swissmedic

Date: 29 July 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Breyanzi

International non-proprietary name: lisocabtagene maraleucel

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:	for intravenous use only
Marketing authorisation holder:	Bristol-Myers Squibb SA
Marketing authorisation no.:	67469
Decision and decision date:	extension of therapeutic indication approved on 2 June 2025

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.

Table of contents

1 Terms, Definitions, Abbreviations

2L	Second-line
AE	Adverse event
$AUC_{0\text{-}28d}$	Area under the blood concentration-time curve from zero to 28 days after dosing
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
DOR	Duration of response
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
RMP	Risk management plan
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)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 4 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 follicular lymphoma (FL) who have received two or more prior lines of systemic therapy.

2.2.2 Approved indication

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy.

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	9 August 2024
Formal control completed	13 August 2024
List of Questions (LoQ)	11 December 2024
Response to LoQ	16 March 2025
Preliminary decision	12 May 2025
Response to preliminary decision	20 May 2025
Final decision	2 June 2025
Decision	approval

3 Medical context

Follicular lymphoma (FL) is an indolent B-cell lymphoma and the most commonly diagnosed type of iNHL, accounting for approximately 35% of all NHLs and 70% of indolent lymphomas in Western Europe and the US. The incidence of FL between 2015-2019 was approximately 2.18 per 100,000 persons in France, Germany, Italy, Spain and the UK.
FL is a heterogeneous pathological entity that includes tumours derived from germinal centre B-cells, both centrocytes and centroblasts. The t(14;18) translocation has been recognised as a genetic hallmark of FL and results in constitutive overexpression of the BCL-2 protein. The disease is characterised by diffuse lymphadenopathy, bone marrow involvement, splenomegaly, and other less common sites of extranodal involvement.
FL is graded 1 to 3 according to the proportion of centrocytes to centroblasts and corresponding disease aggressiveness. Grade 3 FL is further subdivided into grades 3A or 3B, where 3A has a similar clinical course to grades 1 to 2, and 3B is considered an aggressive lymphoma, generally treated in concordance with diffuse DLBCL-focused treatment guidelines. Early-stage FL (stage I to II) is generally rare, as more than 90% of patients present with advanced-stage disease at diagnosis. Histological transformation of FL, most frequently to DLBCL, occurs at a risk of about 2% to 3% per year over at least the first 10 to 15 years.
At initial diagnosis, established prognostic factors include age, the number of involved lymph nodal areas, the largest diameter of the largest involved lymph node, Ann Arbor staging, haemoglobin level, bone marrow involvement, lactate dehydrogenase, and β2 microglobulin. These prognostic factors are included in the commonly used FLIPI and FLIPI-2 prognostic indices. FLIPI was highly predictive of treatment outcomes and separated patients into 3 distinct risk groups with 10-year OS rates of 70.7% (low risk; 0-1 risk factor), 50.9% (intermediate risk; 2 risk factors), and 35.5% (high risk; ≥ 3 risk factors), respectively. In patients with relapsed disease, the types of prior treatments and duration of response to prior treatments may be more important in predicting the outcomes of subsequent treatments.
R/R FL after rituximab-based chemoimmunotherapy is a serious, life-threatening disease that is largely incurable despite advances in treatment over the past two decades, and represents a major therapeutic challenge. In the majority of patients, FL relapses multiple times with a pattern of decreased durability of remission with each subsequent line of therapy and reflects a high unmet need in 3L+ and POD24 patients.
An SLR was performed to identify the current evidence on the clinical efficacy and safety for approved as well as investigational therapies for the treatment of adult patients with R/R FL (grade 1-3a) in the 3L+ population. Additionally, studies investigating outcomes in POD24 patients were included, as POD24 status is an important prognostic factor associated with worse outcomes across lines of therapy. The SLR searched studies published between 1 January 1998 and 26 January 2024 and identified 173 publications representing 71 unique studies.
Treatments in these 71 trials included conventional therapies (eg, lenalidomide, rituximab, obinutuzumab), HSCT (autologous and allogenic), PI3K inhibitors (copanlisib, duvelisib, idelalisib), tazemetostat, and also novel therapies such as CAR T-cell therapies (liso-cel, axi-cel, and tisa-cel) and T-cell engagers (mosunetuzumab, glofitamab, epcoritamab, odronextamab).
Most data in the SLR pertained to the 3L+ setting, with 60 studies (85%) reporting on 3L+ populations or subgroups, of which 34 studies reported response outcomes (ORR, CR, PR, DOR) and 45 studies reported survival outcomes (OS, PFS, disease-free survival).
Pooled estimates from meta-analyses indicated moderate response rates (ORR of 74% and CR rate of 55%) and moderate survival rates (2-year OS/PFS of 69%/45%, 3-year OS/PFS of 78%/54%) among available therapies for 3L+ patients. The most favourable response and survival outcomes were seen with several novel agents that have recently emerged for the treatment of 3L+ R/R FL, including three bispecific CD20-directed CD3 T-cell engagers (epcoritamab, mosunetuzumab, and odronextamab) and two CAR T-cell therapies (axi-cel and tisa-cel). CAR T-cell therapies exhibited higher response rates and longer median survival estimates, with median OS not reached, and median PFS ranging from 37 to 57.3 months, and not reached in a study investigating liso-cel, after median follow-up times ranging from 18.9 months to 53.7 months. This was supported by meta-analytic results, which showed pooled ORR and CR rates of 74% and 55%, respectively, including all treatments (CAR T-cell therapy, T-cell

engagers, HSCT, and others) and pooled ORR and CR rates of 62% and 28%, respectively, in a sensitivity analysis that excluded CAR T-cell therapies, T-cell engagers, and HSCT. Adverse events in patients receiving these newer treatment options were common, including neutropenia, neurotoxicity, and CRS.

