swissmedic

Date: 22 July 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Breyanzi

International non-proprietary name: lisocabtagene maraleucel, contains genetically modified cells (CD4+ or CD8+ cell components, target dose100x10e6 CAR+ T cells in a target 1:1 ratio of CD4+ and CD8+ cell components)

Pharmaceutical form: dispersion for infusion

Dosage strength(s): CD8+ cell components: vials containing 5.1- 322 x 10e6 CAR-positive viable T cells in 4.6 mL (1.1-70 x 10e6 CAR-positive viable T cells/mL).

CD4+ cell components: vials containing 5.1 – 322 x 10e6 CAR-positive viable T cells in 4.6 mL (1.1-70 x 10e6 CAR-positive viable T cells/mL).

Route(s) of administration: Breyanzi is intended for autologous and intravenous use only

Current Marketing Authorisation Holder: Bristol-Myers Squibb SA, Steinhausen

Initial Marketing Authorisation Holder: Celgene GmbH, Zurich

Marketing authorisation no.: 67469

Decision and decision date: approved on 28.03.2022

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for the active substance lisocabtagene maraleucel, which is a CD19-directed genetically modified autologous cellular immunotherapy administered as a defined composition of chimeric antigen receptor (CAR)-positive viable T cells (consisting of CD8+ and CD4+ cell components).

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO, which was granted on 19 May 2020.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 6 June 2019, 5 February 2020, and 14 May 2020.

2.2 Indication and dosage

2.2.1 Requested indication

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 at least 2 prior therapies.

2.2.2 Approved indication

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after at least 2 prior therapies.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Recommended dosage
The target dose is 100 × 10^6 CAR-positive viable T cells (consisting of CD8+ and CD4+ cell components) suspended in 1 or more vials per component.
See the respective Certificate of Release for Infusion (RFI Certificate) for each component, for the actual cell counts and volumes to be infused.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	30 October 2020
Formal control completed	2 November 2020
List of Questions (LoQ)	27 July 2021
Response to LoQ	5 October 2021
Preliminary decision	17 December 2021
Response to preliminary decision	7 March 2022
Final decision	28 March 2022
Decision	approval

3 Medical context

Diffuse large B-cell lymphomas (DLBCL) represent approximately a third of all non-Hodgkin-lymphomas (NHL) and consist of a group of aggressive mature B-cell malignancies, defined in WHO2016 classification by site of origin, histology, immune-phenotype, and genetic profiling/gene expression. The aetiology is unknown, but risk factors, including HIV infection, have been identified.
For nearly 2 decades, standard first-line therapy for the majority of DLBCL cases has been chemotherapy, such as the prototypical regimen consisting of 6–8 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). All-stage 5-year survival rates range from 60% to 70%, 10-year PFS is about 35%, and OS about 40% to 50%.
Approximately 50% of the patients are refractory or will relapse. Poor prognostic factors include early relapse before 1 year, a high International Prognostic Index (IPI) score, bulky disease, and number of extra-nodal sites.
About 30% to 50% of DLBCL patients have chemo-sensitive relapse and can be cured with the established second-line therapy, consisting of salvage chemotherapy followed by high-dose chemotherapy and autologous haematopoietic stem cell transplantation (auto-SCT). Patients who are not eligible for auto-SCT face limited therapeutic options with overall poor outcomes, including selected cases with allogeneic haematopoietic stem cell transplantation.
Recently, CAR T cells have been authorised for patients with r/r DLBCL after 2 or more lines of prior therapy. In pivotal studies, among all leukapheresed patients, CR and mOS in the ranges of 27% to 50% and 8.2 to 17.4 months, respectively, were reported. However, the administration of CAR T cells must be carried out in highly specialised treatment centres managed by specifically trained and experienced teams. Even so, not all leukapheresed patients will have their CAR T cells infused, mostly due to issues with the production of the patient-individual CAR T cells. Moreover, many patients will require bridging therapies to control disease progression until the CAR T cells are available. CAR T cell therapies also cause serious, sometimes life-threatening systemic inflammatory reactions (cytokine release syndrome, CRS) and/or neurotoxicity (immune effector cell-associated neurotoxicity syndrome, ICAN). The management of such toxicities may require intensive care and administration of potent immunomodulatory drugs, including tocilizumab. Despite these limitations, CAR T cell therapies have proven to be a promising therapeutic option for patients with r/rDLBCL who are refractory or relapse after 2 prior lines of therapy.

4 Quality aspects

4.1 Drug substance

Introduction

Breyanzi is a customised, patient-specific gene immunotherapy. Breyanzi consists of 2 autologous components based on selected CD4-positive and selected CD8-positive T cells. Both cellular components are genetically modified *ex vivo* using an integrating, replication-incompetent lentiviral vector carrying the transgene that encodes for the chimeric antigen receptor targeting CD19 antigen (anti-CD19 CAR). The CD19 antigen is expressed at target malignant cells. Upon binding to the target cells, the CAR promotes T-cell activation, expansion, and elimination of the CD19-expressing cells. Breyanzi is classified as an *ex vivo* gene therapy product.

Lentiviral vector

The lentiviral vector (v20006) carrying the transgene for anti-CD19 CAR is used for *ex vivo* gene transfer into the target cells. The vector is based on human immunodeficiency virus 1 (HIV1) containing necessary regulatory sequences and the anti-CD19 CAR transgene. The vector is replication-incompetent, contains self-inactivating sequences, and is pseudo-typed with vesicular stomatitis virus (VSV) envelope glycoprotein. In addition to anti-CD19 CAR, the vector encodes for non-functional extracellular tEGFR (truncated epidermal growth factor receptor) that was introduced as a surrogate marker for anti-CD19 CAR detection in early phases.

The vector is produced by transient transfection in mammalian cells. The cell line is expanded and transfected with a mix of transfer and helper plasmids carrying the transgene and the sequences necessary for the production and assembly of the viral vector. A 2-tiered cell bank system was established and qualified according to ICH Q5. The supernatant of the cell cultures containing the vector is collected, subjected to several purification and concentration steps, the buffer is exchanged by diafiltration, and the final formulation is then filled into sterile primary containers.
Sufficient information on the vector manufacturing process and the control strategy was provided. The process was validated and the submitted data of several batches demonstrated that the manufacturing process is capable of producing vector batches which consistently meet predefined acceptance criteria.
The ability of the vector to infect and stably integrate the transgene into the genome of the target cells was confirmed. Successful production and the activation of the functional anti-CD19 CAR in the patient's cells upon transgene integration was shown.
The vector release specification contains a panel of tests to confirm identity, purity, and biological activity, and to determine potency. In addition to other safety attributes, the absence of replication-competent viruses is confirmed.
Analytical methods were described in sufficient detail. Non-compendial methods have been validated according to ICH guidelines and compendial methods have been verified.
A shelf-life for the vector at the long-term storage condition of -70 ± 10°C was proposed and accepted.

Breyanzi (lisocabtagene maraleucel)
Breyanzi is a patient-specific *ex vivo* gene therapy derived from the patient's own peripheral blood cells (leukapheresis). One manufacturing run initiated from a single patient's leukapheresis corresponds to 1 batch of the drug product. The drug product consists of 2 components: CD4-positive T-cells and CD8-positive T-cells, both expressing the anti-CD19 CAR receptor. The CD4-positive and CD8-positive components are administered in a target ratio of 1:1.
Patient leukapheresis is performed in a qualified centre and the product is transported to the manufacturing site for production of process intermediates under validated conditions. In the first step, the cells undergo a T-cell selection procedure with specific antibody-coated beads using an automated system to enrich target cells and reduce cellular impurities.
Isolated cells for both components (CD4- and CD8-positive) are further processed separately. The selected cells are cryopreserved as intermediates and transported to the drug product manufacturing site. Cryopreserved intermediates can be stored until further processing. Enriched CD4-positive and CD8-positive cells undergo activation with suitable reagents followed by transduction using a replication-incompetent lentiviral vector carrying the anti-CD19 CAR transgene and by cell expansion in a specific selective medium.
The manufacturing process is continuous and proceeds directly to the drug product formulation and filling steps. The drug substance is not isolated and individual specification at this level was not established.
Manufacturing process changes during process development were adequately described and supporting data from comparability studies between batches manufactured using the proposed commercial process and clinical batches were provided.
Overall, the manufacturing process including process parameters and controls was described in sufficient detail.
Process performance qualification (PPQ) was performed using material from healthy donors. Additional process performance qualification was designed to cover additional sites for production of selected cryopreserved intermediates. PPQ runs fulfilled the predefined validation acceptance criteria for process parameters or process controls as well as the release specification. Transport of leukapheresis material as well as transport of cryopreserved process intermediates between 2 manufacturing sites in qualified shippers were validated.
Extended characterisation of the PPQ batches demonstrated that the product's cellular composition is within expected ranges, with variability that can be mainly attributed to the variability of the patient materials.

The biological and physical properties as well as the subcellular composition of components and their impact on biological activity were extensively characterised for both the CD4-positive and CD8-positive anti-CD19 CAR-expressing cells. Product-related and process-related impurities were addressed and, wherever applicable, their removal to acceptable levels was demonstrated.

