0	0
SAE	2 (28.6)	69 (26.3)
CRS[a]	2 (28.6)	111 (42.4)
Grade 3-4	2 (28.6)	6 (2.3)
Grade 5	0	0
SAE	0	44 (16.8)
iiNT[b]	2 (28.6)	78 (29.8)
Grade 3-4	2 (28.6)	25 (9.5)
Grade 5	0	0
SAE	2 (28.6)	37 (14.1)

ECOG PS

The analysis focused on the comparison between the Performance Status (PS) 0 and PS 1 subgroups because the numbers of subjects with Screening ECOG PS of 2 were too small to be clinically meaningful in the Pooled 3L+ DLBCL Set (n= 5) and 017001 DLBCL Treated Set (n= 4).

In the Pooled 3L+ DLBCL Set, no clear differences in the rates of overall TEAEs and AESIs (CRS and /or iiNT) were observed for subjects who had Screening ECOG PS of 0 (n= 156) versus 1 (n= 188).

ALC Prior to Leukapheresis

The rates of overall TEAEs and AESIs (CRS and/or iiNT) were similar for subjects with ALC < 0.3 × 10^9/L prior to leukapheresis and those with ALC ≥ 0.3 × 10^9/L prior to leukapheresis, with the exception of higher rates of Grade ≥ 3 thrombocytopenia in subjects with ALC < 0.3 × 10^9/L prior to leukapheresis (47.1% versus 25.6%, respectively) (Table 98).

Table 98. Treatment-emergent Adverse Events and Adverse Events of Special Interest by ALC Prior to Leukapheresis – Pooled 3L+ DLBCL Set

	ALC < 0.3 × 10^9/L (N = 34) n (%)	ALC ≥ 0.3 × 10^9/L (N = 301) n (%)
Subjects with any TEAE	34 (100)	300 (99.7)
Grade ≥ 3 TEAE	29 (85.3)	249 (82.7)
Grade 5 TEAE	3 (8.8)	7 (2.3)
Treatment-emergent SAE	15 (44.1)	136 (45.2)
AESI Category		
CRS or iiNT[a,b]	13 (38.2)	147 (48.8)
Grade 3-4	6 (17.6)	30 (10.0)
Grade 5	0	0
SAE	8 (23.5)	82 (27.2)
CRS[a]	11 (32.4)	132 (43.9)
Grade 3-4	1 (2.9)	7 (2.3)
Grade 5	0	0
SAE	5 (14.7)	54 (17.9)
iiNT[b]	10 (29.4)	86 (28.6)
Grade 3-4	6 (17.6)	28 (9.3)
Grade 5	0	0
SAE	6 (17.6)	44 (14.6)

Analysis of Adverse Events by Prior Treatment

Prior HSCT and Autologous HSCT

In the Pooled 3L+ DLBCL Set, updated data show that safety was similar between subjects who received prior HSCT (n= 121) and those who did not (n= 238), and between subjects who received prior auto-HSCT (n= 117) and those who did not (n= 242). No clear differences in TEAEs or AESIs were observed.

Prior Allogeneic HSCT

In the Pooled 3L+ DLBCL Set, updated data show that safety was generally similar between subjects who received prior allo-HSCT (n= 9) and those who did not (n= 350), although the rate of JCAR017-related Grade ≥ 3 TEAEs was higher in subjects who did not receive prior allo-HSCT compared with those who did (39.1% versus 11.1%, respectively) (Table 99).

Table 99. Overview of Treatment-emergent Adverse Events by Prior HSCT, by Prior Auto-HSCT, and by Prior Allo-HSCT (Pooled 3L + DLBCL Treated Set)

	Prior HSCT		Prior Auto-HSCT		Prior Allo-HSCT	
	Yes (N = 121) n (%)	No (N = 238) n (%)	Yes (N = 117) n (%)	No (N = 242) n (%)	Yes (N = 9) n (%)	No (N = 350) n (%)
Subjects with any TEAE	120 (99.2)	237 (99.6)	116 (99.1)	241 (99.6)	9 (100)	348 (99.4)
Grade ≥ 3 TEAE	97 (80.2)	193 (81.1)	93 (79.5)	197 (81.4)	9 (100)	281 (80.3)
Grade 5 TEAE	1 (0.8)	10 (4.2)	1 (0.9)	10 (4.1)	0	11 (3.1)
Treatment-emergent SAE	45 (37.2)	115 (48.3)	44 (37.6)	116 (47.9)	3 (33.3)	157 (44.9)
Any JCAR017-related TEAE	90 (74.4)	183 (76.9)	86 (73.5)	187 (77.3)	8 (88.9)	265 (75.7)
JCAR017-related Grade ≥ 3 TEAE	44 (36.4)	94 (39.5)	44 (37.6)	94 (38.8)	1 (11.1)	137 (39.1)
JCAR017-related Grade 5 TEAE	0	6 (2.5)	0	6 (2.5)	0	6 (1.7)
JCAR017-related treatment-emergent SAE	28 (23.1)	81 (34.0)	28 (23.9)	81 (33.5)	1 (11.1)	108 (30.9)
Any LDC-related TEAE	108 (89.3)	202 (84.9)	104 (88.9)	206 (85.1)	9 (100)	301 (86.0)
LDC-related Grade ≥ 3 TEAE	89 (73.6)	174 (73.1)	86 (73.5)	177 (73.1)	8 (88.9)	255 (72.9)
LDC-related Grade 5 TEAE	1 (0.8)	7 (2.9)	1 (0.9)	7 (2.9)	0	8 (2.3)
LDC-related treatment-emergent SAE	21 (17.4)	33 (13.9)	20 (17.1)	34 (14.0)	2 (22.2)	52 (14.9)

3L+ = third line or later; AE = adverse event; Allo-HSCT = allogeneic hematopoietic stem-cell transplantation; Auto-HSCT = autologous hematopoietic stem-cell transplantation; DLBCL = diffuse large B-cell lymphoma; HSCT = hematopoietic stem-cell transplantation; JCAR017 = lisocabtagene maraleucel (liso-cel); LDC = lymphodepleting chemotherapy; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
A treatment-emergent AE (TEAE) is defined as an AE that starts any time from initiation of JCAR017 administration through and including 90 days following the final dose of JCAR017. Any AE occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (BCM-002) will not be considered as a TEAE.
Data cutoff dates: 19 Jun 2020 for Studies 017001 and BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.
Source: D120 SCS Tables 3.1.1.6, 3.1.1.7, and 3.1.1.8.

TEAEs Grade ≥ 3 infections were reported in 16.5% of subjects who received prior HSCT and in 11.3% of subjects who did not receive prior HSCT. There were no clear differences in the types of Grade ≥ 3 infections observed (e.g., bacterial, fungal, viral, pathogen unspecified) in subjects who received prior HSCT versus those who did not. (Table 100)

GVHD. Two chronic GvHD AEs were reported out of 9 liso-cel-treated subjects who had previously undergone prior allo-HSCT. One subject white female, 72 years old at the time of enrolment in Study 017001, reported to have Grade 1 GVHD in the gastrointestinal tract on Study Day 228 (after an unrelated matched volunteer donor allo-HSCT).

One subject white male, 61 years old at the time of enrolment in Study 017001, developed vomiting and diarrhoea, and was reported to have Grade 3 GvHD in the gastrointestinal tract (after allo-HSCT).

Table 100. Treatment-emergent Adverse Events of Special Interest by Category and Grade by Prior HSCT, by Prior Auto-HSCT, and by Prior Allo-HSCT (Pooled 3L + DLBCL Treated Set)

	Prior HSCT		Prior Auto-HSCT		Prior Allo-HSCT	
	Yes (N = 121) n (%)	No (N = 238) n (%)	Yes (N = 117) n (%)	No (N = 242) n (%)	Yes (N = 9) n (%)	No (N = 350) n (%)
CRS or NT	52 (43.0)	114 (47.9)	50 (42.7)	116 (47.9)	4 (44.4)	162 (46.3)
Grade 1-2	43 (35.5)	86 (36.1)	41 (35.0)	88 (36.4)	4 (44.4)	125 (35.7)
Grade 3-4	9 (7.4)	28 (11.8)	9 (7.7)	28 (11.6)	0	37 (10.6)
Grade 5	0	0	0	0	0	0
SAE	24 (19.8)	71 (29.8)	24 (20.5)	71 (29.3)	1 (11.1)	94 (26.9)
CRS	46 (38.0)	102 (42.9)	44 (37.6)	104 (43.0)	4 (44.4)	144 (41.1)
Grade 1-2	44 (36.4)	96 (40.3)	42 (35.9)	98 (40.5)	4 (44.4)	136 (38.9)
Grade 3-4	2 (1.7)	6 (2.5)	2 (1.7)	6 (2.5)	0	8 (2.3)
Grade 5	0	0	0	0	0	0
SAE	15 (12.4)	47 (19.7)	15 (12.8)	47 (19.4)	1 (11.1)	61 (17.4)
NT	34 (28.1)	65 (27.3)	33 (28.2)	66 (27.3)	2 (22.2)	97 (27.7)
Grade 1-2	26 (21.5)	38 (16.0)	25 (21.4)	39 (16.1)	2 (22.2)	62 (17.7)
Grade 3-4	8 (6.6)	27 (11.3)	8 (6.8)	27 (11.2)	0	35 (10.0)
Grade 5	0	0	0	0	0	0
SAE	13 (10.7)	39 (16.4)	13 (11.1)	39 (16.1)	0	52 (14.9)
IRR	3 (2.5)	1 (0.4)	3 (2.6)	1 (0.4)	0	4 (1.1)
Grade 1-2	3 (2.5)	1 (0.4)	3 (2.6)	1 (0.4)	0	4 (1.1)
Grade 3-4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
SAE	0	0	0	0	0	0

	Prior HSCT		Prior Auto-HSCT		Prior Allo-HSCT	
	Yes (N = 121) n (%)	No (N = 238) n (%)	Yes (N = 117) n (%)	No (N = 242) n (%)	Yes (N = 9) n (%)	No (N = 350) n (%)
MAS	0	2 (0.8)	0	2 (0.8)	0	2 (0.6)
Grade 1-2	0	0	0	0	0	0
Grade 3-4	0	2 (0.8)	0	2 (0.8)	0	2 (0.6)
Grade 5	0	0	0	0	0	0
SAE	0	2 (0.8)	0	2 (0.8)	0	2 (0.6)
TLS	0	2 (0.8)	0	2 (0.8)	0	2 (0.6)
Grade 1-2	0	0	0	0	0	0
Grade 3-4	0	2 (0.8)	0	2 (0.8)	0	2 (0.6)
Grade 5	0	0	0	0	0	0
SAE	0	0	0	0	0	0
Grade ≥ 3 infections	20 (16.5)	27 (11.3)	20 (17.1)	27 (11.2)	0	47 (13.4)
Grade 3-4	20 (16.5)	22 (9.2)	20 (17.1)	22 (9.1)	0	42 (12.0)
Grade 5	0	5 (2.1)	0	5 (2.1)	0	5 (1.4)
Grade ≥ 3 bacterial infections	6 (5.0)	9 (3.8)	6 (5.1)	9 (3.7)	0	15 (4.3)
Grade 3-4	6 (5.0)	8 (3.4)	6 (5.1)	8 (3.3)	0	14 (4.0)
Grade 5	0	1 (0.4)	0	1 (0.4)	0	1 (0.3)
Grade ≥ 3 fungal infections	1 (0.8)	3 (1.3)	1 (0.9)	3 (1.2)	0	4 (1.1)
Grade 3-4	1 (0.8)	2 (0.8)	1 (0.9)	2 (0.8)	0	3 (0.9)
Grade 5	0	1 (0.4)	0	1 (0.4)	0	1 (0.3)
Grade ≥ 3 viral infections	2 (1.7)	2 (0.8)	2 (1.7)	2 (0.8)	0	4 (1.1)
Grade 3-4	2 (1.7)	1 (0.4)	2 (1.7)	1 (0.4)	0	3 (0.9)
Grade 5	0	1 (0.4)	0	1 (0.4)	0	1 (0.3)
Grade ≥ 3 infections pathogen unspecified	15 (12.4)	17 (7.1)	15 (12.8)	17 (7.0)	0	32 (9.1)
Grade 3-4	15 (12.4)	15 (6.3)	15 (12.8)	15 (6.2)	0	30 (8.6)
Grade 5	0	2 (0.8)	0	2 (0.8)	0	2 (0.6)

3L+ = third line or later; AE = adverse event; Allo-HSCT = allogeneic hematopoietic stem-cell transplantation; Auto-HSCT = autologous hematopoietic stem-cell transplantation; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; HSCT = hematopoietic stem-cell transplantation; IRR = infusion-related reaction; JCAR017 = lisocabtagene maraleucel (liso-cel); MAS = macrophage activation syndrome; MedDRA = Medical Dictionary for Regulatory Activities; NT = neurologic toxicity; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event; TLS = tumor lysis syndrome.

A treatment-emergent AE (TEAE) is defined as an AE that starts any time from initiation of JCAR017 administration through and including 90 days following the final dose of JCAR017. Any AE occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment or start of combination therapy (BCM-002) will not be considered as a TEAE.

CRS includes TEAE with MedDRA PT = Cytokine release syndrome. CRS is graded based on the Lee criteria (Lee, 2014). NT is defined as a central nervous system AE that is reported by investigator as related to JCAR017. IRR includes TEAEs with MedDRA PT = Infusion-related reaction reported as related to JCAR017. MAS includes TEAE with MedDRA PT = Histiocytosis haematophagic. TLS includes TEAEs with MedDRA PT = Tumour lysis syndrome. Infection includes Grade 3 or higher TEAEs from Infections and Infestations SOC, by AE high level group term.

Data cutoff dates: 19 Jun 2020 for Studies 017001 and BCM-001; 01 Aug 2019 for Studies BCM-002 and 017007.

Source: D120 SCS Tables 4.1.1.6, 4.1.1.7, and 4.1.1.8.

Analysis of Adverse Events by Comorbidity

In the 017001 DLBCL Treated Set, no clear differences in TEAEs or AESIs were observed between subgroups for CrCl prior to LDC (< 60 mL/min [n= 51] versus ≥ 60 mL/min [n= 218]) or LVEF at screening (≥ 40 to < 50% [n= 13] and ≥ 50% [n= 256]), except for higher rates of Grade ≥ 3 anaemia in the < 60 mL/min group versus the ≥ 60 mL/min group (58.8% versus 32.6%, respectively) (Table 101).

Table 101. Treatment-emergent Adverse Events and Adverse Events of Special Interest by CrCl Prior to LDC and LVEF at Screening in Study 017001, DLBCL Cohort – JCAR017-treated Set

	CrCl < 60 mL/min (N = 51) n (%)	CrCl ≥ 60 mL/min (N = 218) n (%)	LVEF ≥ 40 to < 50% (N = 13) n (%)	LVEF ≥ 50% (N = 256) n (%)
Subjects with any TEAE	51 (100)	216 (99.1)	13 (100)	254 (99.2)
Grade ≥ 3 TEAE	47 (92.2)	166 (76.1)	9 (69.2)	204 (79.7)
Grade 5 TEAE	5 (9.8)	2 (0.9)	1 (7.7)	6 (2.3)
Treatment-emergent SAE	26 (51.0)	96 (44.0)	5 (38.5)	117 (45.7)
AESI category				
CRS or iiNT[a,b]	30 (58.8)	97 (44.5)	6 (46.2)	121 (47.3)
Grade 3-4	10 (19.6)	19 (8.7)	1 (7.7)	28 (10.9)
Grade 5	0	0	0	0
SAE	15 (29.4)	56 (25.7)	4 (30.8)	67 (26.2)
CRS[a]	27 (52.9)	86 (39.4)	4 (30.8)	109 (42.6)
Grade 3-4	1 (2.0)	5 (2.3)	0	6 (2.3)
Grade 5	0	0	0	0
SAE	8 (15.7)	36 (16.5)	2 (15.4)	42 (16.4)
iiNT[b]	22 (43.1)	58 (26.6)	4 (30.8)	76 (29.7)
Grade 3-4	10 (19.6)	17 (7.8)	1 (7.7)	26 (10.2)
Grade 5	0	0	0	0
SAE	11 (21.6)	28 (12.8)	2 (15.4)	37 (14.5)

AE = adverse event; AESI = adverse event of special interest; CNS = central nervous system; CrCl = creatinine clearance; CRS = cytokine release syndrome; iiNT = investigator-identified neurologic toxicity; LDC = lymphodepleting chemotherapy; LVEF = left ventricle ejection fraction; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] CRS includes TEAE with MedDRA PT = Cytokine release syndrome. CRS is graded based on the Lee criteria (Lee, 2014).

[b] iiNT is defined as a CNS AE that is reported by investigator as related to JCAR017.