Two trials investigated response and survival outcomes for CAR T-cell therapies in 3L+ POD24 patients. In the ZUMA-5 trial of axi-cel, at a median follow-up of 23.3 months, the ORR and CR rate were 92% and 75%, respectively, with a median DOR of 38.6 months at a median follow-up of 30.9 months for POD24 patients treated with axi-cel. In the ELARA trial of tisa-cel, the ORR, CR rate, and PR rate were 82%, 59%, and 23%, respectively, for 61 POD24 patients who received tisa-cel at a median follow-up of 53.7 months.

In the ZUMA-5 trial, 70 POD24 patients who received axi-cel had a 24-month OS rate of 78% and a 36-month PFS rate of 59%, at a median follow-up of 53.7 months. The median OS was not reached, and the median PFS was 57.3 months. In the ELARA trial, 61 POD24 patients who received tisa-cel had 36-month OS and PFS rates of 83% and 50%, respectively, at a median follow-up of 40.6 months. The median OS was not reached, and the median PFS was 30.8 months.

4 Clinical aspects

4.1 Clinical pharmacology

Liso-cel, as a cellular therapy, expands in vivo. This expansion may depend on patient-specific factors, such as antigen load and inflammatory state. Additionally, long-term persistence of the therapy can be assessed using PK measurements.
The clinical pharmacology of liso-cel in subjects with FL has been characterised on the basis of results from the FL cohorts (cohorts 1, 2, and 3) of study FOL-001. This section provides an overview of the clinical pharmacology of liso-cel for subjects with R/R FL including 4L+ (cohort 1), 3L (cohort 2), 3L+ (cohorts 1 and 2), 2L (cohort 3) or 2L+ (cohorts 1, 2, and 3) groups. Results from the 3L+ group (cohorts 1 and 2) are highlighted in this section.
Overall, liso-cel concentration in peripheral blood over time showed a similar pattern in the 4L+, 3L, and 2L groups. In all 3 groups, the liso-cel concentration in the peripheral blood, as detected by ddPCR, exhibited rapid expansion followed by monophasic decline up to 28 days after infusion.
In the 3L+ group, median C_{max}, $AUC_{(0-28)}$, and T_{max} were 31336 copies/µg, 253400 day x copies/µg, and 10.0 days, respectively. Median T_{max} occurred at 10 days in the 4L+, 3L, and 2L groups. Median C_{max} and $AUC_{(0-28)}$ in the 2L group were higher than the 3L group, followed by the 4L+ group. However, inter-subject variability was large for C_{max} and $AUC_{(0-28)}$ (geometric CV% > 150%) with exposure ranges overlapping across the groups.
In the 3L+ group, no relevant differences in transgene PK parameters (C_{max}, T_{max}, $AUC_{[0-28]}$) by subgroups (e.g. age, sex, region, bulky disease [defined as any mass > 7 cm, or 3 or more masses [each > 3 cm] at screening based on investigator assessment], pre-LDC SPD status per IRC, FLIPI risk category and modified GELF criteria) were observed.
No apparent differences in transgene PK parameters were observed between 3L+ FL in study FOL-001 and 2L LBCL in the liso-cel arm of study BCM-003, both of which used ddPCR to detect liso-cel transgene. Furthermore, 2L and 3L+ LBCL exhibited similar transgene PK parameters . Thus, transgene PK parameters were similar across 2L LBCL, 3L+ LBCL, and 3L+ FL.
Persistence of liso-cel transgene in the peripheral blood is defined as a transgene count ≥ the LOD. In the 3L+ and 2L+ groups, persistence of liso-cel transgene was observed up to month 36 (day 1095). However, the number of evaluable subjects at month 36 (day 1095) was small in the 3L+ and 2L+ groups (N = 2 and N = 3, respectively). At month 30 (day 910), persistence of liso-cel transgene was observed in 25.0% (7 of 28 subjects) and 23.5% (8 of 34 subjects) in the 3L+ and 2L+ groups, respectively.

4.2 Dose finding and dose recommendation

The liso-cel dosing recommendation of 100 × 10^6 CAR+ viable T cells in study FOL-001 was selected based on dosing experience in study 017001, a phase 1 study in adult subjects with R/R DLBCL, NOS (de novo and transformed from indolent lymphoma), HGBCL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL, FL3B, and MCL. Subjects in study 017001 with 3L+ LBCL were assigned to one of the following four dose regimens:

- Dose level 1 (50 × 10^6 CAR+ T cells), single-dose regimen (DL1S)
- Dose level 1 (50 × 10^6 CAR+ T cells), 2-dose regimen (DL1D)
- Dose level 2 (100 × 10^6 CAR+ T cells), single-dose regimen (DL2S)
- Dose level 3 (150 × 10^6 CAR+ T cells), single-dose regimen (DL3S)

In accordance with the recommendation of the Steering Committee (based on preliminary evidence for a possible dose-response relationship with efficacy and acceptable safety in both DL1S and DL2S, and as further discussed in study CSR), a single target dose of 100 × 10^6 CAR+ T cells (ie, DL2S) was selected for the DLBCL cohort dose confirmation group. This was also ultimately chosen as the dose and regimen across the liso-cel development programme in B-cell malignancies in adults.