4.2 Drug product

Breyanzi is a single-dose cellular dispersion for transfusion. The final product comprises 2 individual components: anti-CD19 CAR-expressing CD4-positive T-cells and anti-CD19 CAR-expressing CD8-positive T-cells. Each component is formulated separately in a cryogenic medium and filled into cryogenic polyolefin vials. Per component up to 4 vials with a fill volume of 5 mL can be filled and each vial contains 5.1 – 322 x10^6 viable anti-CD19 CAR-expressing T-cells in an extractable volume of 4.6 mL.
The target dose is 100 x 10^6 anti-CD19 CAR-expressing viable T cells combined from anti-CD19 CAR-expressing CD4-positive T cells and anti-CD19 CAR-expressing CD8-positive T cells in a target ratio of 1:1 (50x10^6 anti-CD19 CAR-expressing viable T cells per component target dose).
The dose range may vary between 44 and 120 x10^6 viable anti-CD19 CAR-expressing T cells.
The drug product is supplied cryopreserved and administered by infusion after thawing. The volume required is calculated based on the concentration of formulated anti-CD19 CAR-expressing viable T cells. Each component may require a different volume or number of vials to achieve the target dose.
The excipients used for formulation of the drug product are multiple electrolytes injection solution type I (an aqueous solution containing sodium chloride, sodium gluconate, sodium acetate, potassium chloride, magnesium chloride), human serum albumin in 0.3% final concentration, and cryopreservation medium containing 7.5% dimethylsulfoxide (CryoStor CS10).
The primary container used for storage of the components of Breyanzi is a cryogenic, cyclin olefin co-polymer vial with 3 ports (for loading, retrieval, and pressure equalisation during product withdrawal).
The suitability of the primary container for the drug product was demonstrated. Materials in contact with the drug product are of compendial quality.
The secondary container is a folding box holding up to 4 vials.

The manufacturing process of the drug product consists of buffer exchange at the end of expansion, formulation, filtration of the cell suspension, followed by filling into the primary containers. After that, the drug product is cryopreserved and stored in the vapour phase of liquid nitrogen.
The manufacturing process was validated as a continuous process. Transport to healthcare centres is performed using qualified dry shippers in the vapour phase of liquid nitrogen and was validated.

The drug product release specification covers all relevant tests to confirm identity, purity, potency, and safety. Analytical methods were adequately described. Non-compendial methods have been validated according to ICH guidelines and compendial methods verified for corresponding matrices.

The drug product is stored at a temperature not higher than -130 °C in the vapour phase of liquid nitrogen in its original container. A shelf-life of 13 months has been granted based on the data provided during assessment.
The proposed in-use shelf-life for the thawed drug product is up to 2 hours at room temperature. The drug product is thawed at room temperature prior to administration, and the 2 components are administered subsequently, starting with the CD8-positive anti-CD19 CAR component. Compatibility with commercial administration sets was demonstrated.

It can be concluded that the manufacturing process of Breyanzi, as well as that of the lentiviral vector, incorporates adequate control measures to prevent contamination and maintain control with regard to adventitious agent contamination

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Lisocabtagene maraleucel is a genetically modified autologous CD8+ and CD4+ T cell immunotherapy directed toward CD19+ cells. The patient's purified and separated CD4+ and CD8+ T cells are transduced with a third-generation, replication-incompetent SIN-LV vector encoding for an anti-CD19 CAR. The CAR construct consists of an FMC63 single-chain variable fragment, an IgG4 hinge region, a CD28 transmembrane, a 4-1BB costimulatory domain, and a CD3ζ activation domain. A non-functional truncated epidermal growth factor receptor (EGFRt) co-expressed on the cell surface with the CAR was added to the CAR transgene for analytical detection, or in human patients as a potential target for removal of the genetically modified cells by anti-EGFR antibodies in case of severe adverse drug reactions.

In vitro characterisation of lisocabtagene maraleucel was performed to evaluate the binding affinity and specificity of the FMC63 scFv binding domain to CD19, cell activation and proliferation of CD4+ and CD8+ cells, cytokine production, and cytotoxic killing of CD19+ target cells. Cytotoxic activity was demonstrated in co-cultures against CD19+ follicular lymphoma and primary mediastinal B-cell lymphoma cells. Similarly, cytolytic activity of lisocabtagene maraleucel derived from NHL-treated patients against CD19+ tumour cells was reported. The proliferation of both CD4+ and CD8+ T cell components of lisocabtagene maraleucel was observed upon co-culturing with CD19+ cells. A CD4+:CD8+ cell ratio of 1:1 was shown to be advantageous in terms of cell growth as compared to CD8+ cells alone. The FMC63 binding domain of the CAR construct showed specific interaction with the human CD19 epitope without cross-reactivity with other species. In addition, selective binding of lisocabtagene maraleucel to human CD19+ cells was reported by flow cytometry binding assay.

To assess the *in vivo* pharmacology of lisocabtagene maraleucel in a mouse tumour model, immune-deficient NOD/SCID/IL-2Rγ^{null} mice were intravenously administered 5.0 x 10^5 human CD19+ Raji Burkitt's lymphoma cells expressing a red-shifted firefly luciferase transgene and green fluorescent protein. A dose-dependent tumour burden reduction and increased mouse survival were reported following administration of lisocabtagene maraleucel cells from both healthy and patient donors during the entire studied periods as compared to the control group. Significant manufacturing-dependent effects on mouse survival were reported between the v3.0 and v4.0 processes.

Several drug interaction studies were carried out to investigate the compatibility of lisocabtagene maraleucel therapy with standard-of-care cancer treatments. Durvalumab (anti-PD-L1 Ab), ibrutinib, and acalabrutinib (BTKi) demonstrated no negative effects on the activation and performance of CAR T cells. Considerable immune parameter variations were observed when CC-122 (cereblon modulator) and lenalidomide were combined with lisocabtagene maraleucel.

5.2 Pharmacokinetics

Conventional pharmacokinetic studies were not performed. In view of the type of product and the limited translational prediction of the available nonclinical models, this is considered acceptable. However, *in vivo* persistence and monitoring over time of circulating concentrations of CD4+ and CD8+ lisocabtagene maraleucel cells in NOD/SCID/IL-2Rγ^{null} mice were investigated. While peak circulating levels of CD8+ lisocabtagene maraleucel cells at the high dose ($2x10^6$ CAR T cells per mouse) were observed at Day 8, medium ($5x10^5$ CAR T cells per mouse) and low doses ($1.25x10^5$ CAR T cells per mouse) peaked at Day 14. In contrast, circulating levels of CD4+ lisocabtagene maraleucel cells showed increased variation across manufacturing and donor sources, in particular high doses of v3.0 and v4.0 CD4+ CAR T cells unexpectedly displayed either expansion or absence of expansion among donors. At low and medium doses, T cell expansion was absent for both CD4+ cells derived from both manufacturing processes.

Cetuximab efficacy in depleting lisocabtagene maraleucel cells was investigated in a Raji xenograft mouse model. Two doses (0.25 and 0.125 mg/mouse) were administered and reduction of lisocabtagene maraleucel cells was quantified in peripheral blood, spleen, or bone marrow. In addition, tumour burden changes and animal survival were assessed. Increased CAR T cell numbers were reported on Day 13 post-infusion in the lymphoid tissues. Upon cetuximab administration on Days 7, 9, 11, and 13, a significant reduction in cells was noted in the blood, spleen, and bone marrow. Another study showed that cetuximab administered on Days 12, 14, 16, 18, 20, 22, and 24 resulted in a significant reduction in CAR T cells in the blood and spleen but not in the bone marrow. Low survival and tumour growth were observed with the combination of lisocabtagene maraleucel and cetuximab treatment, with evidence of a reduction in CAR T cell numbers.

5.3 Toxicology

Due to the nature of this product, conventional toxicity studies were not performed. The genotoxic potential of lisocabtagene maraleucel was assessed by lentiviral integration site analysis. Results showed that the integration pattern was not affected by the CAR construct and no enhanced integration was observed near known proto-oncogenes or at loci associated with an increased risk of insertional mutagenesis.

An IL-2-independent CAR T cell proliferation study was performed to provide information on the carcinogenic potential of lisocabtagene maraleucel. It was shown that after 60 days in culture and in the absence of IL-2, the lisocabtagene maraleucel cell count was below the LLOQ. Data on CAR T cell characterisation by flow cytometry were insufficient to confirm that lisocabtagene maraleucel was comparable in terms of purity and identity over time.

5.4 Nonclinical conclusions

A series of *in vitro* assays and *in vivo* studies using a tumour xenograft immunocompromised mouse model were performed to demonstrate the proof of principle and to determine the major effects of lisocabtagene maraleucel. CAR-T cells bind specifically to human CD19 and demonstrate no mouse or non-human primate cross-reactivity. Following human CD19 engagement, lisocabtagene maraleucel cells showed activation, proliferation, target cell killing, and cytokine production. Raji Burkitt's lymphoma xenografts were established in NOD/SCID/IL-2Rγ^{null} mice, and in light of the autologous cell therapy properties, this model was considered appropriate. While dose- and donor-dependent antitumour efficacy of lisocabtagene maraleucel cells was demonstrated, cell potency varied for the same donor with change in the manufacturing process. Similar dose, donor, and manufacturing variability of the CD4+ and CD8+ cells' *in vivo* expansion was noted. It must be noted that only the 1:1 CD4+:CD8+ ratio was comprehensively evaluated in the nonclinical studies, which support a 1:1 ratio in clinical conditions. As expected, a potent depletion of lisocabtagene maraleucel cells upon administration of cetuximab (anti-EGFR) was reported. Among the tested interactions of lisocabtagene maraleucel with other cancer treatments, comprising L
lenalidomide, durvalumab, ibrutinib, acalabrutinib, and CC-122, an absence of negative effects on lisocabtagene maraleucel were reported for durvalumab, ibrutinib, and acalabrutinib. Based on genomic mapping data, T-cell transformation resulting from lentiviral-induced insertional mutagenesis is considered very low. Similarly, no carcinogenic potential for lisocabtagene maraleucel was observed based on IL-2-independent proliferation assays. The potential effects of lisocabtagene maraleucel on fertility and embryonic, prenatal, postnatal, and juvenile development were not investigated in nonclinical studies.

6 Clinical aspects

6.1 Clinical pharmacology

Biopharmaceutical development

The autologous CD3-positive T cells that have been transduced with an anti-CD19 CAR using a lentiviral vector are defined as the drug substance, whereas these transduced T cells formulated in a cryopreservation medium constitute the drug product for IV infusion. The final drug product JCAR017 (lisocabtagene maraleucel, trade name Breyanzi™) consists of autologous CD8+ (killer) and CD4+ (helper) T cells in a 1:1 ratio, which are individually prepared in the cryopreservation medium.