Note: Adverse events are coded using MedDRA version 21.0. A TEAE is defined as an AE that starts any time from initiation of JCAR017 administration through and including 90 days following the final dose of JCAR017. Any AE occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment was not considered as a TEAE. Creatinine clearance calculated by Cockcroft-Gault formula.

Data cutoff date: 12 Aug 2019.

Source: SCS Tables 3.1.2.3, 3.1.2.4, 4.1.2.6, and 4.1.2.7.

Extrinsic Factors

Analysis of Adverse Events by Region

In the Pooled 3L+ DLBCL Set, safety was generally similar between subjects from the US (n= 312), Europe (n= 27), and Japan (n= 10), with lower rates of treatment-emergent SAEs observed in subjects from Japan (10.0%) than in subjects from Europe (40.7%) or the US (45.5%). Rates of JCAR017-related Grade ≥ 3 TEAEs were higher in subjects from Japan and subjects from Europe compared with those from the US (70% and 55.6% versus 34.6%, respectively). The rates of Grade 5 TEAEs in Europe, the US, and Japan were 7.4%, 2.9%, and 0%, respectively. No clear differences in AESIs were observed between subjects from the US, Europe, and Japan.

As of the updated safety data cutoff date of 19 Jun 2020 (Day 120 Update) for Studies 017001 and BCM-001, the percentages of subjects who had Grade 5 TEAEs was 5.6% in Europe (change in denominator in Study BCM-001 due to increase in study population with 9 subjects), while they remained the same in the US (2.9%), and Japan (0%).

Summary of Safety Findings in Subjects Receiving Outpatient Treatment

In the 017001 DLBCL Treated Set, 25 subjects were treated in the outpatient setting. All have had TEAEs, and 17 (68.0%) subjects had Grade ≥ 3 events. There were no Grade 5 TEAEs. The most frequent Grade ≥3 events were neutropenia (44.0%), anaemia (40.0%), thrombocytopenia (12.0%), and febrile neutropenia (12%). Cytokine release syndrome was reported in 12 out of 25 subjects (48.0%); 1 subject (4.0%) had Grade 3 or 4 CRS. Investigator-identified neurologic toxicity was reported in 11 out of 25 subjects (44.0%); 2 subjects (8.0%) had Grade 3 or 4 iiNT. Out of the 25 subjects treated in an

outpatient setting, 18 (72.0%) were admitted to hospital, with a median of 5.0 days after JCAR017 administration (range 3 to 22 days).

Summary of Safety Findings in Subjects Treated with Nonconforming Product

Thirty-one subjects received a nonconforming product. Reasons for why such product was considered nonconforming in Studies 017001 DLBCL and BCM-001 are provided in Table 102. As of 19 Jun 2020, no additional subjects from Studies 017001 and BCM-001 have received nonconforming product.

Table 102. Treatment-emergent AESIs by Nonconforming Reason – Subjects Who Received Nonconforming Product in Study 017001 DLBCL Cohort and Study BCM-001 Cohorts 1+3

AESI	Total	Received 1 component only		Received both components, nonconforming due to 1 component not meeting the following specification			
		CD8+	CD4+	Viability	Potency	Purity	Sterility
N	31	10	3	8	7	2	1
CRS[a]	9	2	1	4	1	1	0
iiNT[b]	5	1	2	1	1	0	0
Grade ≥ 3 infection[c]	6	3	1	1	1	0	0
Prolonged cytopenia[d]	13	4	1	4	2	2	0

AE = adverse event; AESI = adverse events of special interest; CNS = central nervous system; CRS = cytokine release syndrome; DLBCL = Diffuse large B-cell lymphoma, iiNT = investigator-identified neurologic toxicity; MedDRA = medical dictionary of regulatory activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] CRS is defined as MedDRA PT = Cytokine release syndrome. CRS is graded based on the Lee, et al (Lee, 2014) grading criteria.

[b] iiNT is any investigator-identified CNS TEAE related to JCAR017.

[c] Infection includes Grade 3 or higher TEAEs from Infections and Infestations SOC, by AE high level group term.

[d] Prolonged cytopenia is defined as any Grade ≥ 3 laboratory result of hemoglobin decreased, neutrophil count decreased or platelet count decreased at the Study Day 29 visit. Protocol defined window for Day 29 Visit is 29 +/- 2 days after JCAR017 administration (dose 1 for single dose subjects; dose 2 for double dose subjects). If multiple test results are available in the window, the maximum grade is selected. Results after the initiation of subsequent anticancer therapy or JCAR017 retreatment will not be considered.

Data cutoff date: 12 Aug 2019 for Study 017001 and 13 Sep 2019 for Study BCM-001.

Source: SCS Table 4.20.3.3.

In the 017001 DLBCL Cohort, the overall frequencies of TEAEs, Grade 3 or 4 TEAEs, AESIs, and Grade 5 TEAEs reported in subjects treated with the nonconforming product appeared to be similar to those treated with JCAR017 (Table 103).

Table 103. Overview of Treatment-emergent Adverse Events – Subjects Who Received Nonconforming Product in Study 017001 DLBCL Cohort and Study BCM-001 Cohorts 1+3 and Subjects Who Received JCAR017 in the 017001 DLBCL Treated Set

	Received nonconforming product			Received JCAR017
	017001 DLBCL Cohort (N = 25) n (%)	BCM-001 Cohorts 1+3 (N = 6) n (%)	Total 017001 DLBCL Cohort & BCM-001 Cohort 1+3 (N = 31) n (%)	017001 DLBCL Treated Set (N = 269) n (%)
Subjects with any TEAE	25 (100)	6 (100)	31 (100)	267 (99.3)
Grade ≥ 3TEAE	20 (80.0)	6 (100)	26 (83.9)	213 (79.2)
Grade 5 TEAE	1 (4.0)	0	1 (3.2)	7 (2.6)
Treatment-emergent SAE	12 (48.0)	1 (16.7)	13 (41.9)	122 (45.4)
Any JCAR017-related TEAE	14 (56.0)	6 (100)	20 (64.5)	201 (74.7)
JCAR017-related Grade ≥ 3 TEAE	9 (36.0)	5 (83.3)	14 (45.2)	93 (34.6)
JCAR017-related Grade 5 TEAE	0	0	0	4 (1.5)
JCAR017-related treatment-emergent SAE	6 (24.0)	1 (16.7)	7 (22.6)	79 (29.4)

DLBCL = diffuse large B-cell lymphoma; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an adverse event that started any time from initiation nonconforming JCAR017 administration through and including 90 days following the final dose of nonconforming JCAR017. Any adverse event occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment was not considered a TEAE.

Data cutoff date: 12 Aug 2019 for Study 017001 and 13 Sep 2019 for Study BCM-001.

Source: SCS Table 3.1.3.1 and CSR 017001 Table 14.3.1.2.1.a.

Clinical outcomes across manufacturing process versions (CLOVER Report): Safety Evaluation

In Study 017001, JCAR017 was manufactured using 4 different manufacturing processes, and all but 3 subjects were treated with drug product manufactured with either the two precommercial processes (v2 and v3) or the proposed commercial process (v4). Within v4, lentiviral vector was produced at two different sites as v1.0 and v1.2 respectively. A summary of the incidence of TEAEs in the DLBCL Treated Set, DL1S and DL2S, for the precommercial and proposed commercial manufacturing processes and by vector manufacturing site is shown in Table 104. The overall incidence and severity of adverse events were generally similar between manufacturing process versions. Between the vector manufacturing sites, the overall incidence of TEAEs was similar (100% in both v4 vector groups). While the percentage of subjects with Grade 3-4 and serious TEAEs, and JCAR017-related TEAEs and higher grade or serious JCAR017-related TEAEs was higher in one (vector v1.0)subgroup, the differences were often based on small numbers of subjects in vector v1.2 group and all differences were < 15%.

Table 104. Overview of Treatment-emergent Adverse Events by Manufacturing Process Version and Vector Manufacturing Site, DLBCL Treated Set, DL1S+DL2S

Process Version:	v2+v3	v4			Total
Vector Mfg Site:	v1.0	v1.0	v1.2	v1.0 + v1.2	
	N=93 n (%)	N=110 n (%)	N=16 n (%)	N=126 n (%)	N=219 n (%)
Any TEAE	92 (98.9)	110 (100)	16 (100)	126 (100)	218 (99.5)
Any Grade 3-4 TEAE	70 (75.3)	87 (79.1)	11 (68.8)	98 (77.8)	168 (76.7)
Any Grade 5 TEAE	2 (2.2)	3 (2.7)	1 (6.3)	4 (3.2)	6 (2.7)
Any Serious TEAE	38 (40.9)	54 (49.1)	6 (37.5)	60 (47.6)	98 (44.7)
Any JCAR017-related TEAE	61 (65.6)	87 (79.1)	11 (68.8)	98 (77.8)	159 (72.6)
Any JCAR017-related Grade 3-4 TEAE	32 (34.4)	36 (32.7)	3 (18.8)	39 (31.0)	71 (32.4)
Any JCAR017-related Grade 5 TEAE	1 (1.1)	2 (1.8)	1 (6.3)	3 (2.4)	4 (1.8)
Any JCAR017-related serious TEAE	27 (29.0)	32 (29.1)	3 (18.8)	35 (27.8)	62 (28.3)

DL1S = Dose Level 1, single dose; DL2S = Dose Level 2, single dose; DLBCL = diffuse large B-cell lymphoma; Mfg = manufacturing; TEAE = treatment-emergent adverse event.

Data as of the 12 Aug 2019 cutoff.

Source: Table 14.3.1.2.1.d

A summary of the incidence of adverse events considered related to JCAR017 occurring in ≥ 10% of subjects in the DLBCL Treated Set, DL1S and DL2S, is shown by preferred term in Table 105.

Table 105. JCAR017-related TEAEs Occurring in ≥ 10% of Subjects Overall, DLBCL Treated Set, DL1S+DL2S

Process Version:	v2+v3	v4			Total
Vector Mfg Site:	v1.0	v1.0	v1.2	v1.0+ v1.2	
	N=93 n (%)	N=110 n (%)	N=16 n (%)	N=126 n (%)	N=219 n (%)
Subjects with any JCAR017-related TEAEs	61 (65.6)	87 (79.1)	11 (68.8)	98 (77.8)	159 (72.6)
Cytokine release syndrome	36 (38.7)	40 (36.4)	8 (50.0)	48 (38.1)	84 (38.4)
Neutropenia	14 (15.1)	21 (19.1)	4 (25.0)	25 (19.8)	39 (17.8)

Process Version:	v2+v3	v4			Total
Vector Mfg Site:	v1.0	v1.0	v1.2	v1.0+ v1.2	
	N=93 n (%)	N=110 n (%)	N=16 n (%)	N=126 n (%)	N=219 n (%)
Fatigue	18 (19.4)	17 (15.5)	2 (12.5)	19 (15.1)	37 (16.9)
Headache	15 (16.1)	16 (14.5)	1 (6.3)	17 (13.5)	32 (14.6)
Anaemia	16 (17.2)	13 (11.8)	2 (12.5)	15 (11.9)	31 (14.2)
Thrombocytopenia	10 (10.8)	15 (13.6)	3 (18.8)	18 (14.3)	28 (12.8)
Hypotension	14 (15.1)	12 (10.9)	0	12 (9.5)	26 (11.9)
Confusional state	7 (7.5)	13 (11.8)	3 (18.8)	16 (12.7)	23 (10.5)
Tremor	8 (8.6)	13 (11.8)	2 (12.5)	15 (11.9)	23 (10.5)
Dizziness	8 (8.6)	13 (11.8)	1 (6.3)	14 (11.1)	22 (10.0)

DL1S = Dose Level 1, single dose; DL2S = Dose Level 2, single dose; DLBCL = diffuse large B-cell lymphoma; Mfg = manufacturing; TEAE = treatment-emergent adverse event.

Note: Preferred terms are sorted in descending order of incidence in the Total column.

Data as of the 12 Aug 2019 cutoff.

Source: Table 14.3.1.12.d

2.6.8.6. Immunological events

Immunogenicity

The applicant provided immunogenicity results from Studies 017001 and BCM-001 based on longer follow-up data (cut-off date 19th June 2020). In the pooled studies, pre-existing anti-therapeutic antibodies (ATAs) were detected in 9.3% (29/309) of patients, and treatment-induced or treatment-boosted ATAs were detected in 15.1% (46/304) of patients. The relationships between ATA status and efficacy, safety or pharmacokinetics were not conclusive due to a limited number of patients (see also PK/PD section).

2.6.8.7. Safety related to drug-drug interactions and other interactions

JCAR017 is a cellular product that is generally administered as a one-time infusion. Because it is a cellular product, it is not cleared by the usual mechanisms that apply to small molecules or antibodies. No controlled clinical studies have been performed to directly address drug interactions with JCAR017.

False Positive HIV Tests

Human immunodeficiency virus nucleic acid amplification tests and HIV viral load testing can be falsely positive and may not reflect true HIV infection.

Anti-EGFR Monoclonal Antibody JCAR017 Ablation

A truncated epidermal growth factor receptor (EGFR) is expressed on the chimeric antigen receptor that is part of JCAR017. The applicant underlines that, unrelated to prior JCAR017 treatment, patients can develop incidental EGFR-expressing malignancies such as colorectal carcinoma, head and neck squamous cell carcinoma, or non-small-cell lung cancer, for which anti-EGFR monoclonal antibody (mab) may be indicated. Administration of anti-EGFR mabs, such as cetuximab, panitumumab, or necitumumab, to

treat such malignancies could also deplete the number of persistent JCAR017 cells and reduce activity against the lymphoma for which the JCAR017 was previously administered.

2.6.8.8. Use in pregnancy and lactation

There is no information regarding JCAR017 treatment of pregnant women. No animal reproductive and development toxicity studies have been conducted with JCAR017 to evaluate whether it can cause foetal harm when administered to a pregnant female. It is not known whether JCAR017 has the potential to be transferred to the foetus. Based on the JCAR017 mechanism of action, the transduced cells could theoretically cross the placenta and cause foetal B-cell lymphocytopenia and worsen the temporary hypogammaglobulinaemia of infancy. Therefore, JCAR017 is not recommended in women who are pregnant, and pregnancy after JCAR017 infusion should be discussed with the treating physician.

There is no information regarding the presence of JCAR017 in human milk, effects on the breastfed infant, or effects on milk production.

Contraception

There is no information to provide a recommendation concerning duration of contraception following treatment with JCAR017.

Infertility

There are no data on the effect of JCAR017 on fertility.

2.6.8.9. Overdose, drug abuse and withdrawal and rebound

In Study 017001, a single subject received 2 doses of Dose Level 2 (2 doses of 100×10^6 CAR+ T cells), with each dose administered 14 days apart. No Grade ≥ 3 TEAEs or treatment-emergent SAEs were reported for this subject.

2.6.8.10. Effects on ability to drive or operate machinery or impairment of mental ability

Breyanzi can have a major influence on the ability to drive and use machines, due to the potential for neurologic events, including altered mental status or seizures.

2.6.8.11. Transgene Persistence

Transgene persistence (defined by presence of transgene above the lower limit of detection) in the Study 017001 DLBCL Treated Set (single-dose schedule) was observed in 98% of subjects (236 out of 240 subjects) on Day 29, 77% (126 out of 163 subjects) on Day 90, 63% (72 out of 114 subjects) on Day 180, 52% (35 out of 67 subjects) on Day 365, and 45% (9 out of 20 subjects) on Day 730. No clear difference in transgene persistence was observed among the different dose levels.

In Cohort 1 of Study BCM-001, transgene persistence was observed in 95% of subjects (20 out of 21 subjects) on Day 29, 63% (5 out of 8 subjects) on Day 90, 20% (1 out of 5 subjects) on Day 180, and 33% (1 out of 3 subjects) on Day 270. In Cohort 3 of Study BCM-001, persistence of JCAR017 transgene was observed in 100% of subjects (10 out of 10 subjects) on Day 29, 100% (7 out of 7 subjects) on Day 90, and 33% (1 out of 3 subjects) on Day 180.

2.6.8.12. Replication-competent Lentivirus (RCL)

Replication-competent lentivirus testing was assessed using qPCR to detect viral vector envelope sequences on DNA obtained from peripheral blood. Through the data cutoff point in Study 017001, blood was tested for RCL in 208 subjects in the DLBCL Cohort in the JCAR017-treated Set on Day 90, 158 subjects on Day 180, 92 subjects on Day 365, and 27 subjects at the end of the study (24-month visit). Moreover, through the data cut-off point for Cohort 1 of Study BCM-001, the presence of RCL was tested in 12 out of 27 subjects on Day 90 and 7 out of 27 subjects on Day 180. None of these samples tested positive for RCL.