4.3 Efficacy

As of the 10 January 2024 data cutoff date, all FL cohorts (cohorts 1, 2, and 3) had been enrolled. A total of 154 subjects were screened, and 139 underwent leukapheresis. Of these, 130 (93.5%) received LDC and liso-cel infusion and formed the liso-cel-treated analysis set. Of these 130 subjects, 107 subjects comprised the 3L+ FL group (cohorts 1 and 2).
Overall, 128 (98.5%) subjects completed the treatment period and continued to the post-treatment follow-up period. Two (1.5%) discontinuations during the treatment period were either due to AE (N = 1 subject in cohort 3) or subject withdrawal (N = 1 subject in cohort 2). In the 3L+ FL group, all but one subject completed the treatment period (days 1 to 29), and 82.2% of 3L+ FL subjects were ongoing in the post-treatment follow-up period (day -30 to month 60). A pre-specified, primary analysis (data cutoff: 27 Janurary 2023; median on-study follow-up: 18.9 months) was conducted for hypothesis testing, and primary (ORR) and secondary (CRR) endpoints were met for the 3L+ and 4L+ FL cohorts of study FOL-001. In 3L+ FL subjects, ORR (per IRC Charter) was 97.0% ($p < 0.001$) and CRR was 94.1% ($p < 0.001$).
The efficacy results with longer follow-up (median 29.72 [min, max: 0.3, 39.6] months), based on the 10 Jan 2024 clinical cut-off date, continue to show clinically meaningful efficacy, survival outcomes, and ongoing durable responses with liso-cel, including in 3L+ R/R FL subjects with similar ORR and CR rates, DOR, PFS, and OS to those that had been reported in the interim CSR for study FOL-001, based on a clinical cut-off date of 27 January 2023.
The current efficacy analysis with longer follow-up (3L+ FL; N = 103) includes 2 additional subjects compared to the primary analysis for hypothesis testing (3L+ FL; N = 101). The 2 additional subjects included in the current analysis (liso-cel-treated efficacy analysis set) had provided additional images demonstrating PET-positive disease by IRC before liso-cel administration.
Overall, in subjects with 3L+ R/R FL:

- The primary endpoint for ORR per IRC using the Lugano Classification was 97.1% (95% CI: 91.7, 99.4) in the liso-cel-treated efficacy analysis set.
- The key secondary endpoint for CRR per IRC was 94.2% (95% CI: 87.8, 97.8) in the liso-cel-treated efficacy analysis set.
- Sensitivity analyses of ORR and CRR, in the leukapheresed (ITT) set and per investigator assessment in the liso-cel-treated efficacy analysis set were consistent with the results of the primary efficacy analysis for IRC-assessed ORR and CRR.
- ORR and CRR were consistent across all subgroups including, age, sex, FLIPI, number of prior systemic lines of therapy, prior PI3K inhibitors, prior ASCT, bulky disease, POD24 status, double refractory status, prior treatment with R2, bridging therapy, and meeting at least one of the modified GELF criteria. This was as expected, given the > 90% response rate, with almost all subjects responding to treatment.
- Liso-cel demonstrated high, rapid, and durable responses in extended follow-up.
  - Median DOR (subjects with CR or PR) per IRC Charter was not achieved (95% CI: 30.85, N.A.; median follow-up: 23.13 [95% CI: 22.93, 23.26] months).
  - The median time to first response (subjects with CR or PR; n = 100 [97.1%]) was 0.95 months (range: 0.6, 3.3). The median time to first CR (n = 97 [94.2%]) was 0.95 months (range: 0.6, 3.3).
- Based on a median follow-up for PFS of 23.98 months (95% CI: 23.82, 24.15; range: 1.0, 35.9+), median PFS per IRC Charter was not achieved.
- Based on a median follow-up for OS of 29.47 months (95% CI: 26.51, 29.93), median OS (months) was not achieved.
- HRQoL assessments consistently revealed improvements in scores over the assessment timepoints, further highlighting the clinical significance of the results observed in the efficacy and safety endpoints.