ADME

Considering the level of complexity of adoptive cell therapies, including CAR T cells, classical pharmacological concepts such as ADME and other pharmacokinetic aspects are hardly applicable to these emerging new medicinal products. Pharmacokinetic parameters are used to describe cellular kinetics in terms of expansion ("absorption", "distribution") and persistence ("elimination"): the maximum expansion and the time when maximum expansion is reached are described by C_{max} and t_{max}; information about the persistence of CAR T cells is provided by AUC, $t_{1/2}$ and t_{last}.

The pharmacokinetic and pharmacodynamic properties of JCAR017 were investigated in a Phase 1 study and a Phase 2 study in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (NHL). A population PK analysis was conducted to further characterise the cellular kinetics of JCAR017.

Following a target dose of 100 x 10^6 anti-CD19 CAR T cells consisting of CD8 and CD4 components in a 1:1 ratio, the median peak blood cell levels of 25,098.5 copies/µg were reached on average 11 days post-infusion. The median $AUC_{0\text{-}28d}$ was determined at 22,9062.6 day*copies/µg. Overall, the cellular kinetics of JCAR017 were subject to a high degree of inter-individual variability. Flow cytometry analyses revealed higher expansion of CD8+ CAR T cells compared with CD4+ CAR T cells. It was shown that the different C_{max} and $AUC_{0\text{-}28}$ ratios of CD8+ and CD4+ CAR T cells were not associated with different clinical outcomes as measured by BOR, DOR, PFS, CRS, and iiNT.

An explorative analysis of the relationship of transgene levels from blood and bone marrow in patients with both samples indicated a high correlation, suggesting a substantial distribution to the bone marrow.

The elimination was bi-exponential, characterised by a rapid decline followed by a slower decrease towards baseline. Anti-CD19 CAR T cell levels were still detectable at the last time point, i.e. after 730 days, suggesting considerable persistence.

Three different doses were investigated, i.e. 50 x 10^6, 100 x 10^6, and 150 x 10^6 viable CAR+ T cells. No clear relationship between dose and JCAR017 levels was observed. Furthermore, a 2-dose schedule was investigated for the 50 x 10^6 dose, where the second dose was administered 14 days after the first dose. Interestingly, the anti-CD19 CAR T cell exposures were lower after the second dose.

Special populations / intrinsic factors

No studies in patients with renal and hepatic impairment were conducted.

In the context of a subgroup analysis, no significant differences in pharmacokinetic parameters were observed for the baseline and demographic characteristics of sex, race, ethnicity, body weight, body mass index, serum creatinine, ALT, AST, and total bilirubin. 2.91-fold and 2.30-fold higher median C_{max} and $AUC_{0\text{-}28}$, respectively were observed in subjects <65 years old compared with subjects ≥65 years old. Furthermore, the potential impact of the baseline disease characteristics of LDH prior to LDC (≥500 U/L versus <500 U/L), SPD per IRC prior to LDC (≥50 cm^2 versus <50 cm^2), baseline CRP

(≥20 mg/L versus <20 mg/L), prior HSCT status, prior response status, prior chemo-response status, CNS disease status, and cell of origin were investigated. In subjects with an SPD of ≥50 cm^2, 2.46-fold and 2.88-fold higher median C_{max} and AUC_{0-28}, respectively, were observed compared to subjects with an SPD of <50 cm^2. Furthermore, significant differences in median AUC_{0-28} were reported in subjects with and without prior HSCT. Differences in t_{max} were observed in both subjects relapsed and refractory to last therapy as well as in subjects with a CRP of ≥20 mg/L and <20 mg/L.
Overall, these correlative analyses should be interpreted with caution considering the high variability of the cellular kinetics of JCAR017.

CAR T cell levels were increased in the Japanese cohort; however, significant inter-individual variability was observed and the sample size was small.

A population PK analysis was performed using data for the 3 investigated single dose levels. JCAR017 cellular kinetics were well-described by a model containing lag, growth, and bi-exponential decline phases. Overall, the model, i.e. expansion followed by bi-exponential decline, is consistent with current understanding of the cellular kinetics of CAR T cells.
A battery of covariates was investigated, whereof only age on C_{max} and T_{dbl}, SPD per IRC prior to LDC on HLα, tocilizumab and/or corticosteroid use (for the treatment of CRS or iiNT) on C_{max} and HLα, and manufacturing process version (proposed commercial process versus original and precommercial processes) on T_{lag} were included in the final model. The impact of the covariates confirmed earlier observations. The simulations suggest that the magnitude of the covariate effect on exposure metrics was smaller than the residual inter-individual variability in the population; therefore, their impact does not seem clinically meaningful.

Interactions
No pharmacokinetic drug-drug interactions are anticipated for adoptive cell therapies. Therefore, no dedicated DDI studies were conducted.

Tocilizumab and corticosteroids were administered for the treatment of CRS and iiNT. Patients who received the concomitant medications had considerably higher anti-CD19 CAR T cell levels. It is likely that the increased anti-CD19 CAR T cell levels were not caused by the administration of these medications but by the fact that higher cell levels were associated with more severe AEs.

Mechanism of action and primary pharmacology
JCAR017 is an autologous cancer immuno-cellular therapy using genetically engineered T cells. Following binding to CD19-positive target cells, downstream signalling pathways are triggered by the CD28, 4-1BB, and CD3ζ co-stimulatory domains leading to T cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. Ultimately, this series of events results in the killing of the CD19-positive target cells.

A panel of 41 serum markers were investigated, including homeostatic/proliferative markers, inflammatory and immune modulating markers, chemokines, and other analytes. Peak elevation of most of the soluble biomarkers was observed within the first 14 days after JCAR017 infusion and returned to baseline levels within 28 days.
Serum CRP and ferritin are both inflammatory markers and their baseline values have been shown to be associated with an increased risk of CRS and iiNT. Serum CRP was increased prior to infusion and decreased substantially within the first 28 days following the administration of JCAR017. Serum ferritin was increased at baseline and the levels remained unchanged during the first 28 days after JCAR017 infusion.

Secondary pharmacology (safety)
B-cell aplasia as a potential on-target, off-tumour effect was investigated. Although a substantial number of subjects were already depleted of B cells at baseline due to prior rituximab or other anti-CD20 therapies, the number of subjects without detectable levels of B cells increased following the

administration of JCAR017. Overall, B-cell aplasia was long-lasting and limited B-cell recovery was observed, consistent with the CAR T cell persistence.

No replication-competent lentivirus was detected in Studies 017001 and BCM-001.

Relationship between plasma concentration and effect
The relationship between exposure and response was assessed based on retrospective and exploratory correlative analyses;, therefore, the validity of these post hoc findings must be viewed with caution.

PK/PD relationships
The following relationships were observed at a statistically significant level:

- AUC_{0-28} and baseline TGFβ3 and TNF-α.
- t_{max} and baseline IL-5, IL-7, IL-15, and ferritin.
- C_{max} and peak levels of IFN-γ, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, TNFα, MCP1, MIP1α, and MIP1β.
- AUC_{0-28} and peak levels of CCL17, IFNγ, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, TNFα, MCP1, MIP1α, MIP1β, VCAM1, and ferritin.
- t_{max} and peak levels of IL-7, VEGF-D, and ferritin.

PK/efficacy relationships
3.55-fold and 2.72-fold higher median C_{max} and AUC_{0-28} were observed in responders compared to non-responders.

PK/safety relationships
2.29-fold and 2.36-fold higher median C_{max} and AUC_{0-28} were observed in subjects with any grade CRS compared to subjects without any grade CRS. 3.34-fold and 3.77-fold higher median C_{max} were observed in subjects with any grade iiNT.

PD/efficacy relationships
No statistically significant relationships were observed between baseline and peak levels of the soluble biomarkers, CRP, or ferritin and the overall response.

PD/safety relationships
A wide variety of statistically significant relationships between the baseline levels as well as the peak levels of the soluble biomarkers and CRP/ferritin and iiNT or CRS were observed.

6.2 Dose finding and dose recommendation

This application was evaluated based partly on the clinical pharmacology and clinical assessments of the FDA (incl. BLA Clinical Review Memorandum for Breyanzi from 13 Nov 2020, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel) and the EMA (EPAR EMA/134759/2022 from 27 January 2022). The current SwissPAR relating to clinical aspects refers to these publicly available Assessment Reports for Breyanzi. Swissmedic focused its evaluation on pertinent aspects with respect to the indication, which may differ from EMA's and/or FDA's approvals.

Indications
US (USPI):
Breyanzi is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

EU (SmPC):
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 2 or more lines of systemic therapy.
CH (FI):
Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after at least 2 prior therapies.

To ensure patients' optimal access to the product, the applicant requested a wide dose recommendation of 44-120 x 10^6 cells for infusion, which was also investigated in Study 017001. This is acceptable, as no clear association of the dose in this range with efficacy and safety was observed.

6.3 Efficacy

With a CR of 43.6% and an mOS of 14 months in patients with DLBCL, the efficacy of Breyanzi as observed in the pivotal study 017001 was within the expected range for CAR T cell therapies. As only 6 patients with follicular lymphoma grade 3B (FL3B) were included in clinical studies, the evidence available to assess the benefit-risk of Breyanzi® in this subentity of NHL is scarce. Diagnosis and therapeutic options for patients with FL3B are an ongoing matter of debate and not clearly defined (see for instance Barraclough, Bishton, Cheah, et al. The diagnostic and therapeutic challenges of Grade 3B follicular lymphoma. Br J Haematol. 2021 Oct;195(1):15-24). Therefore, an extrapolation of the efficacy to patients with FL3B is not supported by an unequivocal scientific rationale, and this subpopulation is excluded from the indication.

6.4 Safety

The observed risks are consistent with CAR T cell therapy. The most relevant risks are cytokine release syndrome, neurological complications, infections, and cardiovascular side effects. Risk mitigation measures with respect to these risks are described in the "Warnings and precautions" section of the information for healthcare professionals, which focuses on the exclusion of patients at particular risk and the preventive treatment of imminent clinical deterioration.