2.6.8.13. Discontinuation due to AEs

For the pooled 3L+ DLBCL, discontinuation from study after JCAR017 infusion were due to death (29.4%), lost to follow-up (0.4%), withdrew consent (2.8%) and other (1.1%). There were apparently no patients reported that has discontinued treatment due to AE. All subjects who received JCAR017 completed study treatment.

2.6.8.14. Post marketing experience

There are no post marketing data at this time.

2.6.8.15. Comparisons of Therapies Approved for 3L+ Large B-cell Lymphoma

There are 3 EMA-approved therapies for 3L+ large B-cell lymphoma: 2 CAR T-cell interventions (axicabtagene ciloleucel and tisagenlecleucel), and polatuzumab vedotin (in combination with BR). In the absence of patient-level data, ad-hoc cross-study comparisons have been performed. In general, JCAR017 has demonstrated numerically lower AESI rates (CRS, Grade ≥ 3 NT, Grade ≥ 3 infections) than axicabtagene ciloleucel (Yescarta SmPC, 2019), in a poor prognosis and high-risk population (Table 106).

Table 106. Key Safety Results from Study 017001 and Main Studies of Approved CD19 CAR T-Cell Therapies for 3L+ Large B-cell Lymphoma, and Polivy.

Product	JCAR017	Yescarta[a]	Kymriah[b]	Polivy[k]
Study	TRANSCEND (017001)	ZUMA-1	JULIET	GO29365
Analysis population	3L+ large B-cell lymphoma	3L+ large B-cell lymphoma[c]	3L+ large B-cell lymphoma[d]	R/R DLBCL
Sample size (N)	269	108	115	45
TEAEs, n (%)				
All-grade	267 (99)	108 (100)	106/106 (100[j])	45 (100)
Grade 3 or higher	213 (79)	106 (98.1)	Grade 3/4: 88%	38 (84.4)
Grade 5, excluding PD	7 (3)	4 (4)	NA	9 (20), including 1 event of PD
Serious	122 (45)	56 (52)	72/111 (65)[j]	29 (64.4)
AESIs				
Grade ≥ 3 CRS*, n (%)	6 (2)	12 (11)	19/111 (17)[f]	-
Grade ≥ 3 NT, n (%)	iiNT: 27 (10) ND/PD: 40 (15)	SiNT: 35 (32)[g] ND/PD: 34 (31)	SiNT: 11%[h] ND/PD: 19/106 (18)[j]	-
Grade ≥ 3 infections, n (%)	33 (12)	28 (26)	34%	11 (24.4)
Grade ≥ 3 febrile neutropenia, n (%)	24 (9)	35 (32)	17%	5 (11.1)
Grade ≥ 3 prolonged cytopenias, n (%)	100 (37) (by labs) Thrombocytopenia (17.5%) Neutropenia (14.2%) Anemia (6%) (by AEs)	41 (38)[i] Neutropenia (26%) Thrombocytopenia (24%) Anemia (10%) (by AEs)	Decreased thrombocytes (39%) Decreased lymphocytes (29%) Decreased neutrophils (25%) Decreased white blood cells (21%) Decreased haemoglobin (14%) (by labs)	NA

Product	JCAR017	Yescarta[a]	Kymriah[b]	Polivy[k]
Use of toci and/or CS for CRS, n (%)				
Toci and/or CS	53 (20)	NA	16 (15)	-
Any toci	48 (18)	18 (17)	16 (15)	-
Any CS	26 (10)	6 (6)	12 (11)	-
Use of toci and/or CS for CRS and/or NT, n (%)				
Toci and/or CS	74 (28)	51 (47)	NA	-
Any toci	52 (19)	49 (45)	NA	-
Any CS	56 (21)	31 (29)	NA	-
ICU admissions	7%	16%	25% (for CRS)	NA

3L+ = third-line or later; AE = adverse event; AESI = adverse event of special interest; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CS = corticosteroids; DLBCL = diffuse large B-cell lymphoma; EPAR = European Public Assessment Report; HGL = high-grade lymphoma; ICU = intensive care unit; iiNT = investigator-identified neurologic toxicity; NA = not available; ND/PD = AEs in the Nervous System Disorders and Psychiatric Disorders System Organ Classes; NT = neurologic toxicity; PD = progressive disease; PMBCL = primary mediastinal B-cell lymphoma; PT = preferred term; R/R = relapsed or refractory; SiNT = Sponsor-identified neurological toxicity; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event; tFL = DLBCL transformed from follicular lymphoma; toci = tocilizumab; USPI = United States prescribing information.

[a] Source: Yescarta SmPC, 2019
[b] Source: Kymriah SmPC, 2020
[c] Includes DLBCL, PMBCL, tFL,and HGL
[d] Includes DLBCL, tFL, and HGL
[e] CRS is graded based on the Lee grading criteria (Lee, 2014).
[f] Results from Schuster, 2019 (CRS results regraded according to Lee grading criteria) for comparison purposes.
[g] Source: Yescarta SmPC, 2019
[h] Identified as "manifestations of encephalopathy and/or delirium"
[i] Source: Kymriah EPAR, 2018
[j] Kymriah USPI, 2018
[k] Polivy EPAR - Analysis set: Phase 1b + 2, safety evaluable set.
[l] Source: Locke, 2019
Data cutoff date for 017001: 12 Aug 2019.

DAY 120 SAFETY UPDATE (data cutoff date: 19 Jun 2020)

The safety profile of JCAR017, based on data from Day 120 safety update with data cutoff date 19 Jun 2020, is generally consistent with the safety profile that was reported in the original marketing authorisation application (MAA). In the interim, with 10 new subjects added (9 from BCM-001 Cohort 1 and 1 from the 017001 DLBCL cohort) to the Pooled 3L+ DLBCL Treated Set, the median on-study follow-up time increased from **9.17 to 10.74 months** (minimum 0.1 month and maximum 45.2 months), while the total on-study follow-up went from **313.6 to 395.7 patient-years**. The cumulative follow-up in Study 017001 was more than 343 patient-years (including 227.8 patient-years at Dose Level 2 [DL2] and 158.9 patient-years at DL2 version 4 [v4]). In **Study BCM-001 Cohort 1**, in the approximately 9 months between the data cutoff dates of the original MAA and the Day 120 update (13 Sep 2019 to 19 Jun 2020), the median on-study follow-up time increased from **2.40 to 6.36 months**, with the total on-study follow-up going from **10.2 to 23.5 patient-years**. No new subjects were treated in Cohort 3 (10 subjects) and the median on-study follow-up time in BCM-001 Cohort 3 increased from 4.42 to 10.96 months, with a total on-study follow-up going from 4.1 to 7.7 patient-years. **In the long-term follow-up (LTFU) Study GC-LTFU-001**, in the approximately 10 months between the data cutoff dates of the original MAA and the Day 120 update (12 Aug 2019 to 19 Jun 2020), 43 new subjects were enrolled (up from 29 to 72 subjects) from studies BCM-001 and 017001. For subjects from Study 017001, the median on-study follow-up time increased from 0.51 to 0.75 months, while the total on-study follow-up went from 15.31 to 58.61 patient-years. For subjects from Study BCM-001, as of 19 Jun 2020, the median on-study follow-up time for Cohort 1 and Cohort 3 were 0.36 and 0.17 months, respectively, while the total on-study follow-up times were 1.52 and 0.74 patient-years, respectively.

Treatment-emergent Adverse Events. The treatment-emergent safety profile at Day 120 remained consistent with that reported in the MAA, as there were few additional liso-cel-treated subjects with new data in the 017001 DLBCL Cohort (1 subject), BCM-001 Cohort 1 (9 subjects), and the Pooled 3L+ DLBCL Set (10 subjects). No additional subject data was included from the other studies/cohorts of the Pooled 3L+ DLBCL Set (Studies BCM-002, 017007, and BCM-001 Cohort 3).

There were no significant changes in any of the TEAE categories or AESIs in the 017001 DLBCL Treated Set. Almost all of the 270 subjects (n=268; 99.3%) had TEAEs. Grade ≥ 3 TEAEs were reported in 78.9% of subjects, and Grade 5 TEAEs occurred in 2.6% of subjects. One additional subject was reported with a Grade ≥ 3 TEAE related to liso-cel treatment (lymphopenia). Consistent with the original MAA data (SCS Section 2.1.7.1), in the 017001 DLBCL Treated Set, 122 out of 270 subjects (45.2%) reported treatment-emergent SAEs, most frequently in the SOCs of Immune System Disorders (16.3%), Nervous System Disorders (15.2%), and Infections and Infestations (10.4%). CRS (16.3%) and encephalopathy (5.2%) were the most frequently reported treatment-emergent SAEs. There were no major differences in the safety findings of subjects in Study 017001 treated at DL2S (overall or v4) compared to the 017001 DLBCL Cohort or the Pooled 3L+ DLBCL Set.

In BCM-001 Cohort 1, during the interim between the MAA and D120 Safety update data cutoff dates (13 Sep 2019 and 19 Jun 2020), there were an additional 9 subjects with TEAEs and Grade ≥ 3 TEAEs, 7 subjects with treatment-emergent SAEs, and no new Grade 5 TEAEs. The percentages of subjects within each category of TEAE in the updated data remained generally consistent (differences of ≤ 10%) with the MAA. The results by TEAE category were generally similar to those in the 017001 DLBCL Treated Set and the Pooled 3L+ DLBCL Set, with the exception of higher percentages of subjects having Grade ≥ 3 TEAEs in Cohort 1 (94.4%) compared to the 017001 DLBCL Treated Set and the Pooled 3L+ DLBCL Set (78.9% and 80.8%, respectively). The most frequently reported Grade ≥ 3 TEAEs in Cohort 1 were neutropenia (80.6% [66.7% in the MAA]), anaemia (30.6% [33.3% in the MAA]), thrombocytopenia (25.0% [14.8% in the MAA]), leukopenia (22.2% [22.2% in the MAA]), lymphopenia (19.4% [18.5% in the MAA]), and febrile neutropenia (19.4% [11.1% in the MAA]). In agreement with the applicant, this may be due to a higher percentage of subjects receiving anticancer therapy for disease control in Cohort 1 compared to Study 017001 (75% versus 58.9%). Therefore, subjects may have had less bone marrow reserve when they received LDC followed by liso-cel. Grade 5 TEAEs were reported in 2 subjects (5.6%) while treatment-emergent SAEs were reported in 18 subjects (50.0%).

In the Pooled 3L+ DLBCL Set, as of the Day 120 Safety Update data cutoff date (19 Jun 2020) and consistent with the original MAA data, almost all 359 subjects (99.4%) had TEAEs. Grade ≥ 3 TEAEs were reported in 80.8% of subjects (80.5% in the MAA), and Grade 5 TEAEs occurred in 3.1% (3.2% in the MAA) with no Grade 5 TEAEs occurring during the interval of the Safety Update. Treatment-emergent SAEs were reported in 44.6% (44.1% in the MAA), most frequently in the SOCs of Immune System Disorders (17.3%), Nervous System Disorders (15.6%), and Infections and Infestations (10.9%). The most frequently reported treatment-emergent SAE was CRS (17.3%); all other treatment-emergent SAEs were reported in < 5% of subjects. These findings are similar to those for the 017001 DLBCL Treated Set, and the corresponding percentages for the pooled results in the Safety Update are similar to those reported in the original MAA.

Posttreatment-emergent Adverse Events. AEs reported during the posttreatment-emergent period as of the Safety Update data cutoff date for the Pooled 3L+ DLBCL Set were similar to those for the 017001 DLBCL Treated Set and BCM-001 Cohort 1, most frequently in the SOC of Blood and Lymphatic System Disorders. Percentages were consistent with those reported in the original MAA. Only in BCM-001 Cohort 3, the percentages of subjects with any grade and Grade ≥ 3 AEs in the Blood and Lymphatic disorders SOC was higher (80.0% and 70.0%, respectively) than in the total Pooled 3L+ DLBCL Set (23.7% and 18.7%, respectively), although given the small number of subjects from Study BCM-001 Cohort 3, comparisons should be interpreted with caution.

Deaths. In the total 017001 DLBCL Treated Set, 129 out of 270 subjects (47.8%) [122/269 subjects, 45.4% in the MAA], died any time after the first liso-cel infusion. Most of the deaths reported after the first liso-cel treatment were due to disease progression (108 of 129), with 11 due to AEs, 5 due to unknown causes, and 5 due to other causes (stroke unrelated to study, pneumonia, and diffuse intra-abdominal ischemia). Out of 129 deaths after liso-cel treatment, 96 deaths occurred more than 90 days

after the last liso-cel treatment. Nine of the 129 deaths occurred within 30 days after the first liso-cel treatment, with 6 due to disease progression and 3 due to AEs (diffuse alveolar damage, septic shock, and cardiomyopathy). No clear differences were noted in the frequencies or causes of death reported in the subset of subjects treated with DL2S v4 compared with those for the total 017001 DLBCL Treated Set.

In the BCM-001 Cohort 1, 17 out of 36 subjects (47.2%) died any time after the first liso-cel infusion. Of the 17 deaths after liso-cel treatment, 12 deaths occurred more than 90 days after the last liso-cel treatment. One of the 17 deaths occurred within 30 days after the first liso-cel treatment due to AE (respiratory failure). Most of the deaths reported after the first liso-cel treatment were due to disease progression (15 of 17) and 2 were due to AEs. In particular, one death was due to an adverse event (cardiac arrest on Study Day 203). This subject received a nonconforming product.

In the Pooled 3L+ DLBCL Set, 159 out of 359 subjects (44.3%) died any time after the first liso-cel infusion. Most deaths were due to disease progression (133 of 159), 16 were due to AEs, 6 to unknown cause and 5 to other.

Adverse Events of Special Interest. In Study 017001, regarding the additional AESIs of second primary malignancy (SPM), hypogammaglobulinaemia and Grade ≥ 3 infections in the treatment-emergent and posttreatment-emergent period, since the original MAA, 1 additional subject had hypogammaglobulinaemia (5.2% [4.9% in the MAA]) and 2 additional subjects (both with MDS) reported SPMs in the posttreatment-emergent period (17 subjects total [6.8%], from 15 subjects [6.1%] in the MAA). No major differences in the percentages of subjects with AESIs of hypogammaglobulinaemia and second primary malignancies were observed in the posttreatment emergent period for subjects in the 017001 DLBCL Cohort treated at DL2S or with DL2S v4.

In Study BCM-001, there were still only 5 subjects with hypogammaglobulinaemia reported (13.9%; 18.5% in the MAA). One new subject (3.1%) in BCM-001 Cohort 1 had a SPM in the posttreatment-emergent period.

Taking in account the **cumulative SPMs** as of the 19 Jun 2020 data cutoff date for liso-cel-treated subjects in the 017001 DLBCL Cohort and BCM-001 Cohorts 1+3, there were no new treatment-emergent SPMs. In the posttreatment-emergent period, SPMs were reported for 17 subjects from Study 017001 (15 subjects in the MAA) and 1 subject from Study BCM-001 (Cohort 1) (0 subjects in the MAA).

As of 19 Jun 2020, **haematopoietic second malignancies** following liso-cel treatment have been reported in Study 017001. During the treatment-emergent period, single cases of peripheral T-cell lymphoma (PTCL) and myelodysplastic syndrome (MDS) were reported. During the posttreatment-emergent period, 9 subjects in Study 017001 developed new haematopoietic second malignancies: 7 subjects with MDS and 2 subjects with acute myeloid leukaemia (AML), with a cumulative incidence of 2.5% for MDS (n=8 of 316 3L+ DLBCL subjects treated with liso-cel in Study 017001 and BCM-001 Cohorts 1+3 through the 19 Jun 2020 data cutoff date) and 0.6% (n=2 of 316) for AML. Although the incidence rates of MDS and AML are higher than those observed in the general population, they are consistent with those previously described (*Cordeiro et al, 2020*).

As of 19 Jun 2020, **solid tumour second malignancies** have been reported in 13 subjects in Study 017001 and 1 subject in Study BCM-001 (Cohort 1). Most of the solid tumour second malignancies occurred during the posttreatment-emergent period, and all of these SPMs were considered by the investigators not to be related to liso-cel treatment. During the treatment-emergent period, solid tumours were reported in 3 subjects in Study 017001. Malignancies, that were reported in 1 subject each, included cutaneous BCC, endometrial adenocarcinoma, and cutaneous SCC *in situ* (Bowen's disease). During the posttreatment-emergent period, 10 subjects in Study 017001 developed additional solid tumours, including 5 subjects with BCC, 4 subjects with cutaneous SCC, 1 subject with SCC of the

lung, 1 subject with papillary urothelial carcinoma of the bladder, and 1 subject with neoplasm of the appendix. Of note, 1 subject in Study 017001 had multiple SPMs reported (MDS, cutaneous BCC, and cutaneous SCC). One subject in Study BCM-001 Cohort 1 was diagnosed with lung adenocarcinoma during the posttreatment-emergent period. For cutaneous SPM, with a cumulative incidence of 1.6% to 1.9% and a follow-up adjusted incidence rate of 1.3 to 1.7 events/100 patient-years, these rates are in line with those expected for heavily pretreated patients with underlying haematologic malignancies *(Leisenring, 2006, Omland, 2016*).