4.4 Safety

The median time from leukapheresis to liso-cel availability (defined as the date of release for infusion and representing the date the product was available to ship) was 29 days (range: 20 to 55 days), and the median time from leukapheresis to liso-cel infusion was 50 days (range: 31 to 313 days).
Of 139 subjects who underwent leukapheresis, 130 (93.5%) subjects received liso-cel. In the leukapheresed (ITT) set, 16 (11.5%) subjects died during the study: 1 (0.7%) subject from Cohort 1 died after LDC and before liso-cel infusion (due to acute respiratory failure, assessed by the investigator as not related to liso-cel/LDC/the study procedure), 1 (0.7%) subject from cohort 3 died within 30 days of receiving the liso-cel infusion (assessed as related to liso-cel treatment by the investigator because it involved HLH), and 14 (10.1%) subjects died after the 90-day post-infusion period (from day 91 after infusion and mainly due to disease progression). One subject from cohort 1 died of PML on day 190, an event that was considered as related to fludarabine and liso-cel by the investigator. The subject had undergone four prior lines of systemic therapy, three of which included anti-CD20 antibodies (rituximab and obinutuzumab), which are known to be associated with PML.
A total of 4 (2.9%) subjects died from AEs, the PTs included: AML, PML, HLH, and acute hypoxic respiratory failure. A total of 3 (2.2%) subjects died from other causes, which included: COVID-19, COVID-19 pneumonia, and erythema multiforme. One (0.7%) subject died due to a cardiac event.
One (0.8%) subject in Cohort 3 (2L FL) experienced a TEAE (HLH) that resulted in death. The HLH was assessed as related to liso-cel treatment by the investigator.
31 (23.8%) subjects with 2L+ FL experienced at least one serious TEAE of any causality. The most frequently reported serious TEAE PT (in ≥ 5% of all FL subjects) was CRS (12 [9.2%] subjects). 24 (18.5%) subjects with 2L+ FL experienced at least one liso-cel related serious TEAE.
AESIs known to be associated with CAR T-cell therapies as a class occurred in 87 (66.9%) subjects with 2L+ FL. Overall, the most frequently reported AESIs (in ≥10% of subjects) were CRS (57.7%), prolonged cytopenia (22.3%), and iiNT (16.2%). The majority of AESIs were mild to moderate in severity and manageable with protocol-specified guidelines and/or local standard of care. There were no AESIs in the IRR, TLS, and autoimmune disorder categories.
The frequency of AESIs was consistent across cohorts (lines of therapy) and groups.
CRS occurred in 75 (57.7%) subjects with 2L+ FL including 1 (0.8%) subject with grade 3 CRS from cohort 1 (4L+ FL). There were no subjects with grade 4 CRS and no subjects with fatal CRS. The most common symptoms of CRS (≥ 10%) included pyrexia (56.9%) and hypotension (13.8%).
The median time of CRS onset from the time of liso-cel infusion was 6 days (range: 1 to 17 days). CRS resolved in all subjects; the median time to resolution was 3 days (range: 1 to 10 days). Of the subjects who were received concomitant treatment for CRS, 18 (13.8%) received tocilizumab only (median 1 dose [range, 1 to 3]), none received corticosteroids only, 15 (11.5%) received both tocilizumab and corticosteroids, and 2 (1.5%) received vasopressors.
iiNT occurred in 21 (16.2%) subjects with 2L+ FL including 4 (3.1%) subjects with grade 3 iiNT. There were no subjects with grade 4 iiNT and no subjects with fatal iiNT. The most common iiNTs by PT were tremor (7.7%) and aphasia (6.9%). The median time to iiNT onset from the time of liso-cel infusion was 8 days (range: 4 to 16 days). iiNT resolved in all subjects; the median time to resolution was 4 days (range: 1 to 17 days). Of the subjects who were treated with concomitant medications for iiNT, none received tocilizumab only, 9 (6.9%) received corticosteroids only, none received both tocilizumab and corticosteroids, and none received vasopressors. The term ICANS was defined by the ASTCT in a consensus publication from 2019. As enrolment for study FOL-001 began prior to 2019, ICANS was not recorded as a distinct AE in this trial. Instead, CAR-T cell-associated signs and symptoms suggestive of neurotoxicity, which includes ICANS, were reported as iiNT. Consequently, ICANS is not presented separately in study FOL-001.
Prolonged cytopenia, defined as ≥ grade 3 cytopenia at the day 29 (± 2 days) visit based on local laboratory assessments of neutropenia, thrombocytopenia, or anaemia, occurred in 29 (22.3%) subjects with 2L+ FL. A total of 12 SPM events were reported in 9 (6.9%) subjects with 2L+ FL: melanoma (grade 2), colorectal cancer (grade 3), mucoepidermoid carcinoma (grade 2), MDS (grade 4), basal cell carcinoma (grade 1), SCC/Bowen's disease (grade 2), AML (2 grade 4 events and 2 grade