6.5 Final clinical benefit-risk assessment

Breyanzi exhibits an efficacy and safety profile that is prototypic for a CAR T cell product. The treatment effect and adverse drug reactions are within the expected range for a CAR T cell therapy in patients with DLBCL and PMBCL.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Breyanzi was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

Placeholder for text approval stamp

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Breyanzi®

Composition

Active substances

Lisocabtagene maraleucel is a CD19-directed genetically modified autologous cellular immunotherapy administered as a defined composition of chimeric antigen receptor (CAR)-positive viable T cells (consisting of CD8+ and CD4+ cell components).

Excipients

Cryostor CS10 (7.5% DMSO (v/v), Dextran 40) Sodium chloride, Sodium gluconate, Sodium acetate trihydrate, Potassium chloride, Magnesium chloride, Human albumin, Nacetyl-DL-tryptophan, Caprylic acid, Water for injections.
Breyanzi contains up to 100 mg sodium and up to 52 mg potassium per dose.

Pharmaceutical form and active substance quantity per unit

Dispersion for infusion
Slightly opaque to opaque, colourless to yellow, or brownish-yellow cell dispersion.

CD8+ cell component
Vials containing 5.1-322 × 10^6 CAR-positive viable T cells in 4.6 mL (1.1-70 x 10^6 CAR-positive viable T cells/mL).

CD4+ cell component
Vials containing 5.1-322 × 10^6 CAR-positive viable T cells in 4.6 mL (1.1-70 x 10^6 CAR-positive viable T cells/mL).

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

The infusion volume is calculated based on the cryopreserved drug product CAR-positive viable T cell concentration. The volume may differ for each component infused. See the Certificate of Release for Infusion (RFI Certificate) for details.

Indications/Uses

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after at least two prior therapies.

Dosage/Administration

Breyanzi must be administered in a qualified treatment centre with immediate access to appropriate intensive care units by healthcare professionals trained in the use of Breyanzi.

Breyanzi therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with Breyanzi, including the treatment of the cytokine release syndrome and serious neurotoxic side-effects.

A minimum of 2 doses of tocilizumab for use in the event of cytokine release syndrome (CRS) and appropriate emergency equipment must be available for each patient prior to infusion of Breyanzi. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of the previous dose.

Type of use
Breyanzi is intended for autologous and intravenous use only.

Recommended Dosage
The target dose is 100×10^6 CAR-positive viable T cells (consisting of a target 1:1 ratio of CD8+ and CD4+ cell components) within a range of $44\text{-}120 \times 10^6$ CAR-positive viable T cells.
See the respective Certificate of Release for Infusion (RFI Certificate) for each component, for the actual cell counts and volumes to be infused.

The availability of Breyanzi must be confirmed before starting lymphodepleting chemotherapy.

Pretreatment

Administer the lymphodepleting chemotherapy regimen: fludarabine 30 mg/m^2/day intravenously (IV), and cyclophosphamide 300 mg/m^2/day IV for 3 days.

See the prescribing information for fludarabine and cyclophosphamide for information on dose adjustment in renal impairment.

Breyanzi is to be administered 2 to 7 days after completion of lymphodepleting chemotherapy.
Delay the infusion of Breyanzi if the patient has any of the following conditions:

- Unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies.
- Active uncontrolled infection, or inflammatory disorder.
- Active graft-versus-host disease (GVHD).

In clinical trials, the median time between lymphodepleting chemotherapy and infusion with Breyanzi was 4 days (range 2-14). If infusion could not be completed within 14 days, patients were re-treated with lymphodepleting chemotherapy prior to receiving the infusion.

Premedication

To minimize the risk of infusion reactions, premedicate the patient with paracetamol and diphenhydramine (25-50 mg, intravenously or orally), or another H1-antihistamine, 30 to 60 minutes prior to treatment with Breyanzi.
Avoid prophylactic use of systemic corticosteroids, as they may interfere with the activity of Breyanzi.

Monitoring

- The monitoring and follow-up of the patients with a CAR-T cell therapy should be performed at an appropriately qualified clinical facility. Patients should be monitored daily during the first week following infusion at minimum for signs and symptoms of potential cytokine release syndrome (CRS), neurologic events and other toxicities. Afterwards, the patient should be monitored at the physician’s discretion according to the patient’s overall condition. At the first signs or symptoms of CRS and/or serious neurologic events, the patient should be admitted to hospital and monitored.
- Patients should be instructed to remain within proximity of a qualified treatment centre for at least 4 weeks following infusion.

Special dosage instructions

Patients with impaired hepatic function

Formal hepatic impairment studies have not been conducted.

Patients with impaired renal function

Formal renal impairment studies have not been conducted.

Elderly patients

No dose adjustment is required in patients over 65 years of age (42% of the study population were patients aged 65 years and older).

Children and adolescents

The safety and efficacy of Breyanzi in children and adolescents below 18 years of age have not been established.

Important precautions to be taken before handling or administering the medicinal product

When preparing the medicinal product, confirm that the patient's identity with the patient identifiers on the shipper and external Breyanzi carton.
Confirm the patient's identity again with the patient identifiers on the syringe labels before administering Breyanzi.
Do NOT use a leukodepleting filter when administering Breyanzi.
Ensure that tocilizumab and emergency equipment are available before infusion and during the recovery period.
Strictly follow the other important details on handling and administering the medicinal product (see "Other information").

Contraindications

Hypersensitivity to the active substance or to any of the listed excipients.

Contraindications of the lymphodepleting chemotherapy must be considered according to the corresponding summary of product characteristics.

Warnings and precautions

Reasons to delay treatment
Due to the risks associated with Breyanzi treatment, infusion should be delayed if a patient has any of the following conditions:

Advanced-stage lymphoma with serious clinical complications such as unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies; active uncontrolled infections or inflammatory disorders, active graft-versus-host disease (GVHD).

Autologous application

Breyanzi is intended for autologous use only. Before infusion, the patient's identity must match the patient identifiers on the cartons, vials and RFI certificate. Do not infuse if the information on the patient-specific label does not match the intended patient.

Cytokine Release Syndrome (CRS)

CRS including fatal or life-threatening reactions can occur following treatment with Breyanzi. In clinical trials, CRS occurred in 39% (122/314) of patients receiving Breyanzi, including ≥ Grade 3 (Lee grading systema) CRS in 3% (8/314) of patients.
The median time to onset was 5 days (range: 1 to 14 days) and the median duration of CRS was 5 days (range: 1 to 17days).

In clinical studies, 57 of 314 (18%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. 33 (11%) patients received tocilizumab only, 21 (7%) received tocilizumab and a corticosteroid, and 3 (1%) received corticosteroids only.

Monitoring and management of CRS

A minimum of 2 doses of tocilizumab must be available for each patient on site prior to infusion of Breyanzi. The treatment centre should have access to an additional dose of tocilizumab within 8 hours of the previous dose.
Monitor patients daily during the first week at minimum following infusion at the qualified treatment centre for signs and symptoms of CRS.

Monitor patients for signs and symptoms of CRS for at least 4 weeks after infusion. Counsel patients to remain in the vicinity of a qualified treatment centre during this time and to seek immediate medical attention should signs and symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated in Table 1.

Patients who experience CRS should be closely monitored for cardiac and organ functioning until resolution of symptoms. For severe or life-threatening CRS, continuous cardiopulmonary intensive care unit level monitoring and supportive intensive care therapy should be considered.

Identify cytokine release syndrome (CRS) based on clinical presentation. Other causes of fever, hypoxia, and hypotension should be considered. Evaluation for hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS. Treatment of HLH/MAS should be administered per institutional guidelines.

If CRS is suspected, manage according to the recommendations in Table 1. If concurrent neurologic toxicity is suspected during CRS, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Anti-seizure medication according to the neurologic toxicity grade in Table 2.

Table 1. CRS grading and management guidance

CRS Grade[a]	**Tocilizumab**	**Corticosteroids** (For corticosteroid tapering information, see below table)
Grade 1 Fever	If 72 hours or more after infusion, treat symptomatically – as tocilizumab is not recommended. If less than 72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (max.800 mg).	If 72 hours or more after infusion, treat symptomatically – as corticosteroids are not recommended. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 24 hours.
Grade 2 Symptoms require and respond to moderate intervention. Fever, oxygen requirement less than 40% FiO2, or hypotension responsive to fluids or low dose of one vasopressor, or Grade 2 organ toxicity.	Administer tocilizumab 8 mg/kg IV over 1 hour (max. 800 mg).	If 72 hours or more after infusion, consider dexamethasone 10 mg IV every 12-24 hours. If less than 72 hours after infusion, administer dexamethasone 10 mg IV every 12-24 hours.

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab</th><th>Corticosteroids
(For corticosteroid tapering information, see below table)</th></tr>
<tr><td></td><td colspan="2">If rapid progression of symptoms is observed or if no improvement within 24 hours, repeat tocilizumab. Do not exceed 3 doses of tocilizumab in 24 hours or 4 doses total. Escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours).

If no improvement or continued rapid progression, maximise dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants.</td></tr>
<tr><td rowspan="2">Grade 3
Symptoms require and respond to aggressive intervention.

Fever, oxygen requirement greater than or equal to 40% FiO2, or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminitis.</td><td>Per Grade 2.</td><td>Administer dexamethasone 10 mg IV every 12 hours.</td></tr>
<tr><td colspan="2">If rapid progression of symptoms is observed or if no improvement within 24 hours escalate tocilizumab and corticosteroid use as per Grade 2.</td></tr>
<tr><td rowspan="2">Grade 4
Life-threatening symptoms.

Need for ventilator support or continuous veno-venous haemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).</td><td>Per Grade 2.</td><td>Administer dexamethasone 20 mg IV every 6 hours.</td></tr>
<tr><td colspan="2">If rapid progression is observed or if no improvement within 24 hoursescalate tocilizumab and corticosteroid use as per Grade 2.</td></tr>
</table>

[a] Lee criteria for grading CRS

If steroids are initiated, continue steroids for at least 3 doses or until complete resolution of symptoms, and consider steroid taper.