Three new subjects had Grade ≥ 3 infections during the additional follow-up time in BCM-001 Cohort 1.

For the **long-term follow up Study GC-LTFU-001**, at the safety update (19 Jun 2020), the first 4 subjects from Study BCM-001 and additional 39 subjects from Study 017001 were enrolled, thus increasing the total number of subjects of Study 017001 to 68. Only 3 (4.3%) subjects reported AEs (2 subjects, 2.9% with at least 1 Grade 3 or 4 AE, and 1 subject, 1.4% with an SAE).

Justification of Recommended Dose Range: safety aspects

The proposed Breyanzi(liso cel; JCAR017) dose for the indication sought is as follows: "*The target dose is 100 × 10^6 CAR+ viable T cells (consisting of a target 1:1 ratio of CD8+ and CD4+ cell components) within a range of 44 to 120 × 10^6 CAR+ viable T cells*".

The applicant recommends a dose range of 44 to 120 × 10^6 CAR+ T cells to reflect the clinical experience at assigned DL1 and DL2. In each DL, the actual administered dose of liso-cel varied within a range (Table 107).

Table 107. Assigned Dose Level and Administered Dose in Studies 017001 and BCM-001

Study	Assigned Dose Level (CAR+ T Cells)	Administered Dose (range) (CAR+ T Cells)	Number of Liso-cel-treated Subjects
017001	Dose Level 1[a] (50×10^6)	$44 - 104^b \times 10^6$	51
	Dose Level 2 (100×10^6)	$45 - 120 \times 10^6$	178
	Dose Level 3 (150×10^6)	$87 - 156 \times 10^6$	41[c]
BCM-001 Cohort 1	Dose Level 2 (100×10^6)	$71 - 103 \times 10^6$	36

CAR+ = chimeric antigen receptor positive.
[a] Includes 6 subjects assigned to receive Dose Level 1, double dose (DL1D).

Therefore, SmPC Section 4.8 includes the Modified Pooled 3L+ DLBCL Treated Set (n= 314) comprising the 4 studies in the proposed indication, Study 017001 (n= 229), BCM-001 Cohort 1 (n= 36) and Cohort 3 (n= 10), 017007 (n= 17) and the monotherapy phase of BCM-002 (n= 22), for subjects who received an administered dose of 44 to 120 × 10^6 CAR+ viable T cells (assigned DL1+DL2). Four subjects assigned to DL1 in Study BCM-002, who received fewer than 44 × 10^6 CAR+ viable T cells, are excluded from this data set. Studies BCM-001 and 017007 evaluated only DL2 and no subjects in these 2 studies received doses outside the range of 44 to 120 × 10^6 CAR+ viable T cells. **The data cut-off dates used are 04 Jan 2021 for 017001 and BCM-001 and 01 Aug 2019 for 017007 and BCM-002**. Consistent with this representation, the applicant recommends the data in SmPC Sections 5.1 and 4.8 reflecting the entire clinical experience of CD4+:CD8+ cell components ratios (ratio range 0.7 to 2.2) that were administered in the recommended dose range of 44 to 120 × 10^6 CAR+ T cells. However, in the post marketing setting, the applicant will recommend a CD4+:CD8+ cell components ratio equal to 1:1 with a range of 0.8 to 1.2, to minimise variance in clinical outcomes and standardise the contribution of each cell component. The ratio range of 0.8 to 1.2 represents the ratio range administered to > 90% of DL1+DL2 subjects and is associated with similar safety outcomes at DL1+DL2 when compared with the entire clinical experience of CD4+:CD8+ cell components ratios (ratio range of 0.7 to 2.2).

At the cut-off dates mentioned the most common adverse reactions in the Modified Pooled 3L+DLBCL Treated Set (n= 314) of any grade were neutropenia (67%), anaemia (48%), CRS (39%), fatigue (38%),

and thrombocytopenia (37%). The most common serious adverse reactions were CRS (17%), encephalopathy (11%), infection with an unspecified pathogen (6%), neutropenia (4%), thrombocytopenia (4%), aphasia (4%), pyrexia (4%), bacterial infectious disorders (4%), delirium (4%), tremor (4%), febrile neutropenia (3%), and hypotension (3%). The most common Grade 3 or higher adverse reactions included neutropenia (63%), anaemia (35%), thrombocytopenia (29%), leukopenia (21%), infection with an unspecified pathogen (9%) and febrile neutropenia (8%).

2.6.9. Discussion on clinical safety

Subjects in Studies 017001, 017007, and BCM-002 were all from the US, while subjects in BCM-001 Cohorts 1+3 were from Europe (n= 27, Cohort 1; n= 36 at the second cut-off date) and Japan (n= 10, Cohort 3). Overall, the EU population was represented only in a percentage equal to 7.7%. The characteristics of the treated population in the Pooled 3L+ DLBCL Set were representative of the 3L+ large B-cell lymphoma population and were consistent with a heavily treated, poor prognosis population, although a higher percentage of subjects received anticancer therapy for disease control before starting JCAR017 in Study BCM-001 (Cohort 1) compared to Study 017001 (77.8% versus 59.1%). Data from study BCM-001 are considered of particular relevance for EU patients, since subjects are treated with the same manufacturing process that is proposed for commercial use in the EU. On the other hand, the limited sample size, the reduced follow-up and the significant differences in baseline characteristics could represent a concern for the evaluation of the safety profile of this product. The updated safety data and in particular the updated Bridging Analysis Report, referred to by the applicant, provided a comparative analysis of safety parameters, including adverse events (AEs), AESIs, AEs related to liso-cel treatment, and Grade ≥ 3 AEs during the treatment-emergent and post-treatment-emergent periods using the D120 data cut-off date (19 Jun 2020) for Studies BCM-001 and 017001. Of note, at the time of the D120 Bridging Analysis, with additional follow-up time (at least 6 months for all treated subjects in both studies) and with additional subjects enrolled in Study BCM-001 (n= 36 in Cohort 1), the subjects' baseline characteristics became more similar between the two studies. Overall, subjects had similar numbers of prior treatments (≥ 3 prior lines of therapy: 47.2% versus 51.4%, respectively), and similar tumour burden (≥ 500 U/L LDH at pre-LDC visit: 19.4% versus 21.5%, respectively). However, still more subjects in Study BCM-001 were less fit (ECOG PS 2; 8.3% versus 0%) and had received anticancer therapy for disease control when compared with subjects in Study 017001 (75.0% versus 47.7%, respectively). Overall, the incidence of AEs and AESIs in the treatment-emergent (Day 1 to Day 90) and post-treatment emergent (Day 91 to end of Study) periods was generally similar. Grade ≥ 3 liso-cel-related TEAEs were higher in Study BCM-001 compared with Study 017001 (61.1% versus 35.5%, respectively), mainly driven by higher incidences of neutropenia, anaemia and febrile neutropenia. No notable difference in the incidence of individual AESIs between the 2 studies was reported. In the total Pooled 3L+ DLBCL Set, the median age was 63.0 years. Subjects in Study BCM-001 tended to be younger, with more subjects being < 65 years (70.3% as of 13 Sep 2019; 61.1% as of 19 Jun 2020) when compared to the Pooled 3L+ DLBCL Set (56.7%). Therefore, the poor representation of the older European population in Study BCM-001 (n=0 ≥ 75 years), and, more generally, in the context of the total Pooled 3L+ DLBCL Set could represent a concern for the evaluation of the safety profile of this product for the older population. In summary, despite the poor representation of the older population (n=38/359, 10.6% ≥ 75 years old), the proportions of TEAE types observed in subjects ≥ 75 years old were generally similar to those observed in subjects < 65 years old. No pattern of unexpected events or safety signals was observed in the eldest subjects. For all of the specified adverse event (AE) categories, there was no clinically meaningful increase in frequency with increasing age. No clear differences (i.e., ≥ 20% absolute difference) were noted between any of the 3 age subgroups for any of the requested AE categories, or for any other system organ classes (SOCs) or individual preferred terms (PTs). An exception was the SOC of nervous system disorders with a numerical difference (> 10% but < 20%) in

subjects aged 65 to < 75 years (56.3%) compared with those aged 75 to < 85 years (73.0%) and the SOC of vascular disorders, with a numerical difference in subjects aged < 65 years (30.7%) compared with those aged 75 to < 85 years (43.2%). The applicant has included safety in patients ≥ 75 years of age as missing information in the RMP and additional information on the safety of liso-cel in elderly patients will be provided in the post-authorisation safety study (JCAR017-BCM-005).

Most subjects (76.2%) were refractory to their most recent prior treatment and over a third of subjects (34.4%) had received prior HSCT, including 9 subjects (2.6%) having received prior allogeneic stem cell transplantation. Approximately one-third of subjects had at least one measure of high disease burden as defined by SPD ≥ 50 cm2 (33.0%) or LDH ≥ 500 U/L (22.3%), and half (50.6%) of subjects had high baseline inflammatory state as defined by elevated CRP (≥ 20 mg/L) at baseline. Creatinine clearance (CrCl) between 25 and 60 mL/min were present in 19% of patients and 4.8% had screening left ventricular ejection fraction (LVEF) < 50% but ≥ 40%. The lymphodepleting chemotherapy regimens were received by 88.8% of patients, in addition to bridging chemotherapy in 60.2% of patients. Due to the lack of a washout period, toxicities associated with these cytotoxic treatments can carry over into the post-infusion portion of the study. Consequently, the determination of whether a relationship exists between a given AE and JCAR017 infusion can be confounded by this carry-over effect. On this point, with the exception of higher rates of all grade and Grade ≥ 3 anaemia and thrombocytopenia, there were no significant differences in the safety profile between subjects who received intensive bridging therapy, followed by the protocol-specified dose of LDC, and those who did not in the combined 017001 DLBCL Cohort and BCM-001 Cohort 1 liso-cel-treated population. These data also confirmed the potential effects of LDC and/or bridging chemotherapy on the exhaustion of the bone marrow reserve.

Relapses occur often in the setting of tumour cell loss of target antigen expression. Tumours without antigen expression might elicit lower stimulation and expansion of CAR-T and consequently less toxicity. On the other hand, high antigen expression, in combination with high tumour burden, might result in high toxicity. From the data available, CD19 expression levels did not seem to impact the liso-cel safety profile. CD19 loss after treatment with liso-cel seems not identified as a clear escape mechanism to liso-cel. In detail, of the 3 subjects with available CD19 H-scores at both baseline and progressive disease, 1 subject had a decrease in CD19 H-score at progression and 2 subjects had an increase in CD19 H-score at progression. Finally, although tumour burden was associated with higher incidence of CRS and iiNT, CD19 H-score did not correlate with tumour burden as assessed by LDH and SPD. The long-term follow-up study GC-LTFU-001 should allow for the collection of information on the occurrences of loss of target antigen in cases of relapses.

All but 5 subjects (98.6%) had an ECOG performance status of 0 or 1 at Screening. The relatively small number of subjects who had an ECOG performance status 2 is not sufficient for a meaningful comparison with the population with an ECOG status 0-1 at this time (see also efficacy section).

The median administered dose of JCAR017 in the Pooled 3L+ DLBCL Set (n= 349) was 90.8×10^6 CAR+ viable T cells (range, 37×10^6 to 203×10^6). It should be noted that, while the subjects received the expected doses based on the release criteria at the time in a tight range, the administered doses represented a range of doses within each assigned dose regimen. In addition, in Study 017001, the median CD4+:CD8+ cell components ratio showed a wider range than the range reported in Study BCM-001, which could influence the safety profile in patients receiving a product in which the median CD4+:CD8+ cell components ratio is not 1:1 but where one cell component prevails over another. However, logistic regression analysis, performed to evaluate the relationship between CD4+:CD8+ cell components ratio and the probability of CRS and iiNT, indicated that there was no clear relationship between CD4+:CD8+ cell components ratio and the incidence of these AESIs. In both 017001 DLBCL JCAR017-treated dataset and dataset corresponding to DL2S, the cumulative incidence of AESIs reached 40-50 percent by three months followed by plateau, regardless of CD4+:CD8+ cell components ratio (in both 0.8-1.2 and > 1.2 CD4+:CD8+ cell components ratio groups). iiNT cumulative incidence reached

approximatively 30% by 3 months followed by a plateau. Hypogammaglobulinaemia reached approximatively 20% by 3 months and it appeared that cases occurred throughout the 360 days of follow-up, particularly for 0.8-1.2 CD4+:CD8+ group. Similarly, for anaemia, neutropenia, and thrombocytopenia, the cumulative incidence reached a plateau at 3 months. For Grade 3 and above infections, although the cumulative incidence was higher in the first 3 months, a plateau was not reached for 0.8-1.2 CD4+:CD8+ cell components ratio at this timepoint. Grade 3 and above infections continued to accrue after the first 3 months in 0.8-1.2 CD4+:CD8+ cell components ratio group and hypogammaglobulinaemia followed a similar pattern as Grade 3 and above infections. Notably, the cumulative incidence for SPM continued to increase throughout the 360 days of follow-up for the subgroup of patients with CD4+:CD8+ cell components ratio > 1.2, although the numbers of patients at risk were low.

In the PASS JCAR017-BCM-005, as primary safety endpoints, secondary malignancies and infections will be evaluated in patients treated with commercially available liso-cel from the Center for International Blood and Marrow Transplant Research (CIBMTR) and from the European Society for Blood and Marrow Transplantation (EBMT) registries. Aetiology of the infection will be recorded (using SOCs and PTs,), and a small proportion of the infections is expected to remain unspecified or unknown. Post-marketing cumulative data will be reported (in PSURs) by high-level group terms (aetiology groups) and separately for opportunistic infections, as available. Although only serious infections (requiring treatment) will be reported, this is considered acceptable.

A numerically higher incidence of all-grade CRS, all-grade iiNT, and Grade ≥ 3 infection was observed at assigned DL3S (150 x 10^6 CAR+ T cells) when compared with lower assigned DLs (017001 CSR); this is consistent with the results from a retrospective logistic regression modelling (017001 DOVER). Data in SmPC Sections 5.1 and 4.8 reflects the entire clinical experience of CD4+:CD8+ cell components ratios (ratio range 0.7 to 2.2) that were administered in the recommended dose range of 44 to 120 × 10^6 CAR+ T cells. However, in the post marketing setting, a CD4+:CD8+ cell components ratio equal to 1:1 with a range of 0.8 to 1.2 will be recommend, to minimise variance in clinical outcomes and standardise the contribution of each cell component. Because of manufacturing controls, it is anticipated that the majority of patients treated with liso-cel in the post-marketing setting will receive a CD4+:CD8+ cell components ratio of 1:1 (range 0.8-1.2). In rare cases, it may be possible that some patients will receive product outside of this ratio range, such as patients who receive out-of-specification lots with respect to the target CD4+:CD8+ cell components ratio. Therefore, the applicant is recommended to collect data on the numbers of effectively administered CD4+, CD8+ and CD4+:CD8+ cell components ratio in the JCAR017-BCM-005 study.

Based on data as of 19 Jun 2020, with additional follow-up increased from 9.17 to 10.74 months for the Pooled 3L+ DLBCL Set and from 2.40 to 6.36 months for the Study BCM-001 Cohort 1, no clinically important changes in the type, frequency, or severity of any AEs were observed, and no new safety concerns were identified. No clear difference was noted in on-study AE rates during the treatment-emergent period (90 days) and posttreatment-emergent period (2 years) when adjusted for longer duration of follow-up.

Within the observed AEs, some can be directly linked to the conditioning chemotherapy (cytopenias), and other AEs are directly linked to the administration of Breyanzi. The AEs described here are in line with the AEs of CAR T cell products and are a direct consequence of the mode of action of this product. No additional concerns can be identified which would be specific for Breyanzi or for the indication to be treated with Breyanzi. No apparent differences in safety outcomes were observed between Studies BCM-001, BCM-002, 017007 and 017001. For some less common large B-cell lymphoma subtypes, including R/R FL3B and R/R PMBCL, as well as for other clinically relevant subgroups (ECOG PS ≥ 2, secondary CNS lymphoma, DLBCL post-allo HSCT) the evidence is limited due to the small number of patients included. However, overall, the observed JCAR017 safety seems to be consistent across all subgroups.

No clear differences were noted in the frequencies or types of TEAEs in the subset of subjects treated with DL2S v4 compared with those for the total 017001 DLBCL Treated Set, although TEAEs were reported most frequently in the SOC of General Disorders and Administration Site Conditions (78.6%) rather than Blood and Lymphatic System Disorders (75.4%) in subjects treated with DL2S v4.