5 events), rectal cancer (grade 3), and adenocarcinoma of the colon (grade 3). No cases of T-cell malignancies were reported.
Tumour samples were collected from 7 SPM events and analysed using a validated RNAscope ISH for the presence of liso-cel transgene; 3 (AML, mucoepidermoid carcinoma, and adenocarcinoma of the colon) were negative for transgene, 1 (MDS) failed testing due to inadequate sample quality, and 3 (melanoma, SCC/Bowen's disease, and rectal cancer) were pending ISH results as of the data cut-off date of 10 January 2024. No samples were available for the remaining 5 SPM events. Blood samples from subjects with SPM were analysed for transgene and RCL. In the 2 SPM events (AML and colon adenocarcinoma) where the tumour sample tested negative for transgene, blood samples were also negative for transgene and RCL. No blood samples from the remaining 10 SPM events from 8 subjects were available for transgene analysis or RCL testing at the time of the SPM event.
The frequency of TEAEs was consistent across all cohorts (lines of therapy) and groups. TEAEs occurred in 99.2% of subjects with 2L+ FL; most TEAEs were related to liso-cel (115 [88.5%] subjects) or LDC (98 [75.4%] subjects). The most common TEAEs by SOC were blood and lymphatic system disorders (76.9% of subjects), immune system disorders (59.2% of subjects), and gastrointestinal disorders (46.9% of subjects). COVID-19-related TEAEs occurred in 2 (1.5%) subjects; TEAEs resulting in death occurred in 1 (0.8%) subject. Grade ≥ 3 TEAEs occurred in 100 (76.9%) subjects with 2L+ FL; the most frequently reported grade ≥ 3 TEAEs (≥ 10% subjects) were neutropenia (60.8%), lymphopenia (12.3%), leukopenia and thrombocytopenia (11.5%, each), and anaemia (10.0%).
LDC-related TEAEs occurred in 75.4% of all subjects with 2L+ FL. Liso-cel-related TEAEs occurred in 115 (88.5%) subjects with 2L+ FL. The most common liso-cel-related TEAEs by SOC were blood and lymphatic system disorders (61.5% of subjects), immune system disorders (59.2% of subjects), and general disorders and administration site conditions (31.5% of subjects). Liso-cel-related grade ≥ 3 TEAEs occurred in 81 (62.3%) subjects and the most frequently reported grade ≥ 3 TEAEs (≥ 10% subjects) were neutropenia (47.7%) and lymphopenia (11.5%).
9 subjects with 2L+ FL experienced TEAEs in the cardiac disorders SOC, including PT of tachycardia (N=3; grade 1), sinus tachycardia (N=3; grade 1/2), palpitations (N=1; grade 3), bradycardia (N=1; grade 3), atrioventricular block (N=1; grade 3). There were no cardiac disorder-related AEs reported beyond 90 days after liso-cel infusion. All cardiac TEAEs resolved by day 33 post liso-cel infusion. No subsequent cardiac events were reported for these patients.
Among the 9 subjects with cardiac TEAEs, 2 never experienced CRS. There were 5 subjects who developed a cardiac TEAE during or approximately 1 to 2 days prior to or after the CRS event, and 2 subjects developed a cardiac TEAE at least 2 weeks after the CRS had resolved. Two subjects with a cardiac TEAE died of causes not related to their cardiac events; one died on day 29 from grade 5 HLH and the other died on day 169 from COVID-19.
In addition to the above TEAEs classified as cardiac disorders, one subject death was reported on day 171 after liso-cel infusion as a result of the cardiac event of heart failure. The subject was reported to have a history of grade 1 cardiomyopathy. The screening echocardiogram conducted prior to the study treatment showed LVEF of 45%, and the screening ECG was interpreted as abnormal but without clinical significance. No acute cardiac events or CRS were reported for this subject during the TEAE or post-TEAE periods. This death from the cardiac event of heart failure was not reported as a liso-cel-related AE.
In the liso-cel-treated analysis set, changes in haematology laboratory results were consistent with anti-cancer therapy for disease control and LDC prior to liso-cel treatment followed by the expected recovery.
In the liso-cel-treated analysis set, most serum chemistry parameters remained stable over time.
Vector ISA was performed if persistence of CAR vector sequence was detected in ≥ 1% of nucleated blood cells at any time point ≥ 12 months after the liso-cel infusion. In the liso-cel-treated analysis set (2L+ FL), 2 subjects met the criteria for ISA: one subject's transgene percentage was 11.4% at month 12, while the other's was 3.5% at month 24. ISA was performed on both samples. Results for the subject with 11.4% transgene at month 12 showed the sample was polyclonal without evidence of a monoclonal outgrowth. Results for the subject with 3.5% transgene at month 24 were pending as of the data cut-off date of 10 January 2024.
No RCL was detected in the 464 samples tested from the liso-cel-treated analysis set (2L+ FL).

Vital signs in the liso-cel-treated analysis set (2L+ FL) generally remained the same over time.

4.5 Final clinical benefit risk assessment

The benefit risk profile for liso-cel for the treatment of patients with r/r FL after two or more lines of prior systemic therapy is positive.

5 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.

6 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.

▼ 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

- diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), or primary mediastinal large B-cell lymphoma (PMBCL) that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy
- relapsed or refractory (r/r) DLBCL, HGBCL or PMBCL after two or more lines of systemic therapy
- relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy.

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 3-14). 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. Of the patients randomised to the Breyanzi arm in TRANSFORM, 39% were 65 years and older and none were 75 years and older. Of the leukapheresed patients in TRANSCEND 39% of patients were 65 years and older and 8% of patients were 75 years and older. Of the leukapheresed patients with r/r FL after two or more lines of systemic therapy in TRANSCEND-FL 40% were 65 years and older and 9% were 75 years and older.

Children and adolescents

Based on the available data on the safety and efficacy of Breyanzi in children and adolescents below 18 years of age, no safe and effective dose could be established. Therefore, the use of Breyanzi in children and adolescents is not recommended.

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.

DLBCL, HGBCL, PMBCL:
In clinical studies, CRS occurred in 41% (227/561) of patients receiving Breyanzi, including ≥ Grade 3 (Lee grading system[a]) CRS in 2% (10/561) of patients. The median time to onset was 4 days (range: 1 to 63 days, with the upper limit due to CRS onset, without fever, reported in one patient) and the median duration of CRS was 5 days (range: 1 to 17 days).

116 of 561 (21%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. 55 (10%) patients received tocilizumab only, 53 (9%) received tocilizumab and a corticosteroid, and 8 (1%) received corticosteroids only.

FL:
In the clinical study, CRS occurred in 58% (75/130) of patients receiving Breyanzi, including Grade 3 (Lee grading system[a]) CRS in 0.8% (1/130) of patients. The median time to onset was 6 days (range: 1 to 17 days) and the median duration of CRS was 3 days (range: 1 to 10 days).

33 of 130 (25%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. 18 (14%) patients received tocilizumab only, 15 (12%) received tocilizumab and a corticosteroid and no patients 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

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab</th><th>Corticosteroids
(For corticosteroid tapering information, see below table)</th></tr>
<tr><td>Grade 1
Fever</td><td>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).</td><td>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.</td></tr>
<tr><td rowspan="2">Grade 2
Symptoms require and respond to moderate intervention.