Neurologic Toxicities

Neurologic toxicities, which may be severe or life-threatening occurred following treatment with Breyanzi, including concurrently with CRS, after CRS resolution, or in the absence of CRS. In clinical trials, 26% (82/314) of patients experienced neurologic events including ≥ Grade 3 neurologic events in 10% (32/314) of patients. The median time to onset of an initial event was 9 days (range: 1 to 66 days).

Monitoring and management of neurologic toxicities

Monitor patients daily during the first week at minimum following infusion at the qualified treatment centre for signs and symptoms of neurologic toxicities. Monitor patients for signs and symptoms of neurologic toxicities for at least 4 weeks after infusion and treat promptly. Counsel patients to remain in the vicinity of a qualified treatment centre during this period and to seek immediate medical attention should signs and symptoms of neurologic toxicity occur at any time.

Monitor patients for signs and symptoms of neurologic toxicities (e.g., encephalopathy, tremor, aphasia, delirium, dizziness, headache) (Table 2). Rule out other causes of the neurologic symptoms, since these may require different therapies. In the event of severe or life-threatening neurologic toxicities, continuous cardiopulmonary monitoring must be provided and intensive care supportive therapy should be considered. If neurologic toxicity is suspected, manage according to the recommendations in Table 2.

- If concurrent CRS is suspected during the neurologic toxicity, administer:
- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Anti-seizure medication according to the neurologic toxicity grade in Table 2.

Table 2. Neurologic toxicity (NT) grading and management guidance

NT Grade[a]	Corticosteroids and anti-seizure medication
Grade 1	Start non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. If symptoms occur in less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to -24 hours for 2-3 days. If 72 hours or more after infusion, continue observation of patients.
Grade 2	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 mg IV every 12 hours for 2-3 days, or longer for persistent symptoms. Consider taper for a total corticosteroid exposure of greater than 3 days. If worsening of neurologic toxicity is observed or if no improvement after 24 hours, increase the dose and/or frequency of dexamethasone up to maximum of 20 mg IV every 6 hours. If no improvement after another 24 hours or if rapidly progressing symptoms are observed, or if life-threatening complications arise, give methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided 4 times a day; taper within 7 days).

NT Grade[a]	Corticosteroids and anti-seizure medication
Grade 3	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 to 20 mg IV every 8 to 12 hours. Corticosteroids are not recommended for isolated Grade 3 headaches. If worsening of neurologic toxicity is observed or if no improvement after 24 hours, escalate to methylprednisolone (dose and frequency as per Grade 2). If cerebral oedema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m^2.
Grade 4	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 20 mg IV every 6 hours. If worsening of neurologic toxicity is observed or if no improvement after 24 hours or, escalate to methylprednisolone (dose and frequency as per Grade 2). If cerebral oedema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m^2.

[a]CTCAE (Common Terminology Criteria for Adverse Events) criteria for grading neurologic toxicities

Hypersensitivity Reactions

Allergic reactions may occur with the infusion of Breyanzi. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO).

Infections and Febrile Neutropenia

Breyanzi should not be administered to patients with clinically significant active systemic infections. Serious and severe infections, including life-threatening or fatal infections have occurred in patients after Breyanzi infusion (see «Undesirable effects»). In clinical trials, infections at Grade 3 and higher were very frequently observed. Monitor patients for signs and symptoms of infection (including systemic fungal infections, opportunistic bacterial and viral infections, and bacterial and viral reactivation infections) before and after Breyanzi administration and treat appropriately. Administer prophylactic antimicrobials according to institutional guidelines.

In clinical trials, febrile neutropenia has been observed in 8.6% of patients after Breyanzi administration and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and start medically indicated supportive therapies, including broad spectrum antibiotics and fluids.

Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells.
In the clinical trials, patients with active HBV, HCV, or HIV infection were excluded. In the clinical trials, there were no reports of hepatitis reactivation in patients with prior history of HBV or HCV infection treated with Breyanzi. Ten of the 11 patients in the TRANSCEND study with a prior history of HBV were treated with concurrent antiviral suppressive therapy to prevent HBV reactivation during and after Breyanzi therapy.
Screening for HBV, HCV, and HIV should be performed in accordance with clinical guidelines before collection of cells for manufacturing.

Prolonged Cytopenias
Patients may develop prolonged cytopenias (thrombocytopenia, neutropenia, anemia), including cytopenias of Grade 3 or higher, for several weeks following the treatment of lymphodepleting chemotherapy and Breyanzi. In clinical trials, cytopenias of Grade 3 or higher were very frequently observed (see section “Adverse reactions”).

Monitor complete blood counts prior to and after Breyanzi administration.

Hypogammaglobulinemia
B-cell aplasia and hypogammaglobulinemia occurred in patients in clinical trials with Breyanzi (see section «Undesirable effects»). Monitor immunoglobulin levels after treatment with Breyanzi. If necessary, preventive measures against infections, antibiotic prophylaxis, and/or immunoglobulin replacement are indicated.

Secondary Malignancies
Patients treated with Breyanzi may develop secondary malignancies or a recurrence of a previously treated malignancy. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company for reporting and instructions.

Central Nervous System Lymphoma
There is no experience of use of Breyanzi in patients with primary CNS lymphoma. For secondary CNS lymphoma, (see section «Clinical efficacy»).

Lymphoma in the heart
There is no clinical experience on the use of Breyanzi in patients with lymphoma involvement in the heart.

CD19-negative DLBCL

There are no data on the efficacy and safety of Breyanzi in patients with CD19-negative DLCBL (see “Properties/Effects”).

Tumor Lysis Syndrome (TLS)

TLS may occur in patients treated with CAR T therapies. To minimise the risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol or an alternative prophylaxis prior to Breyanzi infusion. Signs and symptoms of TLS should be monitored and managed in accordance with clinical guidelines.

Live Vaccines

The safety of immunisation with live viral vaccines during or following Breyanzi treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Breyanzi treatment, and until restoration of the immune system following treatment with Breyanzi.

HIV Diagnostics

HIV and the lentivirus used to make Breyanzi have a limited, short span of identical genetic material (RNA). As a result, some commercial HIV nucleic acid tests can give false positive results in patients who received Breyanzi.

Blood, Organ, Tissue and Cell Donation

Patients treated with Breyanzi should not donate blood, organs, tissues and cells for transplantation.

Excipients

This medicine contains up to 52 mg of potassium per dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

This medicinal product contains up to 100 mg of sodium per dose, corresponding to 5.0% of the maximum daily sodium intake with food of 2 g recommended by the WHO for an adult.

Interactions

No interaction studies have been performed.

Monoclonal antibodies (mABs) directed against the epidermal growth factor receptor (anti-EGFR mAB)

There is a theoretical risk that anti-EGFR mABs (eg, cetuximab, panitumumab) could reduce the number of Breyanzi cells, as a truncated EGFR is expressed on the CAR T cells and thereby may reduce Breyanzi benefit. Prescribers should carefully assess benefit and risk before using anti-EGFRmAB therapy.

Pregnancy, lactation

Women of childbearing potential

Pregnancy status with women of child-bearing potential should be verified using a pregnancy test prior to starting treatment with Breyanzi.
A safe method of contraception should be used by female patients before starting lymphodepleting chemotherapy and during therapy with Breyanzi. Additional recommendations in this regard concerning fludarabine and cyclophosphamide can be found in the relevant summaries of product characteristics.
There are insufficient exposure data to provide a specific recommendation concerning duration of contraception following treatment with Breyanzi. The transferred CART cells may persist in the body for months or longer.

Pregnancy

There are no data from the use of Breyanzi in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Breyanzi to assess whether it can cause fetal harm when administered to a pregnant woman.

It is not known if Breyanzi has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia.
Therefore, Breyanzi is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the fetus. Pregnancy after Breyanzi therapy should be discussed with the treating physician.

Lactation

It is unknown whether Breyanzi cells are excreted in human milk or transferred to the breast- feeding child. Women who are breast-feeding should be advised of the potential risk to the breast-fed child.

Fertility

There are no data on the effect of Breyanzi on fertility.

Effects on ability to drive and use machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving Breyanzi should refrain from driving or operating heavy or potentially dangerous machines for at least 8 weeks after Breyanzi administration.

Undesirable effects

The safety data described in this section reflect exposure to Breyanzi in 4 pooled studies: TRANSCEND (017001), TRANSCEND WORLD (JCAR017-BCM-001), JCAR017-BCM-002 and 017007, in which 314 adult patients with relapsing or refractory large B-cell lymphoma received a dose within the dose range of 44-120 x 10^6 CAR-positive viable T cells. The median age of the pooled dataset was 63 years (range: 18 to 83); 42% were 65 years or older and 68% were men. The ECOG performance status at screening was 0 in 45%, 1 in 54%, and 2 in 2% of patients. The median on-study follow-up time was 10.8 months (range: 0.1 to 45.2 months).

The most common adverse reactions 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%), 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%), leucopenia (21%), infection with an unspecified pathogen (9%), and febrile neutropenia (8%). 3% of adverse reactions reported had a fatal outcome.