It should be noted that, in Study BCM-001 Cohort 1, Grade ≥ 3 TEAEs in the Blood and Lymphatic System Disorders SOC were observed in a higher percentage of subjects compared with the Pooled 3L+DLBCL Set (92.6% versus 74.5%), probably related to the higher percentage of subjects receiving anticancer therapy for disease control in Study BCM-001 Cohort 1 compared to Study 017001 (77.8% versus 59.1%).

Of note, during the **post-treatment-emergent period**, in Study BCM-002, the percentages of subjects with AEs in the post-treatment-emergent period (21 out of 22 subjects, 95.5%) were generally higher compared with the Pooled 3L+ DLBCL Set (45.4%) but, considering the small number of enrolled patients, as the post-treatment-emergent AEs in Study BCM-002 occurred in the setting of combination therapy, it is hard to find a relationship of these AEs with the only JCAR017.

Of note, in the Pooled 3L+ DLBCL Set and concerning **treatment-emergent SAEs**, the majority of subjects in Study 017007 were monitored as outpatients following JCAR017 administration, whereas all (Study BCM-001) or almost all (Study 017001) subjects were monitored as inpatients in the other trials. This could suggest a concern for the use of JCAR017 in the outpatients setting. The data provided by the applicant indicated that the majority of treatment-emergent SAEs of CRS and tremor were low grade, suggesting that required admission to hospital (thereby becoming a SAE) was implemented, in part, to facilitate careful observation. Therefore, hospitalisation was the defining event of these SAEs, rather than the nature of the AE itself. It has also been clarified that there was no under-reporting of longer-term AEs, as the long-term surveillance schedule and AE reporting requirements in Study 017007 were the same as in Study 017001, and were identical for subjects monitored in the inpatient and outpatient setting.

Of the 269 subjects in the 017001 DLBCL Treated Set, 33 subjects (12.3%) were admitted to the **ICU** at any time during the study; the median number of ICU days was 8.0 (range 1 to 56 days). The applicant provided more information about the AEs that led to ICU admission in the inpatient setting and in the outpatient setting. Of note, only Study 017001 permitted outpatient monitoring following infusion on Day 1 to Day 29 at the discretion of the treating physician, and twenty-five subjects from the 017001 DLBCL Treated Set were monitored as outpatients. As of the 19 Jun 2020 data cut-off date, out of 38 third-line or later (3L+) diffuse large B-cell lymphoma (DLBCL) subjects with intensive care unit (ICU) admissions from studies 017001 and BCM-001, 37 subjects were monitored as inpatients (33 patients from Study 017001 and 4 patients from Study BCM-001) and 1 subject (from Study 017001) was monitored as an outpatient following liso-cel infusion. Reasons for ICU admission were most often due to CRS (CRS; 10 subjects) and/or neurological AEs (11 subjects); 4 patients had infection, and 4 subjects had hypotension. The only (1) outpatient subject admitted to the ICU had CRS.

Overall, the proportions of liso-cel-treated subjects in the Pooled 3L+ DLBCL Set who have died across the 3 regions of the US, Europe, and Japan were similar. The primary cause of death category for most subjects with adverse events (AEs) ongoing at the time of death was lymphoma disease progression.

Based on the totality of JCAR017 safety observations to date and the safety profiles recognised within the class of CD19-directed CAR T-cell therapeutics, the following **AESIs** were identified:

Cytokine Release Syndrome (CRS)

Across the pooled dataset, a total of 145 of 349 subjects (41.5%) experienced CRS of any grade and very few of these events were Grade ≥ 3 (8 out of 349 subjects; 2.3%). The onset of CRS was generally within the first week of JCAR017 treatment (median time to onset 5.0 days [range 1 to 14 days] and the median

time to resolution was 5.0 days [range 1 to 17 days]. The 3 most frequently occurring symptoms of CRS in the Pooled 3L+ DLBCL Set were pyrexia (93.1%), hypotension (44.1%), and tachycardia (35.9%). There were no Grade 5 CRS symptoms. These results were similar to those observed in the other datasets included in the safety analysis. In the Pooled 3L+ DLBCL Set, 19.8% subjects received tocilizumab and/or corticosteroids and 11.2% received tocilizumab only, with a median time from onset of CRS to first administration of tocilizumab of 1.5 days and a median number of doses of 1 (range 1 to 4 doses), most frequently for Grade 2 CRS. At the Day 120 Safety dataset, a total of 148 out of 359 subjects (41.2%) experienced CRS of any grade and 8 out of 359 subjects (2.2%) were with Grade ≥ 3.

Neurologic Toxicities

Serious neurologic events, including cerebral oedema and seizures, observed in clinical studies' subjects treated with Breyanzi, have been generally manageable and reversible with supportive care measures, corticosteroids, and, in the setting of CRS, with tocilizumab.

Because some concomitant medications (e.g., tocilizumab and/or corticosteroids) were given for both CRS and iiNT, the number of subjects receiving tocilizumab or corticosteroids for a concurrent CRS event has be specified and the relevance of tocilizumab use in case of NT has be discussed. Tocilizumab use in subjects with iiNT and concurrent CRS in the liso-cel studies was consistent with the protocol-specified guidance regarding the treatment and management of NT and CRS. It was also consistent with the literature (*Neelapu, 2019; Rivera, 2020; Santomasso, 2019)* and the recommendations in the product label for one of the approved chimeric antigen receptor (CAR) T-cell therapeutics (*Yescarta® Summary of Product Characteristics).* For subjects with NT, tocilizumab is recommended only in the setting of concurrent CRS or macrophage activation system (MAS)/haemophagocytic lymphohistiocytosis (HLH). Exploratory analyses of the potential impact of tocilizumab and corticosteroid use on Breyanzi activity seem not to show differences between the group of subjects that received treatment and the group that did not. However, the results from the planned study analysis showed that subjects who experienced higher grade CRS or iiNT were more likely to be treated and treated earlier than subjects who experienced lower grade CRS or iiNT. This is an expected result based on the protocol treatment algorithm. Of the 26 subjects with maximum Grade 1 iiNT, 5 patients were treated with corticosteroid for iiNT. None of these Grade 1 events occurred early (< 72 hours) but all 5 subjects experienced aphasia with/without encephalopathy, which are considered to be hallmarks of CAR T-cell-associated NT. Furthermore, prior to or concurrent with iiNT, all 5 subjects experienced CRS, for which they received tocilizumab, and 2 received corticosteroids for treating CRS. For this reason, the recommendation for early intervention with corticosteroids and/or tocilizumab for CRS and iiNT, at the discretion of the prescriber, to prevent the development of severe events can be approvable.

In the Pooled 3L+ DLBCL Set, the incidence of TEAEs from the ND/PD SOC was 248 out of 349 subjects (71.1%). The 3 most frequent NESI categories were headache (95 out of 349 subjects; 27.2%); encephalopathy (91 out of 349 subjects; 26.1%); and dizziness (72 out of 349 subjects; 20.6%).

In order to explore whether there were biologic correlations differentiating subjects with iiNT events versus subjects with ND/PD SOC events that were "not iiNT" and versus subjects with "no ND/PD SOC", PK parameters and inflammatory biomarkers were compared. Subjects with all-grade iiNT had higher JCAR017 median maximum observed concentration (Cmax) and area under the concentration-time curve through 28 days after the first infusion (AUC0-28) than subjects with "not iiNT". Similar to PK, the median values of CRP at baseline were significantly higher for subjects with iiNT as compared with those with "not iiNT" and "no ND/PD SOC" events (p= 0.0027 and p= 0.0001, respectively). No statistical difference was observed in the CRP median baseline between subjects with "not iiNT" events and those with "no ND/PD SOC events", although the CRP peak median was 1.80-fold greater in "not

iiNT" than "no ND/PD SOC" (p = 0.0283). These results suggest that differences in baseline and post-JCAR017 biology might influence the occurrence of a neurological event in "iiNT" subjects but did not explain the occurrence of a neurological event in "not iiNT" subjects, who also had ND/PD SOC events not identified as iiNT. Of note, impairment of the central nervous system function is also part of CRS. Therefore, there may be some overlap of CNS impairment following CRS and CNS impairment for other causes. Evidence have been provided that "non-iiNT" events were distinct from CAR T cell-associated neurotoxicity and were not explained by CAR T cell expansion and inflammatory biomarkers. The majority of "non-iiNT" events were low grade and were all suspected by the Investigator to be due to aetiologies other than iiNT, such as disease progression, other documented CNS pathology, orthostatic hypotension, infection or concomitant medication (e.g., fludarabine). Finally, the most frequent symptoms were those considered to be nonspecific for CAR T-cell-associated neurotoxicity (i.e., NESI categories of headache, dizziness, insomnia, and anxiety). In conclusion, the iiNT method used in the liso-cel clinical trials can be considered an accurate reflection of CAR T-cell-associated neurotoxicity in these patients. Seizures and cerebral oedema have also occurred in patients treated with JCAR017. A single event of Grade 2 cerebral oedema confined to the right temporal lobe was reported in a subject who was later determined to have DLBCL involvement of the CNS. At the moment, a potential role of Breyanzi in the cerebral oedema in this patient cannot be ruled out. It is acknowledged that the potential for cerebral oedema warrants representation in product labels of all approved CAR T-cell agents and has been included in the SmPC in the relevant sections. Seven out of 269 subjects in Study 017001 had secondary CNS involvement by lymphoma at the time of JCAR017 treatment. Two of the 7 subjects with secondary CNS involvement (28.6%) had iiNT, representing a similar incidence to that among subjects without secondary CNS involvement (29.8%). Reference in the SmPC in section 5.1 and 4.4 is supported.

Prolonged Cytopenias

Cytopenias are not unexpected in this clinical setting. This was observed in Study 017001 as well as in Study BCM-001, despite some variation (e.g., in Study BCM-001 the prevalence of Grade 3 or 4 thrombocytopenia at Day 365 (25.0%) was higher than in Study 017001 (16.7% at Day 270; 0% at Day 365). This may be explained in part by a small number of subjects in Study 017001 who had samples collected compared to sample collection from all active subjects in Study BCM-001 through Day 365 visit.

Finally, no clinically meaningful differences (≥20%) were observed in the baseline characteristics (including prior HSCT) of subjects with prolonged cytopenia compared with subjects without prolonged cytopenia and subjects in the overall population. There were no clinically meaningful differences in the incidence and severity of CRS, or in treatments administered for CRS. No clinically meaningful differences were noted between resolution of prolonged cytopenia and exposure to lymphodepleting chemotherapy, liso-cel, or treatment for CRS with tocilizumab or corticosteroids.

Infections

Grade 5 infections were reported in 8 subjects and included progressive multifocal leukoencephalopathy (PML; 2 subjects), septic shock (2 subjects), candida sepsis, pneumonia, sepsis, and staphylococcal sepsis (1 subject each). The results of the subgroup analyses of infections any time after liso-cel infusion are consistent with the fact that i) prior to receiving liso-cel, most subjects in the Pooled 3L+ DLBCL Set had at least 1 risk factor for infection, including laboratory-based hypogammaglobulinaemia; ii) hypogammaglobulinaemia (designated as an AE) appeared to more accurately predict the risk of infection than did IgG levels; iii) the IgG level after infusion was not a clinically meaningful way to identify subjects at risk of infection, as exemplified by the similar proportions of subjects with infections independent of IgG level (44.7% and 43.7% with Ig G level < 500 mg/dL and ≥ 500 mg/dL, respectively) and the greater proportion of subjects with Grade 5

infections in the IgG ≥ 500 mg/dL subgroup. Finally, of 359 subjects in the Pooled 3L+ DLBCL Set, 15 (4.2%) subjects were identified as having opportunistic infections and the most frequently reported opportunistic infection was cytomegalovirus infection (6 subjects), followed by candida sepsis, bronchopulmonary aspergillosis, and PML (in 2 subjects). One event of candida sepsis and both PML events were fatal. The SmPC has been updated accordingly to the presented data.

Regarding patients with HCV or hepatitis B, a total of 12 out of 359 (3.3%) subjects (11 in Study 017001 and 1 in Study 017007) had pre-infusion hepatitis B in the Pooled 3L+ DLBCL Treated Set (ten hepatitis B subjects received antiviral suppressive therapy with lamivudine or entecavir and 1 subject had latent hepatitis B without antiviral suppression in Study 017001). A total of 2 subjects had a history of hepatitis C with no active infection at the time of liso-cel administration in Study 017001, and none were associated with reports of hepatitis C infection following infusion. Based on these findings, the BCM-001 study protocol was recently amended to allow enrolment of subjects who are PCR-negative for HBV and HCV viral load. These data suggest that, with patient selection and careful management, patients with a history of hepatitis B or hepatitis C, but not currently active, can be safely treated for 3L+ DLBCL without hepatitis reactivation, in line with recent published data (*Rui Cui et al, Hematol Oncol 2021*). However, the applicant also clarified that the contract manufacturing facility at Cellex (Germany) is not currently accepting leukapheresis material from patients testing positive for HBV or HVC indicating active infection or from patients testing positive for HIV. This statement is now reported in sections 4.4 and 4.2 of the SmPC.

B-cell aplasia

B-cell aplasia was evident at baseline in 92% of subjects (241 out of 262) of the 017001 DLBCL Treated Set. Consistent with transgene persistence, B-cell aplasia was observed in 98% of subjects (240 out of 244) on Day 29, 93% of subjects (153 out of 165) on Day 90, 86% of subjects (100 out of 116) on Day 180, and 73% of subjects (51 out of 70) on Day 365. Similarly, subjects in Study BCM-001 (Cohort 1) exhibited a high rate of B-cell aplasia ranging from 100% on Day 29 (n= 23) and Day 90 (n= 10), 86% (6 out of 7 subjects) on Day 180, and 75% (3 out of 4 subjects) on Day 270. Data are limited after Day 90 due to the median on-study follow-up time of 3.02 months in this analysis. However, given the similar effects of rituximab on B cells and the widespread use of rituximab in DLBCL, the role of B cell aplasia as a marker of persistence of CD19-directed CAR T cell therapy in DLBCL is less certain. B-cell aplasia can be adequately managed by immunoglobulin replacement therapy (*Maude et al 2014*).

EGFRt switch-off system

Specific hypothetical clinical conditions where the use of this switch-off system would be possible are: i) potential clonal T-cell proliferation derived from liso-cel (EGFRt positive [EGFRt+] autonomous T-cell growth); ii) hypothetical tumour cell transduction and amplification giving rise to an EGFRt expressing malignancy; iii) autoimmune reactions related to liso-cel; iv) B-cell aplasia and symptomatic hypogammaglobulinaemia with recurrent infections (on-target off-tumour adverse events) despite adequate supportive therapy. Finally, EGFRt-mediated CAR T-cell ablation could hypothetically be used to treat novel and yet unknown CAR T-cell-mediated adverse effects. Based on current thinking and state of knowledge, the proposed EGFRt-mediated CAR T-cell ablation is only intended for exceptional use (i.e., in life-threatening conditions or chronic toxicities that are not manageable by standard therapies and following individual benefit/risk evaluations, including the risks associated with cetuximab, panitumumab, or necitumumab). Further data on such exceptional use could become available from ongoing clinical trials in case the protocols allow this option for investigators accordingly. In addition, the applicant clarifies that this is unlikely to be used in subjects with a complete response duration of less than 2 years.

About the absence of the expected impact of treatment with tyrosine kinase inhibitors on non-functional EGFRt+ in liso-cel, while only the extracellular domain of the EGFRt (and not the signaling intracellular domain) is expressed on liso-cel cells surface, small molecule kinase inhibitors might have non-specific activity on the immune system and, as most antineoplastic agents, they have theoretically a potential to interfere with CAR T-cell activity.

No subject in the Pooled 3L+ DLBCL Set developed **autoimmune disorders**.