Fever, oxygen requirement less than 40% FiO_2, or hypotension responsive to fluids or low dose of one vasopressor, or Grade 2 organ toxicity.</td><td>Administer tocilizumab 8 mg/kg IV over 1 hour (max. 800 mg).</td><td>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.</td></tr>
<tr><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% FiO_2, 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>Grade 4
Life-threatening symptoms.</td><td>Per Grade 2.</td><td>Administer dexamethasone 20 mg IV every 6 hours.</td></tr>
</table>

CRS Grade[a]	**Tocilizumab**	**Corticosteroids** (For corticosteroid tapering information, see below table)
Need for ventilator support or continuous veno-venous haemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	If rapid progression is observed or if no improvement within 24 hoursescalate tocilizumab and corticosteroid use as per Grade 2.	

[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, including immune effector cell-associated neurotoxicity syndrome (ICANS), which may be severe or life-threatening occurred concurrently with CRS, after CRS resolution or in the absence of CRS following treatment with Breyanzi.
Seizures and cerebral oedema have also occurred in patients treated with Breyanzi.

DLBCL, HGBCL, PMBCL:
In clinical studies, 24% (133/561) of patients experienced neurologic events including Grade ≥ 3 neurologic events in 9% (48/561) of patients. The median time to onset of an initial event was 8 days (range: 1 to 66 days). The median duration of neurologic toxicities was 8 days (range: 1 to 89 days).

FL:
In the clinical study, 16% (21/130) of patients experienced neurologic events, including Grade 3 neurologic events in 3% (4/130) of patients. The median time to onset of an initial event was 8 days (range: 4 to 16 days). The median duration of neurologic toxicities was 3 days (range: 1 to 17 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).
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.

NT Grade[a]	Corticosteroids and anti-seizure medication
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 (e.g., HHV-6 and progressive multifocal leukoencephalopathy)) before and after Breyanzi administration and treat appropriately. Administer prophylactic antimicrobials according to institutional guidelines. The possibility of opportunistic central nervous system infections should be considered in patients with neurologic adverse events and appropriate diagnostic testing should be performed.

In clinical studies, febrile neutropenia has been observed in 8% of patients receiving Breyanzi for DLBCL, HGBCL, or PMBCL and in 5% of patients receiving Breyanzi for FL 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.
Patients with active HBV, HCV (hepatitis C virus), or HIV infection were excluded from Breyanzi clinical trials. There was one report of HBV reactivation in a patient with inactive chronic HBV treated with Breyanzi. There were no reports of HCV reactivation in patients with prior history of HCV

infection. Twenty-four of the 27 patients in clinical studies 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 with the 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 with 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-EGFR mAB 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

DLBCL, PMBCL, HGBCL:
The adverse reactions described in this section were characterised in 561 patients infused with Breyanzi from 6 pooled studies in adult patients with relapsed or refractory large B-cell lymphoma.

The most common adverse reactions of any grade were neutropenia (69%), anaemia (45%), CRS (41%), thrombocytopenia (39%), and fatigue (34%).

The most common serious adverse reactions were CRS (16%), encephalopathy (9%), infection with an unspecified pathogen (5%), pyrexia (4%), neutropenia (3%), bacterial infectious disorders (3%), thrombocytopenia (3%), febrile neutropenia (3%), aphasia (3%), tremor (3%), hypotension (2%), and anaemia (2%).

The most common Grade 3 or higher adverse reactions included neutropenia (65%), anaemia (33%), thrombocytopenia (30%), leukopenia (22%), lymphopenia (11%), febrile neutropenia (7%), and infection with an unspecified pathogen (7%). 3% (14/561) of patients had an adverse reaction with a fatal outcome.

FL:
The adverse reactions described in this section were characterised in 130 adult patients with relapsed or refractory follicular lymphoma infused with Breyanzi in study TRANSCEND-FL.

The most common adverse reactions of any grade were neutropenia (68%), CRS (58%), anaemia (40%), headache (29%), thrombocytopenia (29%) and constipation (21%).

The most common serious adverse reactions were CRS (9%), aphasia (4%), febrile neutropenia (3%), pyrexia (2%) and tremor (2%).

The most common Grade 3 or higher adverse reactions included neutropenia (61%), leukopenia (12%), lymphopenia (12%), thrombocytopenia (12%) and anaemia (10%). 0.8% (1/130) of patients had an adverse reaction with a fatal outcome.

Tabulated list of adverse reactions from all clinical studies
The adverse reactions described in this section were characterised in 691 patients infused with Breyanzi from 7 pooled studies in adult patients with r/r large B-cell lymphoma or r/r follicular lymphoma who received a dose within the dose range of 44-120 x 10^6 CAR-positive viable T cells. The median age of patients in the pooled dataset was 64 years (range: 18 to 86); 48% were 65 years

or older and 63% were men. The ECOG performance status at screening was 0 in 46%, 1 in 50%, and 2 in 4% of patients. The median on-study follow-up time was 16.9 months (range: 0.2 to 45.2 months).