The adverse reactions are listed below by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency (%) and frequency category, using the following convention: very common (≥1/10); common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Infections and infestations[a]

Very common: Infections with unspecified pathogen (21.7%), Bacterial infectious disorders (11.1%)

common: Viral Infectious disorders, Fungal infectious disorders

Blood and Lymphatic System Disorders

very common: Neutropenia (66.6%), Anemia (48.1%), Thrombocytopenia (37.3%), Leukopenia (23.6%)

common: Febrile neutropenia, Lymphopenia, Hypofibrinogenaemia, Pancytopenia

Immune System Disorders

very common: Cytokine release syndrome (CRS) 38.9%), Hypogammaglobulinemia (12.1%)

uncommon: Haemophagocytic lymphohistiocytosis (HLH)

Metabolism and Nutrition Disorders

common: Hypophosphataemia

uncommon: Tumor lysis syndrome (TLS)

Psychiatric Disorders

very common: Insomnia (11.5%), Delirium[b] (10.2%)

common: Anxiety[c]

Nervous System Disorders

very common: Headache[d] (26.1%), Encephalopathy[e] (24.8%), Dizziness[f] (20.1%), Tremor[g] (15.6%)

common: Aphasia[h], Peripheral neuropathy[i], Visual disturbance[j], Ataxia, Taste disorder, Cerebellar syndrome[k], Cerebrovascular disorder[l], Seizure[m]

uncommon: Facial paralysis, Brain edema

Cardiac Disorders

very common: Tachycardia (19.1%)

common: Arrhythmia[n], Cardiomyopathy

Vascular Disorders

very common: Hypotension[o] (22.0%), Hypertension (10.2%)

common: Thrombosis[p]

Respiratory, Thoracic & Mediastinal Disorders

very common: Cough (20.4%), Dyspnoea[q] (14.0%)

common: Pleural effusion, Hypoxia, Pulmonary edema

Gastrointestinal Disorders

very common: Nausea (29.3%), Constipation (22.6%), Diarrhea (22.0%), Abdominal pain (17.5%), Vomiting (16.9%)

common: Gastrointestinal haemorrhage

Skin and Subcutaneous Tissue Disorders

very common: Rash (10.2%)

Renal and Urinary Disorders

very common: Acute kidney injury[r] (11.1%)

General Disorders and Administration Site Conditions

very common: Fatigue (38.2%), Pyrexia (19.7%), Edema[s] (17.2%)

common: Chills

Injury, Poisoning & Procedural Complications

Common: Infusion-related reaction

[a] Infections and infestations are grouped per MedDRA high level group term.
[b] Delirium includes agitation, delirium, delusion, disorientation, hallucination, 'hallucination, visual', irritability, restlessness.[c] Anxiety includes anxiety, panic attack.
[d] Headache includes headache, migraine, sinus headache.
[e] Encephalopathy includes amnesia, cognitive disorder, confusional state, depersonalisation/derealisation disorder, depressed level of consciousness, disturbance in attention, encephalopathy, flat affect, lethargy, leukoencephalopathy, loss of consciousness, memory impairment, mental impairment, mental status changes, paranoia, somnolence, stupor.
[f] Dizziness includes dizziness, presyncope, syncope.
[g] Tremor includes essential tremor, intention tremor, resting tremor, tremor.
[h] Aphasia includes aphasia, disorganised speech, dysarthria, dysphonia, slow speech
[i] Peripheral neuropathy includes hyperaesthesia, hypoaesthesia, hyporeflexia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, sensory loss
[j] Visual disturbance includes blindness, blindness unilateral, gaze palsy, mydriasis, nystagmus, vision blurred, visual field defect, visual impairment.
[k] Cerebellar syndrome includes balance disorder, dysdiadochokinesis, dyskinesia, dysmetria, hand-eye coordination impaired.
[l] Cerebrovascular disorder includes cerebral infarction, cerebral venous thrombosis, haemorrhage intracranial, transient ischemic attack
[m] Seizure includes seizure, status epilepticus.
[n] Arrhythmia includes arrhythmia, atrial fibrillation, atrioventricular block complete, atrioventricular block second degree, supraventricular tachycardia, ventricular tachycardia
[o] Hypotension includes hypotension, orthostatic hypotension.
[p] Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, venous thrombosis limb, vena cava thrombosis.
[q] Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure.
[r] Acute kidney injury includes acute kidney injury, blood creatinine increased, renal failure, renal injury.
[s] Oedema includes oedema, oedema genital, oedema peripheral, generalised oedema, localized oedema, scrotal oedema, peripheral swelling, swelling.

Description of selected adverse effects

Cytokine release syndrome (CRS)

CRS occurred in 39% of patients, 3% of whom experienced Grade 3 or 4 (severe, life threatening) CRS. There were no fatal events. Among patients who died after receiving Breyanzi, 4 patients had ongoing CRS at the time of death. The median time to onset was 5 days (range 1 to 14 days) and the median duration was 5 days (range 1 to 17 days).

The most common manifestations of CRS included pyrexia (37%), hypotension (18%), tachycardia (13%), chills (10%), and hypoxia (9%) see section «Warning and precautions» for monitoring and management guidance.
See "Warnings and Precautions" section for monitoring and handling.

Neurologic adverse reactions
CAR T cell-associated neurologic toxicities, as identified by investigators, occurred in 26% of patients receiving Breyanzi, including ≥ Grade 3 in 10% of patients. The median time to onset of the first event was 9 days (range: 1 to 66 days); 99% of all neurologic toxicities occurred within the first 8 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 10 days (range: 1 to 84 days).

The most common neurologic toxicities included encephalopathy (17%), tremor (10%), aphasia (9%), delirium (6%), dizziness (3%), and headache (3%). Seizures (1%) and cerebral oedema (0.3%) have also occurred in patients treated with Breyanzi. See section «Warning and precautions» for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia has been observed in 9% of patients after receiving Breyanzi. Infections (all grades) occurred in 39% of patients. Grade 3 or higher infections occurred in 12% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 9% of patients, bacterial infections occurred in 4%, and viral and fungal infections occurred in 1% each of patients, respectively. See section «Warning and precautions» for monitoring and management guidance.

Prolonged cytopenias
Grade 3 or higher cytopenias present at Day 29 following Breyanzi administration, occurred in 39% of patients, and included thrombocytopenia (31%), neutropenia (20%) and anaemia (6%). See section (“Warning and precautions”) for monitoring and management guidance.

Hypogammaglobulinaemia

Hypogammaglobulinaemia occurred in 12% of patients. See section «Warning and precautions» for monitoring and management guidance.

Immunogenicity

The immunogenicity of Breyanzi has been evaluated using the assay that detects antibodies against the CD19-binding domain. In the TRANSCEND study, pre-existing anti-therapeutic antibodies (ATA) were detected in 11% of patients. Either treatment-induced or treatment-boosted ATA were detected in 16%, of patients. Due to small number of subjects who had pre-existing ATA, treatment-induced or treatment-boosted ATA, the relationships between ATA status and efficacy, safety or pharmacokinetics were not conclusive.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No data from clinical studies are available regarding overdose of Breyanzi.

Properties/Effects

ATC code

To be confirmed.

Mechanism of action

Breyanzi is a CD19-directed genetically modified autologous cellular immunotherapy administered as a defined composition of CD8+ and CD4+ T-cells. The CAR binding to CD19, which is expressed on the cell surface of tumor and normal B cells, induces the activation and proliferation of CAR-T cells, the release of pro-inflammatory cytokines, and the cytotoxic killing of the target cells. The CAR is comprised of an 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. The CD3 zeta-mediated intracellular signalling is critical for initiating T-cell activation and antitumor activity, while the co-stimulation via 4-1BB (CD137) enhances the cellular expansion and persistence of the CAR-T cells.

Pharmacodynamics

Following Breyanzi infusion, pharmacodynamic responses were evaluated over a 4-week period by measuring transient elevation of soluble biomarkers such as cytokines, chemokines, and other molecules. The concentrations of cytokines and chemokines such as interleukin (IL) IL-6, IL-15, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and macrophage inflammatory protein-1beta (MIP-1β) were analysed. Peak elevation of soluble biomarkers was observed within the first 14 days after Breyanzi infusion and returned to baseline levels within 28 days.
B-cell aplasia, defined as CD19+ B cells comprising less than 3% of peripheral blood lymphocytes, is an on-target effect of Breyanzi. The incidence of B-cell aplasia at baseline was 92% and B-cell aplasia was observed in the majority of patients for up to 1 year following Breyanzi infusion.

Clinical efficacy

The antitumor activity and safety of Breyanzi were evaluated in an open-label, multicentre, single- arm trial TRANSCEND (CSR 017001) in patients with R/R aggressive B-cell non-Hodgkin lymphoma (NHL), defined according to the WHO classification 2016. The trial patients were ≥ 18 years with R/R diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) ~~other~~ DLBCL arising from indolent lymphoma (transformed from follicular lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia/small lymphocytic leukemia, Waldenström's macroglobulinemia, or other), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma (PMBCL), and follicular lymphoma grade 3B, who had received at least 2 lines of therapy (2 lines of therapy N=96, 3 lines of therapy N=58, 4 lines of therapy N=39, ≥ 5 lines of therapy N=28)The study included patients with ECOG performance status ≤ 2 (ECOG 0 N=92, ECOG 1 N=133, ECOG 2 N=4). 38% of patients received prior autologous and/or allogeneic hematopoietic stem cell transplant (HSCT). Patients who received prior CD19-directed therapy were eligible provided CD19-positivity was confirmed on a tumor biopsy at any time after CD19-directed therapy (N=12). Six patients showed a secondary central nervous system (CNS) involvement. The study excluded the following patients: patients with primary CNS lymphoma; patients with an active systemic infection, in particular an active HBV, HCV, or HIV infection; patients being treated with immunosuppressive therapy; patients with renal insufficiency (creatinine clearance of less than 30 mL/min), hepatic insufficiency (alanine aminotransferase > 5 times the upper limit of normal) or cardiac insufficiency (current left ventricular ejection fraction ≤ 40%, heart failure NYHA grade III or IV or other clinically important disorder of heart function). There was no prespecified threshold for blood counts; patients were eligible to enrol if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy.

Treatment consisted of lymphodepleting (LD) chemotherapy, fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day for 3 days, followed 2 to 7 days later by Breyanzi. The median

dose of Breyanzi was 87 × 10^6 CAR-positive viable T cells (range: 44- 120 × 10^6 CAR-positive viable T cells).