During CRS, it is expected that Breyanzi-associated coagulopathy with severe hypofibrinogenaemia is observed. As for other CAR-T products, patients with Grade 4 CRS generally had a lower median fibrinogen level compared with CRS Grade of 1-3 (*Maude SL et al. N Engl J Med 2014;371:1507–17*). In addition, venous thromboembolism developed in 11% of lymphoma patients after CAR T-cell therapy (*Hashmi H et al. Blood Adv 2020;4(17):4086-4090*). At the cut-off date of 19 Jun 2020, of the 359 subjects in the Pooled 3L+ DLBCL Treated Set, 7 subjects (1.9%) reported the TEAE of hypofibrinogenaemia (PT) and 2 subjects (0.6%) reported blood fibrinogen decreased (PT). While the median lowest fibrinogen levels were lower in subjects with Grade 4 cytokine release syndrome (CRS) compared with subjects with Grades 1 to 3 CRS, only a single subject with Grade 4 CRS experienced an adverse event (AE) of hypofibrinogenaemia that was Grade 3 in severity. No subjects with Grade 4 CRS experienced Grade 4 or 5 hypofibrinogenaemia in the Pooled 3L+ DLBCL Set. However, no firm conclusion can be drawn due to the low number of patients with Grade 4 CRS. Few patients received specific treatment for hypofibrinogenaemia and there were no treatment-emergent adverse events (TEAEs) of disseminated intravascular coagulation (DIC) among subjects in the Pooled 3L+ DLBCL Treated Set. The overall incidence of venous thromboembolism (VTE) reported in the Pooled 3L+ DLBCL Treated Set (5.8%) is lower than that previously reported in lymphoma patients receiving CD19-directed CAR T-cell therapy (11%) or in newly diagnosed patients with DLBCL (10% to 13%) and is similar to that reported following ASCT (4%). All 13 subjects with CRS who experienced a treatment-emergent VTE had multiple identified risk factors for VTE, including 5 subjects with a prior medical history of VTE or a pre-existing event of VTE at the time of liso-cel administration. However, none of the liso-cel-treated subjects with VTE and CRS had Grade ≥ 3 CRS, which has previously been reported as potentially associated with VTE following CAR T-cell therapy. All 8 subjects who had treatment-emergent VTE events and did not experience CRS had multiple identified risk factors for VTE, including 5 subjects with a prior medical history of VTE or an ongoing event of VTE at the time of liso-cel administration. Based on updated pooled study data, hypofibrinogenaemia and thrombosis have been added as a common AEs in the SmPC. The applicant will continue to closely monitor and report on additional information on the occurrence of CRS and any associated events (including DVT and PE rates) as collected through ongoing clinical studies and post marketing surveillance.

On the **immunogenicity**, no apparent relationship between pre-existent ATAs (anti therapeutic antibodies) or treatment-induced/boosted ATAs and AESI was observed, but the data are currently very limited.

From the safety analysis of the subgroups, it emerged that:

- No clinically relevant differences were noted between sex, race, or ethnicity subgroups for subjects treated with JCAR017 in the Pooled 3L+ DLBCL Set.
- A numerical increase in the proportion of subjects ≥ 75 years with iiNT compared with those < 75 years of age (36.8% versus 26.4%, respectively) was noted in the Pooled 3L+ DLBCL Set and may reflect the elderly being at increased risk of neurologic AEs, but given the small numbers of elderly subjects, no firm conclusion can be drawn.
- Higher rates of all-grade CRS and/or iiNT were observed in subjects who at baseline had greater tumour burden (higher SPD and/or LDH), greater inflammatory state (higher CRP),

or use of anticancer therapy for disease control prior to LDC. These subjects represent the patient's categories that may be at higher risk of CRS and should be monitored closely. This statement has been reported in the SmPC.

- Similar rates of iiNT were observed among subjects with and without secondary CNS involvement (28.6% and 29.8%, respectively), but given the small numbers of subjects with secondary CNS involvement, no firm conclusion can be drawn at the moment.
- The rates of overall TEAEs and AESIs (CRS and/or iiNT) were similar for subjects with ALC $< 0.3 \times 10^9$/L prior to leukapheresis and those with ALC $\geq 0.3 \times 10^9$/L prior to leukapheresis, with the exception of higher rates of Grade ≥ 3 thrombocytopenia in subjects with ALC $< 0.3 \times 10^9$/L.
- Based on the data submitted, no clear differences were observed in the safety profile of subjects who received prior HSCT (both auto-HSCT and allo-HSCT), versus those who did not. Regarding GVHD, there is a theoretical risk of CAR T cell therapy inducing or aggravating pre-existing GVHD in subjects with prior allo-HSCT. The data provided support this evidence, with the absence of acute GVHD from liso-cel trial and the low incidence of GVHD after liso-cel (only 2 chronic GVHD AEs out of 9 liso-cel treated subjects who had previously undergone prior allo-HSCT). On that basis, subjects with active acute or chronic GVHD were excluded from liso-cel clinical trials, and subjects had to be at least 3 months post allo-HSCT and clinically stable prior to apheresis (as reported in section 4.4 of the SmPC).
- In Study 017001, safety was generally similar in subjects with clinically significant comorbidities of reduced CrCl and reduced cardiac ejection fraction, except for higher rates of Grade ≥ 3 anaemia in subjects with CrCl < 60 mL/min. This is expected because anaemia is an important complication experienced by patients with chronic kidney disease.
- A total of 31 subjects (25 subjects in the 017001 DLBCL Cohort and 6 subjects in Study BCM-001 Cohorts 1 + 3) received a nonconforming product. The overall frequencies of TEAEs, Grade ≥ 3 TEAEs, and AESIs were similar to those treated with JCAR017 in the 017001 DLBCL Treated Set, indicating no apparent relationships between a nonconforming product and the treatment-emergent categories of AEs examined.
- Based on the available data from Study 017001, no significant differences in safety outcomes have been observed across JCAR017 process versions and vector manufacturing sites. The small sample size of subjects who received the product derived from the commercial version of the vector (n=7 in Study BCM-001 Cohort 1) precludes definitive conclusions with respect to the subjects who received the product from vector manufactured as v.1.0. However, preliminary data suggest that there were no clear differences in the rates of AESI among the three different vector subgroups (v1.0, v1.2 and commercial version respectively).

Comparisons of Therapies Approved for 3L+ Large B-cell Lymphoma

With the limits of indirect comparison, safety data from JCAR017, axicabtagene ciloleucel (*Neelapu, 2017*), and tisagenlecleucel (*Schuster, 2019*) reveals that JCAR017 is associated with a numerically lower rate of both all-grade CRS and high-grade (Grade ≥ 3) CRS relative to axicabtagene ciloleucel and tisagenlecleucel. In addition, a numerically lower rate of NT adverse events (particularly events of higher severity) and Grade 5 AEs was observed with JCAR017 compared with axicabtagene ciloleucel. These findings are of interest, especially because they should be considered in the context of the more inclusive Study 017001 subject population. Without a formal comparison across the clinical studies with the approved products for 3L+ large B-cell lymphoma, in the absence of 1) randomised trial

comparisons, or 2) patient-level data from the clinical trials for patient-level meta-analysis accounting for differences in baseline and disease characteristics, study designs, CAR constructs, and follow-up times, no definitive conclusion can be drawn.

2.6.10. Conclusions on the clinical safety

With respect to safety, the toxicity profile of JCAR017 is in line with the known safety of anti-CD19 CAR T-cell products. The important identified risks and the potential risks identified for Breyanzi are similar to those identified for this product class. Adverse events of CRS and NT were generally low-grade and resolved. Importantly, low rate of ≥ Grade 3 CRS occurred in the context of overall use of tocilizumab and/or corticosteroid in less than one-quarter of all patients treated with JCAR017. Despite evidence is limited for some less common large B-cell lymphoma subtypes including R/R FL3B and R/R PMBCL, as well as for other clinically relevant subgroups (ECOG PS ≥2; secondary CNS lymphoma; DLBCL post-allo HSCT) due to the small number of patients included, overall the JCAR017 activity seems to be consistent across these subgroups. Data from study BCM-001 are considered of particular relevance for EU patients, due to the same manufacturing process as proposed for commercial use in the EU. When additional patients have been enrolled in Study BCM-001 (n= 36, Cohort 1), more comparable baseline characteristics have been observed across the pivotal studies. Overall, the incidence of AEs and AESIs in the treatment-emergent (Day 1 to Day 90) and post-treatment emergent (Day 91 to end of Study) periods was generally similar, despite higher Grade ≥ 3 liso-cel-related TEAEs in Study BCM-001 compared with Study 017001, mainly driven by higher incidences of neutropenia, anaemia and febrile neutropenia and no notable difference in the incidence of individual AESIs.

The data presented in the Summary of Product Characteristics (SmPC) reflect the entire clinical experience at the recommended dose range (assigned DL1+DL2). A non-interventional post-authorisation safety study (PASS) based on a registry is planned to assess the safety profile of JCAR017 to treat patients with R/R DLBCL, PMBCL and FL3B lymphoma in the post marketing setting (JCAR017 BCM-005).

The CAT considers the following measures necessary to monitor and investigate in post-marketing settings issues related to safety:

Imposed PASS:

Non-interventional post-authorisation safety study (PASS) JCAR017 BCM-005: In order to further characterise the long-term safety and efficacy of Breyanzi in adult patients with relapsed or refractory DLBCL, PMBCL, FL3B after two or more lines of systemic therapy the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol. Interim reports to be submitted in accordance with the RMP. Final report: Q3-2043

Required studies (Cat 3 in the Pharmacovigilance Plan in the RMP):

Long-term Follow-up Study (Study GC-LTFU-001): Long-term follow-up of safety and efficacy for all paediatric and adult subjects exposed to the product clinical trials. A 15 years follow-up is included for these patients.

Transgene assay service testing of secondary malignancies with insertion site analysis: In Study GC-LTFU-001, testing for liso-cel transgene will be conducted on all secondary malignancies where tissue is available. A structured secondary malignancy CRF will be employed to characterise all new malignancy reports by dates of liso-cel treatment and new malignancy onset, time to onset, stage, history of prior malignancies, previous cancer therapies, prior radiotherapy, other relevant exposures,

family history, and biopsy report. Treatments for the secondary malignancy and clinical outcomes will also be collected. Transgene testing will be conducted for all reported secondary malignancies of suspected T cell origin where a tissue sample is available.

Although reasons for pre-infusion treatment failure will not be collected as part of the imposed PASS, since registries only collect data on patients who receive JCAR017, data collected in the applicant's manufacturing database will be provided post-approval to further investigate the reasons for early treatment failures. The applicant committed to provide all available information on the rate and reasons for Breyanzi manufacturing failures that occur in the post-approval setting in the periodic safety update reports (PSURs).

In addition, the CAT recommended the following point for consideration:

- The applicant is recommended to collect data on the numbers of effectively administered CD4+, CD8+ and CD4+:CD8+ cell components ratio in the JCAR017-BCM-005 study.

The CHMP endorses the CAT conclusion on clinical safety as described above.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	Cytokine release syndrome
	Neurologic toxicity
	Infections
	Hypogammaglobulinaemia
	Macrophage activation syndrome/haemophagocytic lymphohistiocytosis
	Tumour lysis syndrome
	Cytopenia, including bone marrow failure
Important potential risks	Autoimmune disorders
	Aggravation of graft versus host disease
	Secondary malignancies/insertional oncogenesis
	Cerebral oedema
	Generation of replication competent lentivirus
	Immunogenicity
	Transmission of infectious agents
	Reduced viability of liso-cel due to inappropriate product handling
Missing information	Impact on pregnancy and lactation
	Long-term safety
	Safety in patients < 18 years old
	Safety in patients ≥ 75 years

2.7.2. Pharmacovigilance plan

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
PASS (JCAR017-BCM-005)/Planned	Primary Objective: To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with liso-cel in the postmarketing setting, and to monitor for potential clinically important AEs that have not yet been identified as part of the liso-cel safety profile. Secondary Objectives: To assess long-term effectiveness in patients treated with liso-cel in the postmarketing setting. To assess the liso-cel safety and effectiveness profile in certain subgroups including but not limited to: • By large B-cell lymphoma subtypes (eg, FL3B, PMBCL, DLBCL not otherwise specified, high grade B-cell lymphoma). • According to geographical regions (eg, Europe). • Subjects aged ≥ 75 years. • Subjects with comorbid conditions (eg, renal impairment, reduced cardiac function). • Subjects with secondary CNS involvement. • Subjects with ECOG performance score ≥ 2. • By possible prognostic factors (eg, high-risk IPI). • Subjects previously exposed to anti-CD19 therapy. • Subjects with low pre-leukapheresis absolute lymphocyte count (< 0.3×10^9/L). • Subjects treated with out-of-specification product.	CRS/MAS/HLH NT Infections Hypogammaglobulinaemia TLS Cytopenia, including bone marrow failure Secondary malignancies /insertional oncogenesis Impact on pregnancy and lactation (for pregnancy events) Long-term safety Aggravation of GvHD Cerebral oedema Safety in patients ≥ 75 years	Protocol Submission to EMA	29-Jun-2020
			Start of data collection	Q4 2022
			Safety reports	Safety reports every 6 months (eg, aligned with the reporting period of the PSURs); additional reports every 3 months if a new safety concern is identified
			Interim reports	At Year 5, 10, and 15 or when last patient is out of the registry-based study
			Date of Study Completion	Q3 2042
			Date of Final Study Report Submission to EMA	Q3 2043
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
LTFU study (GC-LTFU-001)/ Planned	Long-term follow-up of safety and efficacy for all paediatric and adult subjects exposed do a GM T cell therapy in Bristol-Myers Squibb sponsored, or Bristol-Myers Squibb alliance partner sponsored, clinical trials in accordance with Health Authorities' guidance for long-term (up to 15 years) follow-up of subjects treated with gene therapy products.	Infections Cytopenia, including bone marrow failure Autoimmune disorders Secondary malignancies/insertional oncogenesis Impact on pregnancy and lactation Long-term safety	Subjects to be followed up for 15 years.	
			Interim reports (5 and 10 years from FSFV [Jul 2018]).	Q3 2023 and Q3 2028
			LSLV	Estimated Q3 2038
			Final database lock	Q3 2038

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
		Safety in patients < 18 years old Generation of replication competent lentivirus	Final report of GC-LTFU-001 follow-up of 3L+ large B-cell lymphoma liso-cel treated subjects	Q3 2039
			Safety data will be reported in PSURs.	Submitted in accordance with the EURD list
Transgene assay service testing of secondary malignancies with insertion site analysis as applicable	Tumour tissue sample testing from patients that develop a secondary malignancy	Secondary malignancies/insertional oncogenesis	Safety data will be reported in PSURs.	Submitted in accordance with the EURD list.
			European Commission decision + 5 years	Q2 2026
			European Commission decision + 10 years	Q2 2031
			European Commission decision + 15 years	Q2 2036

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Cytokine release syndrome	**Routine risk minimisation measures:** SmPC Section 4.2 and 4.4, PL Sections 2 and 3 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire
	Additional risk minimisation measures: • Educational programme for HCPs and patients • Controlled Distribution Programme	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)
Neurologic toxicity	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 and 4.7, PL Sections 2 and 3 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire
	Additional risk minimisation measures: • Educational programme for HCPs and patients • Controlled Distribution Programme	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)
Infections	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001)
Hypogammaglobulinaemia	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)
Macrophage activation syndrome/haemophagocytic lymphohistiocytosis	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management discussed SmPC Section 4.8 - histiocytosis haematophagic listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005), considered as part of the spectrum of CRS.
Tumour lysis syndrome	**Routine risk minimisation measures:** SmPC Section 4.8 and PL Section 4 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)
Cytopenia, including bone marrow failure	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001)
Important Potential Risks		
Autoimmune disorders	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001)
Aggravation of graft versus host disease (GvHD)	**Routine risk minimisation measures:** SmPC Section 4.4, PL Section 2 - warnings, advice and management	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
		None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Included under the category of Other AEs considered related to liso-cel treatment in PASS (JCAR017-BCM-005).
Secondary malignancies/insertional oncogenesis	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable
Cerebral oedema	**Routine risk minimisation measures:** SmPC Section 4.4 - warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire (as part of NT)
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Included under the category of NT considered related to liso-cel treatment in PASS (JCAR017-BCM005).
Generation of replication competent lentivirus	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001).
Immunogenicity	**Routine risk minimisation measures:** SmPC Section 4.2 and PL Section 3 - premedication with paracetamol and diphenhydramine or another H1-antihistamine SmPC Section 4.8 - listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None proposed.
Transmission of infectious agents	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 and 6.6, PL Section 2 and Labelling Section 10 - handling instructions	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Reduced viability of liso-cel due to inappropriate product handling	**Routine risk minimisation measures:** SmPC Sections 4.2, 6.3, 6.4, 6.5 and 6.6, PL Section 5 and Labelling Section 9 - handling instructions	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: • Educational programme for HCPs • Controlled Distribution Programme	**Additional pharmacovigilance activities:** None proposed.
Missing Information		
Impact on pregnancy and lactation	**Routine risk minimisation measures:** SmPC Section 4.6, PL Section 2- warnings and advice	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) for pregnancy events LTFU study (GC-LTFU-001).
Long-term safety	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005) LTFU study (GC-LTFU-001).
Safety in patients < 18 years old	**Routine risk minimisation measures:** SmPC Section 4.2, PL Section 2 - warnings and advice	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001).
Safety in patients ≥ 75 years	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS (JCAR017-BCM-005)

Conclusion

The CAT considers that the risk management plan version 1.0 is acceptable.