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 (17.2%)

common: Bacterial infectious disorders, Viral infectious disorders, Fungal infectious disorders

Blood and Lymphatic System Disorders

very common: Neutropenia (68.6%), Anaemia (43.8%), Thrombocytopenia (36.8%), Leukopenia (22.3%), Lymphopenia (12.7%)

common: Febrile neutropenia, Hypofibrinogenaemia

uncommon: Pancytopenia

Immune System Disorders

very common: Cytokine release syndrome (CRS) (43.7%)

common: Hypogammaglobulinemia

uncommon: Haemophagocytic lymphohistiocytosis (HLH)

Metabolism and Nutrition Disorders

common: Hypophosphataemia

uncommon: Tumor lysis syndrome (TLS)

Psychiatric Disorders

very common: Insomnia (10.4 %)

common: Anxiety[c], Delirium[b]

Nervous System Disorders

very common: Headache[d] (26.0%), Encephalopathy[e] (19.0%), Dizziness[f] (15.8%), Tremor[g] (13.7%)

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

uncommon: Cerebrovascular disorder[l], Seizure[m], Paresis[n], Brain edema

Cardiac Disorders

very common: Tachycardia (12.6%)

common: Arrhythmia[o]

uncommon: Cardiomyopathy

Vascular Disorders

very common: Hypotension[p] (17.2%),

common: Thrombosis[q], Hypertension

Respiratory, Thoracic & Mediastinal Disorders

very common: Cough (14.6%)

common: Dyspnoea[r], Pleural effusion, Hypoxia

uncommon: Pulmonary edema

Gastrointestinal Disorders

very common: Nausea (23.0%), Diarrhea (20.0%), Constipation (20.0%), Abdominal pain (12.6%), Vomiting (11.7%)

common: Gastrointestinal haemorrhage

Skin and Subcutaneous Tissue Disorders

very common: Rash (10.4%)

Renal and Urinary Disorders

common: Acute kidney injury[s]

General Disorders and Administration Site Conditions

very common: Fatigue (30.4%), Pyrexia (19.7%), Edema[t] (13.2%)

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, migraine with aura 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, dizziness postural, presyncope, syncope.
[g] Tremor includes essential tremor, intention tremor, resting tremor, tremor.
[h] Aphasia includes aphasia, disorganised speech, dysarthria, dysphonia, slow speech, speech disorder
[i] Peripheral neuropathy includes carpal tunnel syndrome, demyelinating polyneuropathy, 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 sinus thrombosis, embolic cerebral infarction, haemorrhage intracranial, transient ischemic attack.
[m] Seizure includes seizure, status epilepticus.
[n] Paresis includes facial paralysis, facial paresis, vocal cord paralysis.
[o] Arrhythmia includes arrhythmia, atrial fibrillation, atrioventricular block complete, atrioventricular block second degree, extrasystoles, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia.
[p] Hypotension includes hypotension, orthostatic hypotension.
[q] Thrombosis includes deep vein thrombosis, embolism, embolism venous, pulmonary embolism, thrombosis, venous thrombosis, venous thrombosis limb, vena cava thrombosis.
[r] Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure.
[s] Acute kidney injury includes acute kidney injury, blood creatinine increased, renal failure, renal injury.
[t] Oedema includes face oedema, oedema, oedema genital, oedema peripheral, generalised oedema, localized oedema, scrotal oedema, peripheral swelling, swelling, swelling face.

Description of selected adverse effects

Cytokine release syndrome (CRS)

DLBCL, HGBCL, PMBCL:

CRS occurred in 41% of patients, 2% of whom experienced Grade 3 or 4 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 4 days (range 1 to 63 days, with the upper limit due to CRS onset, without fever, reported in one patient) and the median duration was 5 days (range 1 to 17 days).

The most common manifestations of CRS included pyrexia (40%), hypotension (16%), tachycardia (10%), chills (7%), and hypoxia (7%).

116 of 561 (21%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. 55 (10%) patients received tocilizumab only, 53 (9%) received tocilizumab and a corticosteroid and 8 (1%) patients received corticosteroids only.

FL:

CRS occurred in 58% of patients, 0.8% of whom experienced Grade 3 CRS. There were no fatal events. The median time to onset was 6 days (range 1 to 17 days) and the median duration was 3 days (range 1 to 10 days).

The most common manifestations of CRS included pyrexia (57%), hypotension (14%), chills (4%), hypoxia (2%), and tachycardia (0.8%).

33 of 130 (25%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. 18 (14%) patients received tocilizumab only, 15 (12%) received tocilizumab and a corticosteroid and no patients received corticosteroids only.

See "Warnings and Precautions" section for monitoring and handling.

Neurologic adverse reactions
DLBCL, HGBCL, PMBCL:
CAR T cell-associated neurologic toxicities, as identified by investigators, occurred in 24% of patients receiving Breyanzi, including ≥ Grade 3 in 9% of patients. There were no fatal events. The median time to onset of the first event was 8 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 8 days (range: 1 to 89 days).

The most common neurologic toxicities included encephalopathy (16%), tremor (7%), aphasia (7%), delirium (5%), and dizziness (3%). Seizures (1%) and cerebral oedema (0.2%) have also occurred in patients treated with Breyanzi.

FL:
CAR T cell-associated neurologic toxicities, as identified by investigators, occurred in 16% of patients receiving Breyanzi, including Grade 3 in 3% of patients. There were no fatal events. The median time to onset of the first event was 8 days (range: 4 to 16 days); all neurologic toxicities occurred within the first 8 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 3 days (range: 1 to 17 days).

The most common neurologic toxicities included tremor (8%), aphasia (8%), encephalopathy (5%), delirium (4%), and headache (2%).

See section «Warning and precautions» for monitoring and management guidance.

Immune effector-cell associated neurotoxicity syndrome (ICANS) has been identified as an adverse event during post-approval use of Breyanzi. Because reports are from a population of unknown size, an estimate of frequency cannot be made.

Febrile neutropenia and infections
Febrile neutropenia has been observed in 8% of patients receiving Breyanzi for DLBCL, HGBCL or PMBCL and 5% of patients after receiving Breyanzi for FL.