A bridging anticancer therapy for disease control was permitted between apheresis and lymphodepletion at the investigator's discretion. Of the 229 patients treated with Breyanzi, 60% received anticancer therapy for disease control

Of 298 patients who underwent leukapheresis, for whom Breyanzi was manufactured in the dose range of 44-120 × 10^6 CAR-positive viable T cells, 229 patients received Breyanzi and 69 patients did not. Of these 69 patients, there were 27 manufacturing failures, including 2 patients who did not receive Breyanzi and 25 patients who received treatment with investigational product that did not meet release specifications. Forty-two other patients were not treated with Breyanzi, the most frequent reasons being death or disease complications.

According to the treatment team's discretion, Breyanzi was administered in the inpatient (212 patients) or outpatient setting (17 patients). Safety and efficacy were consistent across the two groups.

The number of patients who were evaluable for efficacy was 216. The median on-study follow-up time was 19.9 months (range 0.2 to 45.2 months). Thirteen patients were not evaluable for efficacy, including 10 patients who did not have baseline PET-positive disease, or in whom, after an anticancer therapy (after leukapheresis and before the planned Breyanzi infusion), an Independent Review Committee (IRC) did not confirm PET-positive disease, and 3 patients for other reasons. The median time from leukapheresis to product availability was 24 days (range: 17 to 51 days), and the median time from leukapheresis to infusion was 37 days (range: 27 to 224 days).
Table 3 summarizes the baseline patient and disease characteristics in the TRANSCEND trial.

Table 3: 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)

Characteristic	All leukapheresed (N=298)	Breyanzi-treated (N=229)
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)
Large B-cell lymphoma 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.

Efficacy was established on the basis of the primary endpoint, overall response rate (ORR), in addition to secondary endpoints which included complete response (CR) rate, duration of response (DOR) as determined by an independent review committee and overall survival (OS) (Table 4).

Table 4: TRANSCEND clinical study: Response rate, duration of response and overall survival, IRC assessment

	Leukapheresed set (N=298)	Patients treated with Breyanzi and evaluable for efficacy (N=216)
Overall response rate (ORR)[a], n [95% CI]	179 (60.1%) [54.3%, 65.7%]	157 (72.7%) [66.2%, 78.5%]
Complete response (CR), n [95% CI]	128 (43.0%) [37.3%, 48.8%]	115 (53.2%) [46.4%, 60.0%]
Partial response (PR), n [95% CI]3	51 (17.1%) [13.0%, 21.9%]	42 (19.4%) [14.4%, 25.4%]
Duration of response (DOR)[a] (months) Median [95% CI][b] Range	n = 179 16.8 [8.0, NR] 0.0- 27.4	n = 157 20.2 [8.2, NR] 0.0-27.4

	Leukapheresed set (N=298)	Patients treated with Breyanzi and evaluable for efficacy (N=216)
DOR if best response is CR[a] (months)	n=128	n=115
Median	26.1	26.1
[95% CI][b]	[23.1, NR]	[23.1, NR]
Range	0.0, 27.4	0.0, 27.4
DOR if best response is PR[a] (months)	n =51	n = 42
Median	2.1	1.9
[95% CI][b]	[1.3-2.6]	[1.1-2.3]
Range	0.0, 23.3	0.0, 23.3
Median follow-up for DOR (months)		
Median	23.0	23.0 [22.9, 23.2]
[95% CI][c]	[23. 0, 23. 2]	
Overall survival (OS) (months)		
Median	13.3	27.3
[95% CI][b]	[10.2, 22.6]	[12.7, 45.2]
Range	0.1+, 56.7+	0.2, 53.4+
Probability of OS, %		
≥ 6 months	69.2	73.1
[95% CI][b]	[63.5-74.1]	[66.6-78.5]
≥ 12 months	53.0	57.5
[95% CI][b]	[47.1-58.5]	[50.6-63.8]
≥ 24 months	43.0	50.1
[95% CI][b]	[37.2-48.6]	[43.2-56.6]

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

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

[+] Ongoing.

The median time to first response (CR or partial response [PR]) was 1.0 months (range: 0.7 to 8.9 months). The median time to first 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 TRANSCEND study. 3 patients achieved CR and their 3 patients achieved a CR and the duration of response was ongoing at 23 months in 2 patients and was 1.9 months in the third patient. 11 patients received prior CD19-directed therapy and had efficacy and safety outcomes similar to the overall population. All patients had CD19 expression prior to Breyanzi infusion.

Outcomes in patients with rare histologic subtypes.

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. No unexpected safety signals were observed.

In the Efficacy set, the ORR results within patients with DLBCL transformed (t) from prior indolent lymphoma of FL, marginal cell lymphoma (MZL), chronic lymphocytic leukaemia/small lymphocytic

lymphoma; (CLL/SLL), and Waldenstrom macroglobulinemia (WM) were 86% (38/44 patients), 43% (3/7 patients), 50% (2/4 patients) and 50% (1/2 patients), respectively. CR rates were 61.4% for tFL, 29% for tMZL, 25% for tCLL/SLL (Richter's syndrome), and 0% for WM, respectively. No unexpected safety signals were observed in these subtypes.

Clinical Study TRANSCEND WORLD (JCAR017-BCM-001)
TRANSCEND WORLD is an ongoing single-arm, multi-cohort, multicentre, phase 2 study. The EU cohort is of a comparable design to TRANSCEND and its purpose is to investigate the efficacy and safety of Breyanzi in a European patient population for treatment of adult patients 3L+ large B-cell lymphoma, including R/R DLBCL (DLBCL NOS [de novo]), transformed FL, high-grade B-cell lymphoma, and FL3B. Patients previously treated with anti-CD19-targeted therapy were excluded.

At the time of the data cut-off (04 January 2021), 45 patients in the EU cohort had been leukapheresed and 36 treated with Breyanzi, with a median follow-up time of 11.6 months. The median time from leukapheresis to product availability was 29 days (range: 24 to 38 days). In the Breyanzi- treated group, the ORR was 61.1% (95% CI:43.5-76.6), and the CR rate was 33.3% (95% CI: 18.6-51.0). No new safety-related aspects were observed. The disease burden and baseline demographics were indicative of advanced, aggressive disease characteristics.

Safety and efficacy in elderly patients

In clinical trials of Breyanzi, 89 (39%) of the 229 patients in TRANSCEND were 65 years of age or older, and 19 (8%) were 75 years of age or older. No clinically important differences in safety or efficacy of Breyanzi were observed between these patients and younger patients.

Pharmacokinetics

Absorption

The median time of maximal expansion in peripheral blood occurred 12 days after the first infusion. Breyanzi was present in peripheral blood for up to 2 years.

Responders (N=150) had a 2.85-fold higher median C_{max} than nonresponders (N=45) (33,766.0 vs.11,846.0 copies/µg). Responders had a 2.22-fold higher median $AUC_{0\text{-}28d}$ than nonresponders (257,769.0 vs. 116,237.3 day*copies/µg).

Some patients required tocilizumab and corticosteroids for the management of CRS and neurologic toxicities. Patients treated with tocilizumab (N=47) had a 4.15-fold and 4.06-fold higher median C_{max} and $AUC_{0\text{-}28d}$, respectively, compared to patients who did not receive tocilizumab (N=198).

Similarly, patients who received corticosteroids (N=46) had a 4.39-fold and 3.90-fold higher median C_{max} and AUC_{0-28d}, respectively, compared to patients who did not receive corticosteroids (N=199).

Distribution

Breyanzi was present in bone marrow.

Metabolism

Information is not relevant to Breyanzi (a CAR-T cell product).

Elimination

Breyanzi is composed of human autologous T cells, and the expected metabolites are typical cellular degradation products resulting from normal cellular clearance mechanisms. Therefore, the CAR-T cells are expected to be degraded over time. Following infusion, Breyanzi exhibited an initial expansion followed by a bi-exponential decline. Breyanzi was present in peripheral blood for up to 2 years.

Kinetics in specific patient groups

Sex, race, ethnicity, and body weight did not show clear relationships to C_{max} or AUC_{0-28d}.

Hepatic impairment

Studies on liver dysfunction with Breyanzi have not been performed.

Renal impairment

Studies on renal dysfunction with Breyanzi have not been performed.

Elderly patients

Patients < 65 years old (N=144) had a 2.91-fold and 2.30-fold higher median C_{max} and AUC_{0-28d}, respectively, compared to patients ≥ 65 years old (N=101).

Preclinical data

Mutagenicity/Carcinogenicity

Genotoxicity assays and carcinogenicity studies were not conducted. *In vitro* expansion studies using T cells from healthy donors and patients showed no evidence for transformation and/or immortalization and no preferential integration near genes of concern in Breyanzi.

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

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf-life

Do not use this medicine after the expiry date ("EXP") stated on the carton.
Unopened vial when stored in vapor phase of liquid nitrogen at ≤ -130 °C.
13 months.
After thawing

The product should be administered immediately after thawing. In-use storage times and conditions should not exceed 2 hours at room temperature (15°C -25°C).

Special precautions for storage

Store and transport frozen (≤ -130°C).
Keep out of the reach of children.

Instructions for handling

Precautions to be taken before handling or administering the medicinal product

Breyanzi contains human blood cells that are genetically modified with replication incompetent, self-inactivating lentiviral vector. Healthcare professionals handling Breyanzi should take appropriate precautions (wearing gloves and glasses) for the handling and disposal, to avoid potential transmission of infectious diseases (see section “Special preacutions for disposal and other handling”).