The CHMP endorses the CAT conclusion on the RMP as described above.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP and CAT considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 5 February 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Breyanzi (lisocabtagene maraleucel) is included in the additional monitoring list as:

- It contains new active substances which, on 1 January 2011, were not contained in any medicinal product authorised in the EU;
- It has a PASS imposed either at the time of authorisation or afterwards.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

3.1.2. Available therapies and unmet medical need

Most patients with aggressive mature B-cell lymphomas, including DLBCL, PMBCL and FL3B, are able to achieve long-term disease control/cure with frontline immunochemotherapy (e.g., R-CHOP), yet 30% to 40% still experience relapse or are refractory to treatment. The long-accepted standard in this setting was non-cross-resistant salvage immunochemotherapy to (re-)induce remission followed, in younger and fit patients, by high dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT). Approximately 50% of patients who receive ASCT eventually achieve long-lasting disease control. A higher unmet medical need can be recognised, however, for patients who fail salvage chemotherapy or ASCT.

Recently, novel agents have been approved for the treatment of patients with r/r large B-cell lymphomas who have not benefited from standard immunochemotherapy +/- ASCT, namely the anti-CD19 CAR T-cell advanced medicinal products Yescarta (KTE-C19) and Kymriah (CTL019) and the anti-CD79b MMAE-conjugated monoclonal antibody polatuzumab vedotin. Treatment with CARTs, in particular, resulted in long-lasting remissions in up to 30% to 50% of subjects, setting a new efficacy threshold in such advanced setting of disease, although at the cost of a non-negligible toxicity.

3.1.3. Main clinical studies

The pivotal clinical data to support the MAA of Breyanzi (JCAR017) in the target indication mainly come from two open-label uncontrolled studies: Study 017001 and study BCM-001 as described above.

3.2. Favourable effects

Study 017001

At the most recent data cut-off date of 04 Jan 2021, the ITT-set (leukapheresed set) of study 017001 included 298 patients which were treated with the recommended dose rage of 44 - 120 × 106 CAR+ viable T cells, from which 216 were included in the efficacy set with IRC assessment. At this cut-off date, ORR was 60.1% (95%CI 54.3, 65.7) and 72.7 % (95%CI 66.2, 78.5) and CRR was 43.0% (37.3, 48.8) and 53.2% (95%CI 46.4, 60.0) for the leukapheresed and the efficacy set respectively. With a median follow-up for DOR of 23.0 months, median DOR was 16.8 months (95%CI 8.0, NR) in the leukapheresis set and 20.2 months (95%CI 8.2, CR) in the efficacy set. PFS and OS data provided for contextualisation were supportive, with K-M plots showing a plateau phase starting approximately from month 12-18 onwards, suggesting the possibility of long-term disease control in a subset of patients.

Subgroup analyses in study 017001 indicated consistent results across various evaluable subgroups including target lymphoma subtypes. In this regard, particularly favourable results were observed in patients with r/r PMBCL (ORR 79% and CRR 50%), with KM-plots showing a high rate of durable responses. Moreover, all patients with r/r FL3B who received JCAR017 across all studies achieved CR with JCAR017, and all patients were alive in ongoing remission at the last data cut-off date (19 Jun 2020), with one response lasting 23 months.

Study BCM-001

At the most recent data cut-off date of 04 Jan 2021, results from the primary analysis of the EU cohort (Cohort 1) of study BCM-001 (n=36) in infused patients showed an ORR by IRC of 61.1% (95%CI 43.5, 76.9) and a CRR by IRC of 33.3% (95%CI 18.6, 51.0). Results as per Investigator assessment were consistent with the primary analysis, and ORR and CRR by IRC in the ITT set (n=45) were 55.6% (95%CI 43.5, 76.9) and 31.1% (95%CI 18.2, 46.6), respectively.

With a shorter median follow-up compared to study 017001 (i.e. 11.37 months), median DOR in the EU cohort of study BCM-001 was 3.50 months (95%CI 2.20, 11.27; estimated 6-month DOR rate 40.9%).

3.3. Uncertainties and limitations about favourable effects

Study design

- Studies 017001 and BCM-001 were single-arm, open-label, exploratory trials, and the interpretation of time-to-event endpoints in the absence of proper control is difficult and prone to bias, since tumour-related variables such as growth rate cannot be properly accounted for.

Relevance of efficacy analysis datasets

- While the main efficacy analyses focused on the patients who actually received infusion with JCAR017 conforming product, 22-25% of patients who intended to be treated with JCAR017 and were leukapheresed in studies 017001 and BCM-001 did not eventually receive JCAR017, and among those 16 and 6 patients were treated with nonconforming products in studies 017001 and BCM-001, respectively.
- Overall, 58.6% and 75% of patients in studies 017001 and BCM-001 received bridging anticancer therapy after leukapheresis and prior to infusion. The possibility of a direct impact of bridging therapy on tumour microenvironment and CAR T-cell activity cannot be excluded at present. In this regard, subjects who needed bridging therapy for disease control in study 017001 (n=150) fared worse than patients who did not require additional treatments before JCAR017 infusion, with lower ORR and CRR (66.7% 44%, respectively) and shorter DoR, PFS and OS (9.1, 4.6 and 13.3 months, respectively). Nonetheless, durable remissions could still be observed in subjects who needed bridging therapy.
- Long-term efficacy data with JCAR017 are currently limited. Further data will be provided by more mature analyses from the Post-Authorisation Efficacy Studies 017001 and JCAR017-BCM-001.

Differences in clinical outcomes from US study 017001 and EU study BCM-001

- A clinically relevant difference could be observed in the duration of response across JCAR017 studies, with subjects in US study 017001 faring better than EU patients in study BCM-001. The reasons behind the lower response rate and shorter response duration observed in phase II study BCM-001 are not completely understood, although limited numbers do not exclude the possibility of random findings. Post-approval data from the imposed non interventional studies (registry) will provide additional information for patients treated in the EU that will receive commercial product post-approval (expected subjects in the EU subset of PASS study JCAR017-BCM-005 N=200).
- A similar fraction of subjects (~14%) was excluded from trial participation due to screening failure in the two studies. Compared to study BCM-001, however, more subjects in study 017001 (~20%) failed screening procedures due to issues in their ability to comply with study protocol. Although this difference did not result in an enrichment in physically fitter subjects in the US study, as demonstrated by the similar rates of subjects excluded because of ECOG PS score ≥2 at screening in both studies (15.2% vs. 18.2% in study 017001 and BCM-001, respectively) and by the overall consistent patient characteristics in the ITT sets, the possibility of selection bias cannot be completely ruled out.

Additional uncertainties on treatment effect

- Sensitivity efficacy analyses in the ITT population defined by leukapheresed population were conducted and showed inferior efficacy results in both studies, though ORR and CR rate in the study 017001 (n=344 ORR 60.5% [95% CI: 55.1, 65.7] and CRR 43.6% [95% CI: 38.3, 49.0]) were still statistically significantly higher than the prespecified benchmark of 40% and 20%, respectively.

Efficacy in mature B-cell lymphoma subtypes

- The broad indication claimed by the applicant includes PMBCL, yet only 15 patients with PMBCL received JCAR017 in study 017001 and no patient with PMBCL was enrolled in study BCM-001.

- Limited data are currently available in patients with FL3B: across all JCAR017 studies only 8 patients with r/r FL3B received JCAR017: 4 in study 017001, 2 in study BCM-001 and 2 in study BCM-002. Based on a review of histology reports, a diagnosis of "pure" FL3B, as per WHO criteria, could only be confirmed for 4 out of 6 subjects treated in studies 017001 and BCM-001, while a "composite" status could not be excluded for the remaining 2 subjects. A sample size of 4 or 6 subjects is, per se, too limited for specific B/R evaluations, even though promising responses have been observed. Considering the rarity of this condition, limited additional data in FL3B can be expected from ongoing clinical trials and in the post-marketing setting; post-approval data will nonetheless be collected from the CIBMTR and EBMT registries (PASS BCM-005) to further characterise the efficacy and safety of JACR017 in this condition.

- A reduced efficacy was observed in DLBCL arising from indolent NHLs other than tFL (i.e. the tIL subset), which is a heterogenous group of aggressive lymphomas arising from different indolent conditions, including CLL/SLL (i.e. Richter's syndrome, RS) and Waldenstrom macroglobulinaemia (WM). Based on the available data, it is uncertain whether the anti-tumour activity of JCAR017 in RS/tWM, as observed in terms of ORR/CRR, can be translated in prolonged remission, which is the ultimate measure of clinical benefit is such advanced stages of disease. This uncertainty is highlighted in the SmPC, specifying that although durable remissions (i.e. DoR $\geq$12 months) have been observed in subjects with tFL and tMZL, the maximum duration of response in patients with RS and tWM in study 017001 was 2 months and 5 months, respectively. The B/R of JCAR017 in the rarer histologic subgroups cannot be characterised due to the limited sample size.

JCAR017 fixed CD4+:CD8+ cell components ratio and manufacturing process

- The individual contribution of the CD4+ and CD8+ cell components to JCAR017 efficacy is unclear, especially with regard to the clinical relevance of the CD4+ cell component in the anti-tumour activity. In this regard, based on the limited experience with patients treated with non-conforming product consisting of only one cell component, whether differences in baseline patient/disease/immune cells characteristics could have contributed to the failure of one or both cell components is not clear and is recommended to be further investigated, including but not limited to low absolute peripheral blood counts of CD4+ and/or CD8+ T-cell or phenotypic characteristics of these cells. The clinical relevance and potential impact of the defined 1:1 ratio on time-to-event endpoints at longer term are not fully characterised at present. Data on this uncertainty to be collected in the imposed PASS.

- Although the available data support pooling of results across product and LVV manufacturing process versions, clinical data with JCAR017 manufactured using the LVV in its final commercial version (n=7), for the EU patients, are currently limited. Further efficacy/safety data with the intended commercial product and vector version will be provided post-approval from registry study BCM-005 (in which at least 1000 subjects are anticipated to receive the product

manufactured with this LVV) and from ongoing study BCM-001 (with 24 subjects anticipated to receive JCAR017 manufactured with this LVV).

- The evaluation of re-treatment is hampered by the limited available data and no clinically relevant activity has been observed.

JCAR017 activity in relevant subgroups

- Overall, the interpretation of subgroup analyses (e.g. patient with renal and cardiac impairments) is hampered by the relatively limited sample size, especially in the study JCAR017-BCM-001. Efficacy uncertainties in clinically relevant subgroups will be further investigated in the post-approval setting, in LTFU study GC-LTFU-001, in registry PASS BCM-005 as per an agreed protocol, and as recommended, from Study JCAR017-BCM-003.
- Clinical experience with JCAR017 in patients exposed to prior CD19-directed therapy is limited.

3.4. Unfavourable effects

The unfavourable effects for patients treated with Breyanzi do not only occur as a consequence of Breyanzi treatment, but the bridging therapy and conditioning chemotherapy may also induce such effects.

Cytokine release syndrome (CRS)

Across the pooled dataset, a total of 145 out of 349 subjects (41.5%) experienced CRS of any grade and very few of these events were Grade ≥ 3 (8 out of 349 subjects; 2.3%). There were no Grade 5 events attributed to CRS. The median time to onset of CRS was 5 days (range: 1 to 14). As of the first data cut-off date, CRS resolved in 141/145 subjects, with a median duration of 5 days (range: 1 to 17). 19.8% of all the subjects used tocilizumab and/or corticosteroid. At the Day 120 Safety dataset, a total of 148 out of 359 subjects (41.2%) experienced CRS of any grade and 8 out of 359 subjects (2.2%) were with Grade ≥ 3.

Neurologic Toxicity (NT)

Serious neurologic events, including cerebral oedema and seizures, observed in subjects enrolled in clinical studies and treated with Breyanzi, have generally been manageable and reversible with supportive care measures, corticosteroids, and, in the setting of CRS, with tocilizumab. In the Pooled 3L+ DLBCL Set, all-grade iiNT was reported in 96 out of 349 subjects (27.5%). Events were Grade 3 or 4 in 34 out of 349 subjects (9.7%) and were SAEs in 50 out of 349 subjects (14.3%). There were no Grade 5 events attributed to iiNT. The median time to onset of a neurologic event was 8.5 days (range: 1 to 66) and iiNT events generally resolved in less than 2 weeks (median duration: 9 days, range: 1 to 86). Resolution of iiNT occurred within 4 weeks of onset for 87.4% of the subjects in the Pooled 3L+DLBCL Set who had resolution as of the cut-off date. Treatment for iiNT included corticosteroids and/or tocilizumab in 15.5% of subjects, corticosteroids alone in 12.9% of subjects and both corticosteroids and tocilizumab in 2.3% of subjects. These data were similar to those of the Day 120 Safety dataset (any grade iiNT was reported in 99 out of 359 subjects (27.6%), with Grade ≥ 3 in 35 out of 359 patients (9.7%).

In the Pooled 3L+ DLBCL Set, the incidence of TEAEs from the ND/PD SOC was 248 out of 349 subjects (71.1%).

Cytopenia and Prolonged cytopenia

Almost all subjects (316 out of 349 subjects; 90.5%) in the Pooled 3L+ DLBCL Set experienced laboratory-based cytopenias within the first month (Day 1 to 29) following infusion of JCAR017.

Of the 316 total subjects treated in Studies 017001 and BCM-001 (Cohort 1), who had Day 29 laboratory findings of Grade 3-4 thrombocytopenia (n=95) or Grade 3-4 neutropenia (n=65) or Grade 3-4 anaemia (n=19), and for whom follow-up laboratory cytopenia results were available, the median time (min, max) to resolution (cytopenia recovering to Grade 2 or less) was as follows (in days): thrombocytopenia 37 days (5, 328); neutropenia 29 days (2, 328); and anaemia 30 days (3, 150).

Infections

In the Pooled 3L+ DLBCL Set, all-grade TEAEs in the SOC of Infections and Infestations were reported in 133 out of 349 subjects (38.1%). Treatment-emergent AEs of infection considered Grade ≥ 3 in severity were reported in 44 out of 349 subjects (12.6%) with pathogen unspecified reported in 30 subjects (8.6%), bacterial in 14 subjects (4.0%), and viral and fungal in 4 subjects each (1.1%). Events were Grade 5 in 5 out of 349 subjects (1.4%). Hepatitis B virus (HBV) reactivation following JCAR017 therapy was not observed in subjects who had pre-treatment evidence of latent or suppressed HBV infection. As of the 19 Jun 2020 safety update, taking into account the overall incidence of Grade ≥ 3 infections in 58 out of 359 (16.2%) subjects in the Pooled 3L+ DLBCL (with Grade ≥ 3 infections occurring in 13.1% of subjects (47/359) during the treatment-emergent period), data showed that Grade ≥ 3 infections generally occurred at higher frequencies in subjects who had severe neutropenia or febrile neutropenia, hypogammaglobulinaemia AEs, and who received IVIG therapy.

Tumour lysis syndrome (TLS)

Tumour lysis syndrome was reported in 2 out of 349 subjects (0.6%) in the Pooled 3L+ DLBCL Set (both subjects in the 017001 DLBCL Treated Set). Both events were Grade 3 and neither was reported as SAE.

Hypogammaglobulinaemia/B-cell aplasia

In the Pooled 3L+ DLBCL Set, TEAEs of hypogammaglobulinaemia were noted in 43 out of 349 subjects (12.3%; n=43/359, 12% at the Day 120 safety cut-off date) during the treatment-emergent period and for 14 out of 302 subjects (4.6%) during the posttreatment-emergent period. All events of hypogammaglobulinaemia were Grade 1 or 2.

B-cell aplasia was evident at baseline in 92% (241 out of 262 subjects) of the 017001 DLBCL Treated Set. Consistent with transgene persistence, B-cell aplasia was observed in 98% of subjects (240 out of 244 subjects) on Day 29, 93% (153 out of 165 subjects) on Day 90, 86% (100 out of 116 subjects) on Day 180, and 73% (51 out of 70 subjects) on Day 365.

Subjects in Study BCM-001 (Cohort 1) exhibited a similar high rate of B-cell aplasia ranging from 100% on Day 29 (N = 23) and Day 90 (N = 10), 86% (6 of 7 subjects) on Day 180, and 75% (3 of 4 subjects) on Day 270.

These patients were treated with intravenous immunoglobulin replacement therapy following the institutional guidelines.

MAS/HLH

Among the 349 subjects treated in the Pooled 3L+ DLBCL Set, 2 subjects (0.6%) in Study BCM-001 developed Grade 4 MAS. Both subjects had post-mortem findings consistent with MAS, but deaths were suspected of being from other causes (the first due to respiratory failure and the second to candida sepsis).

Second primary malignancy

During treatment-emergent period SPM was reported in 6 patients (1.7%) and 17 (5.6%) during posttreatment-emergent period. According to the applicant, the most common malignancies reported were cutaneous squamous cell carcinoma, cutaneous basal cell carcinoma, and myelodysplastic

syndrome (MDS). As of 19 Jun 2020, 26 out of 359 (7.2%) subjects treated with liso-cel in the Pooled 3L+ DLBCL Set had developed 1 or more SPMs.