Prepariation of Breyanzi for infusion

What is needed:

- protective clothing (gloves, goggles)
- cryogloves
- scissors
- protective barrier pads
- Luer-lock tip syringes
- alcohol wipe

- 20 gauge, 1-1 ½ inch needle
- sodium chloride 9 mg/mL (0.9%) solution for injection

Before thawing the vials

- Confirm the patient's identity with the patient identifiers on the shipper and external Breyanzi carton.
- Read the RFI Certificate (affixed inside the shipper) for information on the number of syringes you will need to administer the CD8+ and CD4+ cell components (syringe labels are provided with the RFI Certificate). There is a separate RFI Certificate for each cell component.
- The Breyanzi vials must not be removed from the cartons if the information on the patient-specific label does not match the intended patient. The company must be contacted immediately if there are any discrepancies between the labels and the patient identifiers.
- Open each inner carton and visually inspect the vial(s) for damage. If the vials are damaged, contact the market authorization holder.
- Confirm the infusion time in advance and adjust the start time of Breyanzi thaw such that it will be available for infusion when the patient is ready.
- Note: Once the vials of CAR-positive viable T cells (CD8+ cell component and CD4+ cell component) are removed from frozen storage, the thaw must be carried to completion and the cells administered within 2 hours.
- Carefully remove the vials from the cartons, place vials on a protective barrier pad, and thaw at room temperature. Thaw all vials at the same time. **Take care to keep the CD8+ and CD4+ cell components separate.**

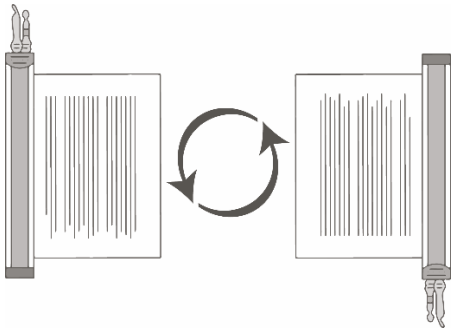
Dose preparation

- Based on the concentration of CAR-positive viable T cells for each component, more than one vial of each of the CD8+ and CD4+ cell components may be required to complete a dose. A separate syringe should be prepared for each CD8+ or CD4+ cell component vial received. Note: The volume to be drawn up and infused may differ for each component.
- Each 5 mL vial contains a total extractable volume of 4.6 mL of CD8+ or CD4+ cell component T cells. The RFI Certificate for each component indicates the volume (mL) of cells to be drawn up into each syringe. Use the smallest Luer-lock tip syringe necessary (1 mL to 5 mL) to draw up the specified volume from each vial. A 5 mL syringe should not be used for volumes less than 3 mL.
- Prepare the syringe(s) of the CD8+ cell component first. Confirm that the patient identifiers on the CD8+ cell component syringe label match the patient identifiers on the CD8+ cell component vial label. Affix the CD8+ cell component syringe labels to the syringe(s) prior to pulling the required volume into the syringe(s).

- Repeat the process for the CD4+ cell component.
  Note: It is important to verify that the volume drawn up for each component matches the volume specified in the respective RFI Certificate.

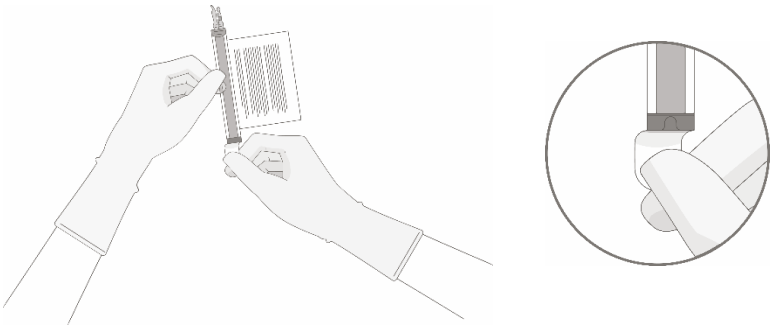
Withdrawal of the required volume of cells from each vial into a separate syringe should be carried out using the following instruction:

1. Hold the thawed vial(s) upright and gently invert the vial(s) to mix the cell product. If any clumping is apparent, continue to invert the vial(s) until clumps have dispersed and cells appear to be evenly resuspended.



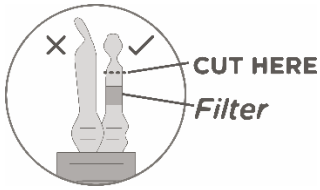
Vial upright Vial inverted

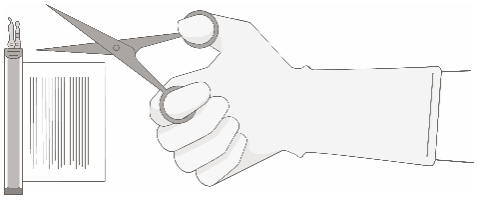
2. Visually inspect the thawed vial(s) for damage or leaks. Do not use if the vial is damaged or if the clumps do not disperse; contact the company. The liquid in the vials should be slightly opaque to opaque, colourless to yellow, or brownish-yellow.
3. Remove the polyaluminium cover (if present) from the bottom of the vial and swab the septum with an alcohol wipe. Allow to air dry before proceeding.



NOTE: The absence of the polyaluminium cover does not impact the sterility of the vial.

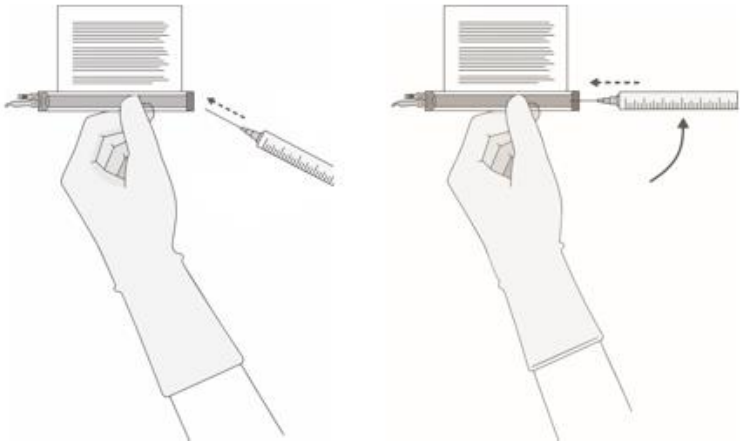
4. Keeping the vial(s) upright, cut the seal on the tubing line on the top of the vial immediately above the filter to open the air vent on the vial.
   NOTE: Be careful to select the correct tubing line with the filter. Cut ONLY the tubing with a filter.



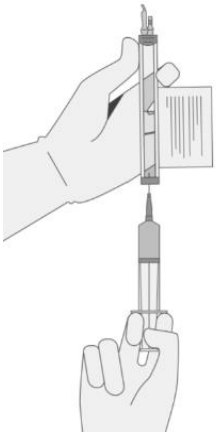


5. Hold a 20 gauge, 1-1 ½ inch needle, with the opening of the needle tip away from the retrieval port septum.
   a. Insert the needle into the septum at a 45-60° angle to puncture the retrieval port septum.
   b. Increase the angle of the needle gradually as the needle enters the vial.

a. b.

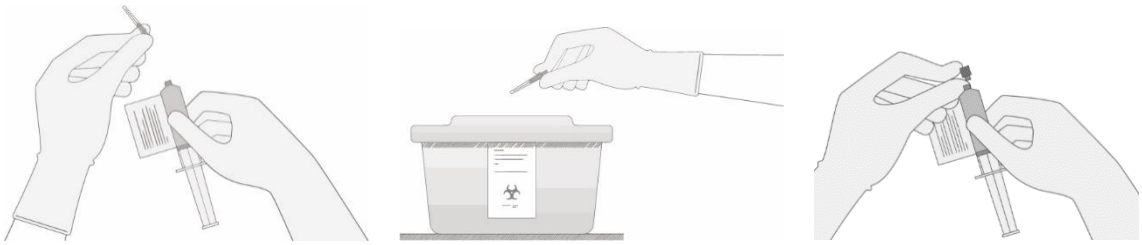


6. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the RFI Certificate).



7. Carefully inspect the syringe for signs of debris prior to proceeding. If there is debris, contact the company.
8. Verify that the volume of CD8+/CD4+ cell component matches the volume specified for the relevant component in the RFI Certificate.

Once the volume is verified, remove the syringe/needle from the vial, carefully detach the needle from the syringe and cap the syringe. Continue to keep the vial horizontal and return it to the carton to avoid leaking from the vial.



9. Dispose of any unused portion of Breyanzi (according to local biosafety guidelines).

Administration

- **Do NOT** use a leukodepleting filter.
- Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Confirm the patient's identity matches the patient identifiers on the syringe label.
- Once Breyanzi components have been drawn into syringes, proceed with administration as soon as possible. The total time from removal from frozen storage to patient administration should not exceed 2 hours.
- Use intravenous sodium chloride 9 mg/mL (0.9%) solution for injection to flush all the infusion tubing prior to and after each CD8+ or CD4+ cell component administration.
- Administer the CD8+ cell component first. The entire volume of the CD8+ cell component is administered intravenously at an infusion rate of approximately 0.5 mL/minute, using the closest port or Y-arm.
- If more than one syringe is required for a full cell dose of the CD8+ cell component, administer the volume in each syringe consecutively without any time between administering the contents of the syringes (unless there is a clinical reason to hold the dose, e.g., infusion reaction). After the CD8+ cell component has been administered, flush the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection.
- Administer the CD4+ cell component immediately after administration of the CD8+ cell component is complete, using the same steps described for the CD8+ cell component. Following administration of the CD4+ cell component, flush the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection, using enough flush to clear the tubing and the length of the IV catheter.
- The time for infusion will vary and will usually be less than 15 minutes for each component.

Special precautions for disposal and other handling

Breyanzi contains genetically modified human blood cells. It is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Breyanzi may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Breyanzi to avoid potential transmission of infections.

Work surfaces which have or may have been in contact with Breyanzi must be decontaminated with appropriate disinfectant Local biosafety guidelines should followed for unused medicinal products or waste material. All material that has been in contact with Breyanzi (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

Authorisation number

67469 (Swissmedic)

Packs

Breyanzi is supplied in cryopreservation vials made of cyclic olefin co-polymer. Each vial contains 4.6 mL cell dispersion. [A]

Each carton of CAR-positive viable T cells (CD8+ cell component or CD4+ cell component) contains up to 4 vials of each component, depending upon the cryopreserved drug product CAR-positive viable T cell concentration.

The cartons of CD8+ cell component and CD4+ cell component are contained in an outer carton and shipped in a liquid nitrogen shipper.

Marketing authorisation holder.

Celgene GmbH, Steinhausen

Date of revision of the text

March 2022