Deaths due to AEs

In the Pooled 3L+ DLBCL Set, 119 out of 143 deaths (34.1% of 340 patients in total) after the first JCAR017 treatment were due to disease progression, 16 deaths (4.6%) were due to Grade 5 AEs, 5 deaths (1.4%) were due to unknown causes, and 3 deaths (0.9%) were due to other causes. **Grade 5 TEAEs** were reported in 11 out of 349 subjects (3.2%) and were considered related to JCAR017 in 6 subjects (diffuse alveolar damage, pulmonary haemorrhage, multiple organ dysfunction syndrome, cardiomyopathy, candida sepsis and respiratory failure).

Grade 5 AEs were reported for 5 out of 349 subjects (1.4%) during the post-treatment emergent period. Events were considered related to JCAR017 in 1 subject who had Grade 5 progressive multifocal leukoencephalopathy. At the Day 120 Safety dataset, in the Pooled 3L+ DLBCL Set, 159 out of 359 subjects (44.3%) had died any time after the first liso-cel infusion. Most deaths were due to disease progression (133 out of 159), 16 were due to AEs (4.5%), 6 to unknown cause and 5 to other.

3.5. Uncertainties and limitations about unfavourable effects

- In rare cases, it may be possible that some patients will receive product outside of the target CD4+:CD8+ cell components ratio range, such as patients who receive out-of-specification lots with respect to the target CD4+:CD8+ cell components ratio. Therefore, as there is currently no confirmation (only the JCAR017-BCM-005 protocol was amended for the time being), the applicant is recommended to collect data on the numbers of effectively administered CD4+, CD8+ and CD4+:CD8+ cell components ratio in the JCAR017-BCM-005 study.
- Finally, besides the immediate risks identified for this product (CRS, NT, infections, cytopenias), there are certain potential risks for which conclusive data could not be obtained due to the limited follow-up time (10.74 months). Therefore, aspects regarding secondary malignancies, replication competent lentivirus analysis need to be appropriately assessed in the follow-up JCAR017-BCM-003.

3.6. Effects Table

Table 108. Effects Table for Breyanzi for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after two or more lines of systemic therapy.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	The proportion of subjects with a BOR of either CR or PR by IRC assessment based on the Lugano 2014 criteria	%	Study 017001 Efficacy set 72.7% ITT set 60.1% Study BCM-001 Efficacy set 61.1% ITT set 55.6%	NA	A clinically relevant difference could be observed in the duration of response across JCAR017 studies, with subjects in US study 017001 still faring significantly better than EU patients in study	-

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
CRR	The proportion of subjects achieving a BOR of CR by IRC assessment based on the Lugano 2014 criteria	%	Study 017001 Efficacy set 53.2% ITT set 43.0% Study BCM-001 Efficacy set 33.3% ITT set 31.1%		BCM-001. The reasons behind the shorter response duration observed in the phase II study are not completely understood, although limited numbers and reduced follow-up do not exclude the possibility of random findings.	-
Median DOR	Duration of response evaluated based on IRC assessments for subjects who achieved a CR or PR per the Lugano 2014 criteria and following the censoring rules per EMA guidelines	months	Study 017001 Efficacy set 20.2 ITT set 16.8 Study BCM-001 Efficacy set 3.5 ITT set 4.30	NA		-
Unfavourable Effects						
CRS	Any grade TEAEs Grade ≥ 3 TEAEs	%	39 3	NA	The median time to onset of CRS was 5 days (range: 1 to 14). As of the first data cutoff date, CRS had resolved in 141/145 subjects; the median duration of CRS was 5 days (range: 1 to 17). 19.8% of all the subjects used tocilizumab and/or corticosteroid. 57 of 314 (18%) patients received tocilizumab and/or corticosteroid	Modified Pooled 3L+DLBCL Treated Set

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
iiNT	Any grade TEAEs Grade ≥ 3 TEAEs	%	26 10	NA	The median time to onset of a neurologic event was 8.5 days (range: 1 to 66) and iiNT events generally resolved in less than 2 weeks (median duration: 9 days, range: 1 to 86). Resolution of iiNT occurred within 4 weeks of onset for 87.4% of the subjects. Treatment for iiNT included corticosteroids and/or tocilizumab in 15.5% of subjects, corticosteroids alone in 12.9% of subjects and both corticosteroids and tocilizumab in 2.3% of subjects.	Modified Pooled 3L+DLBCL Treated Set
Prolonged Cytopenia (Grade ≥3 at Day 29)	Any cytopenia Anaemia Neutropenia Thrombocyto-penia	%	39 6 20 31	NA		Modified Pooled 3L+DLBCL Treated Set
Infections	Any grade Grade ≥ 3 TEAEs	%	39 12	NA	As of the 19 Jun 2020 data cut-off date of 359 subjects in the Pooled 3L+ DLBCL Set, 15 (4.2%) subjects were identified as having opportunistic infections. The most frequently reported opportunistic infection was cytomegalovirus infection (6 subjects). Candida sepsis, bronchopulmonary aspergillosis, and PML occurred in 2 subjects each.	Modified Pooled 3L+DLBCL Treated Set
Hypogammaglobulinaemia	Any grade	%	12	NA		Modified Pooled 3L+DLBCL Treated Set

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
MAS	Any grade Grade ≥ 3 TEAEs Grade 5 TEAEs	%	0.6 0.6 0	NA	Two reports of MAS occurred in subjects with progressive disease and fungal sepsis	Modified Pooled 3L+DLBCL Treated Set
TLS	Any grade Grade ≥ 3 TEAEs Grade 5 TEAEs	%	0.6 0.6 0	NA	Two reports of TLS occurred in subjects with DLBCL NOS and were Grade 3	Modified Pooled 3L+DLBCL Treated Set
Deaths due to AEs	Grade 5 AEs Grade 5 AEs	% (n)	4.6 (16/349) 4.5 (16/359)	NA	Grade 5 TEAEs were considered related to JCAR017 in 6 subjects (diffuse alveolar damage, pulmonary haemorrhage, multiple organ dysfunction syndrome, cardiomyopathy, candida sepsis and respiratory failure).	Pooled 3L+DLBCL Set Day 120 Safety Update – 19 Jun 2020 (Pooled 3L+DLBCL Set)
Grade 5 AEs	Within 90 days after JCAR017 > 90 days after JCAR017	% (n)	3.2 (11/349) 1.4 (5/349) 3.1 (11/359)	NA		Pooled 3L+DLBCL Set 1 Day 120 Safety Update – 19 Jun 2020 (Pooled 3L+DLBCL Set)3

Abbreviations: ACC= Analytic Comparison Cohort; AE= adverse event; CRR= complete response rate; CRS= cytokine release syndrome; DLBCL= diffuse large B-cell lymphoma; DOR= duration of response; ICU= intensive care unit; iiNT= investigator-identified neurological toxicity; ITT= intention-to-treat; JTAC= JCAR017-treated Analysis Cohort; MAIC= Matching-adjusted indirect comparison; MAS= macrophage activation syndrome; NA= not applicable; ORR= objective response rate; OS= overall survival; PFS= progression-free survival; QCC= Qualified comparison cohorts; TEAE= treatment-emergent adverse event; TLS= tumour lysis syndrome.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

JCAR017 is a novel anti-CD19 CAR T-cell product which is characterised by a target 1:1 CD4+/CD8+ T-cell composition. While supported by preclinical data, the clinical relevance of this 1:1 ratio remains

uncertain. Only retrospective analysis of limited data with different ratios is available and the observed relationships with efficacy and safety outcomes are only indicative. A better control of toxicity is suggested as regards acute toxicity, yet the potential impact on long term efficacy and safety outcomes is still not fully characterised. Data will be provided in the post authorisation setting in the imposed non interventional study.

Uncertainties on the magnitude and duration of the treatment effect remain, but larger study 017001, with longer follow-up, reported compelling ORR and CR rates. Further data will be provided by more mature analyses from the imposed Post-Authorisation Studies 017001, JCAR017-BCM-001.

With the intrinsic limits of naïve indirect comparisons, the results observed with JCAR017 in terms of response rate, depth and duration of response, although not clearly outstanding, can still be considered of relevance when contextualised in the current treatment landscape, as highlighted by the provided SLR, MAIC and by a recent meta-analysis investigating the efficacy of second-generation CAR T-cell therapy in DLBCL (see Al-Mansour M et al, Mol Clin Oncol 2020). Adjusted analyses from historical study NDS-NHL-001 also showed higher ORR, CRR, PFS and OS in the reference dataset from study 017001 compared to the historical cohorts. In study 017001, KM curves for time-to-event endpoints showed a plateau phase starting approximately from month 12-18 onwards, which suggests the possibility for long-term disease control in a subset of patients.

When the single-arm, open-label, adaptive design of US study 017001 is considered, however, replication of results is of pivotal importance to demonstrate the reliability of the observed treatment effect. In this regard, results from the smaller EU cohort of Phase II study BCM-001, especially in terms of duration of response, are less convincing. The reasons behind the shorter response duration observed in the phase II study are not completely understood, yet limited numbers do not exclude the possibility of random findings. Data from the imposed non interventional study (registry) will be used to provide additional post-approval information from EU subjects that will receive the commercial product.

With respect to the rarer lymphoma subtypes claimed by the broad indication, only limited clinical information were available in JCAR017 studies. In particular, at the time of the most recent data cut-off date, only 8 patients with FL3B had received JCAR017 across all clinical studies. FL3B is a rare form of aggressive B-cell lymphoma and an unmet medical need exists for patients who have received at least 2 prior lines of therapy can be recognised. The current sample size in the FL3B subset would be, per se, too limited for specific B/R evaluations, even though responses have been observed. It is noted, however, that the distinction between FL3B and DLBCL is mainly based on histology but that there is a large overlap in gene expression profile, clinical presentation and behaviour/biology. Importantly, the same treatment options are available for FL3B and DLBCL and response to treatment appears to be similar. The long-lasting remissions observed with JCAR017 in patients with R/R FL3B, despite failure of multiple prior lines of chemotherapy, are suggestive of an efficacy that is at least similar to that observed in DLBCL NOS. Based on these similarities, the results observed with JCAR017 in the overall study population are considered to provide support for the efficacy seen in the very few FL3B patients and the inclusion of indication in FL3B patients in section 4.1 is, therefore, accepted. Considering the rarity of this condition, limited additional data in FL3B patients can be expected from ongoing clinical trials and in the post-marketing setting. Information will nonetheless be collected from the CIBMTR and EBMT registries (PASS BCM-005) to further characterise effects in patients with FL3B subtype.

The efficacy of JCAR017 in the following clinically relevant subgroups will be further investigated in the post-approval setting:

- Patients with rarer histological subgroups (including FL3B, PMBCL, HGL, and DLBCL transformed from indolent non-Hodgkin lymphoma other than FL)
- Patients with secondary CNS lymphoma involvement

- Frailer patients due to age ≥ 75 years or co-morbidities (e.g. renal impairment and reduced cardiac function)
- Patients with possible adverse prognostic factors (eg, high International Prognostic Index [IPI] score, extranodal involvement, and Eastern Cooperative Oncology Group [ECOG] performance status ≥ 2)
- Patients previously exposed to anti-CD19 therapy
- Patients with low pre-leukapheresis ALC.

Although reasons for pre-infusion treatment failure will not be collected as part of the PASS, since registries only collect data on patients who actually receive JCAR017, data collected in the applicant's manufacturing database will be provided to further investigate the reasons for early treatment failures. The applicant has committed to provide all available information on the rate and reasons for liso-cel manufacturing failures that occur in the post-approval setting in the periodic safety update reports (PSURs).

Regarding safety, JCAR017 was generally well tolerated in patients with 3L+ large B-cell lymphoma, with a toxicity profile overall in line with that of the approved anti-CD19 CAR T-cell products, with the exception that, based on the available data, CRS and NT AEs were more likely to be low-grade and resolved. However, the median on-study follow up is short, long-term data are missing and some adverse effects might not be observable yet. Secondary malignancies are of particular concern and long-term collection of data is crucial.

3.7.2. Balance of benefits and risks

Despite the limits of the clinical development programme and the remaining uncertainties, the available efficacy and safety data with JCAR017 are considered of relevance and support a positive B/R for full approval in the claimed indication.

The remaining uncertainties will be addressed post-marketing in the framework of imposed post-authorisation measures.

3.8. Conclusions

The overall B/R of Breyanzi in subjects with r/r DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy, is considered positive.

The CHMP endorse the CAT conclusion on the benefit-isk balance as described above

4. Recommendations

Similarity with authorised orphan medicinal products

The CAT by consensus is of the opinion that Breyanzi is not similar to Yescarta, Kymriah, Polivy, Gazyvaro and Minjuvi within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

The CHMP endorses the CAT conclusion on similarity as described above.

Outcome

Based on the CAT review of data on quality, safety and efficacy, the CAT considers by consensus that the benefit-risk balance of Breyanzi is favourable in the following indication(s):

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

The CAT therefore recommends the granting of the marketing authorisation subject to the following conditions:

Based on the draft CHMP opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Breyanzi in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

<u>Availability of tocilizumab and site qualification via the controlled distribution programme</u>

The MAH will ensure that hospitals and their associated centres that dispense Breyanzi are qualified in accordance with the agreed controlled distribution programme by:

- ensuring immediate, on-site access to 1 dose of tocilizumab per patient prior to Breyanzi infusion. The treatment centre must also have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage

that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.

- healthcare professionals (HCPs) involved in the treatment of a patient have completed the educational programme.

Educational Programme

Prior to the launch of Breyanzi in each Member State, the MAH must agree on the content and format of the educational materials with the National Competent Authority.

HCP Educational Programme
All HCPs who are expected to prescribe, dispense and administer Breyanzi shall be provided with a healthcare professional guide, which will contain information about:

- identification of CRS and serious neurologic adverse reactions;
- management of CRS and serious neurologic adverse reactions;
- adequate monitoring of CRS and serious neurologic adverse reactions;
- provision of all relevant information to patients;
- ensuring immediate, on-site access to 1 dose of tocilizumab per patient prior to Breyanzi infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on-site;
- contact details for tumour sample testing after development of a secondary malignancy of T cell origin;.
- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study;
- ensure that adverse reactions are adequately and appropriately reported;
- ensure that detailed instructions about the thawing procedure are provided.

Patient educational programme
All patients who receive Breyanzi shall be provided with a patient card, which will contain the following key messages:

- the risks of CRS and serious neurologic adverse reactions associated with Breyanzi;
- the need to report the symptoms of suspected CRS and neurotoxicity to their treating doctor immediately;
- the need to remain in the proximity of the location where Breyanzi was received for at least 4 weeks following Breyanzi infusion;
- the need to carry the patient card at all times;
- a reminder to patients to show the patient card to all HCPs, including in conditions of emergency, and a message for HCPs that the patient has been treated with Breyanzi;
- fields to record contact details of the prescriber and batch number.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
In order to further assess the consistency of product quality and clinical outcomes, the MAH shall submit batch analysis and corresponding clinical safety and effectiveness data from a minimum of thirty (30) lots of Breyanzi finished product used to treat patients included in a non-interventional study based on secondary use of data from existing registries, according to an agreed protocol. Based on this data the MAH should also provide an evaluation on the need for a revision of the finished product specifications. Interim reports should be provided	Interim reports to be submitted in accordance with the RMP. Final report by 31

after approximately 15 lots and any significant out of trend results should be reported immediately.	December 2026
Non-interventional post-authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of Breyanzi in adult patients with relapsed or refractory DLBCL, PMBCL, FL3B after two or more lines of systemic therapy the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Interim reports to be submitted in accordance with the RMP. Final report: Q3-2043
In order to further characterise the long-term efficacy and safety of Breyanzi in patients treated for relapsed or refractory DLBCL, PMBCL, FL3B after two or more lines of systemic therapy, the MAH should submit 24 months post Breyanzi infusion follow-up data (in the enrolled and treated population) of the study 017001.	Q4-2022
In order to further characterise the long-term efficacy and safety of Breyanzi in patients treated with relapsed or refractory DLBCL, PMBCL, FL3B after two or more lines of systemic therapy, the MAH should submit 24 months post Breyanzi infusion follow-up data (in the enrolled and treated population) of the study JCAR017-BCM-001 Cohort 1.	Q4-2022

The CHMP endorses the CAT conclusion on the obligation to conduct post-authorisation measures as described above.

New Active Substance Status

Based on the review of available data on the two active substances which are covered by the single INN lisocabtagene maraleucel, the CAT considers that:

- CD19-directed genetically modified autologous cell-based product consisting of purified CD8+ T cells (CD8+ cells)
- CD19-directed genetically modified autologous cell-based product consisting of purified CD4+ T cells (CD4+ cells)

are to be qualified as new active substances in themselves as they are not constituent of a medicinal product previously authorised within the European Union.

The CHMP endorses the CAT conclusion on the new active substance status claim.