DLBCL, HGBCL, PMBCL:
Infections (all grades) occurred in 34% of patients. Grade 3 or higher infections occurred in 11% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 7% of patients, bacterial infections occurred in 4%, and viral and fungal infections occurred in 1% of patients each.

FL:
Infections (all grades) occurred in 20% of patients. Grade 3 infections occurred in 5% of patients. Grade 3 infections with an unspecified pathogen occurred in 4% of patients, bacterial infections occurred in 2%, viral infections occurred in 1%, and fungal infections occurred in none of the patients.

See section «Warning and precautions» for monitoring and management guidance.

Prolonged cytopenias
DLBCL, HGBCL, PMBCL:
Grade 3 or higher cytopenias present at Day 29 (or at Day 35 for patients in TRANSFORM) following Breyanzi administration, occurred in 37% of patients, and included thrombocytopenia (30%), neutropenia (23%) and anaemia (8%).
The median time (min, max) to resolution (cytopenia recovering to Grade 2 or less) was as follows in days: thrombocytopenia 32 days (2, 329); neutropenia 30 days (3, 339); and anaemia 21 days (3, 78).

FL:
Grade 3 or higher cytopenias present at Day 29 following Breyanzi administration, occurred in 22% of patients, and included thrombocytopenia (15%), neutropenia (15%) and anaemia (5%).
The median time (min, max) to resolution (cytopenia recovering to Grade 2 or less) was as follows in days: thrombocytopenia 36 days (16, 694); neutropenia 30 days (5, 110); and anaemia 36 days (8, 64).

See section (“Warning and precautions”) for monitoring and management guidance.

Hypogammaglobulinaemia

Adverse events of hypogammaglobulinaemia occurred in 11% of patients receiving Breyanzi for DLBCL, HGBCL or PMBCL and in 2% of patients receiving Breyanzi for FL. 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 patients with r/r DLBCL, r/r HGBCL or r/r PMBCL after fist line immunochemotherapy, pre-existing anti-therapeutic antibodies (ATAs) were detected in 0.6% of patients, and treatment-induced ATAs were detected in 4% of patients.

In patients with r/r DLBCL, r/r HGBCL or r/r PMBCL after two or more prior lines of systemic therapy pre-existing ATAs were detected in 9% of patients. Either treatment-induced or treatment-boosted ATAs were detected in 15% of patients.

In patients with r/r FL, pre-existing ATAs were detected in 2% of patients, and treatment-induced or treatment-boosted ATAs were detected in 27% 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.

Elderly patients
No clinically important differences in safety of Breyanzi were observed between elderly and younger patients.

Paediatric population

The safety and efficacy of lisocabtagene maraleucel in paediatric patients (<18 years old and weight ≥ 6 kg) with r/r B-cell acute lymphoblastic leukaemia (B-ALL) was evaluated in the dose escalation phase of the clinical study TRANSCEND PEDALL (BCM-004). A total of 14 patients received lisocabtagene maraleucel at doses of 0.05 – 0.50 x 10^6 CAR-positive T cells / kg body weight.
The most common adverse reactions of any grade were anaemia (79%), CRS (64%), thrombocytopenia (57%), leukopenia (43%), and neutropenia (43%). Twelve (86%) patients experienced at least one Grade 3/4 adverse reaction. Nine (64%) patients experienced at least one serious adverse reaction. Four (27%) patients experienced CAR T cell-associated neurologic toxicities, as identified by investigators, including 2 patients experiencing Grade 4 cerebral oedema. Based on the data from TRANSCEND PEDALL no safe and effective dose could be established.

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

L01XL08 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. B-cell aplasia was observed in 56% of patients in TRANSFORM, 73% of patients in TRANSCEND and 65% of patients with r/r FL who received two or more prior lines of systemic therapy in TRANSCEND-FL at 1 year following Breyanzi infusion.

Clinical efficacy

TRANSFORM

The efficacy and safety of Breyanzi was compared to the standard of care (SOC) in a phase 3, randomized, open-label, parallel group, multicentre study, TRANSFORM (BCM-003), in adult patients with large B-cell non-Hodgkin lymphoma primary refractory to or relapsed within 12 months of first line therapy, who were candidates for HSCT. The SOC consisted of salvage immunochemotherapy followed by high dose chemotherapy (HDCT) and autologous HSCT. Patients with diffuse large B-cell lymphoma (DLBCL) (not otherwise specified (NOS), de novo or transformed indolent NHL), high grade B-cell lymphoma with DLBCL histology and MYC and BCL2 and/or BCL6 rearrangements (double/triple hit lymphoma [DHL/THL]), primary mediastinal B-cell lymphoma (PMBCL), T cell/histiocyte rich B cell lymphoma (THRBCL) or follicular lymphoma Grade 3B (FL3B) qualified for the study. The study included patients with ECOG performance status ≤ 1, and secondary CNS lymphoma involvement. Inclusion and exclusion criteria were chosen to ensure adequate organ function, and blood counts for HSCT. The study excluded patients with a creatinine clearance of less than 45 mL/min, alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN) or left ventricular ejection fraction (LVEF) < 40%, and absolute neutrophil count (ANC) < 1.0×10^9 cells/L and platelets < 50×10^9 cells/L in absence of bone marrow involvement. Also excluded were patients with a clinically significant cardiovascular event in the 6 months preceding the study, patients with active hepatitis B or C, and HIV-positive patients.

Patients were randomized 1:1 to receive either Breyanzi or SOC. Randomization was stratified by response to first-line therapy, and secondary age adjusted international prognostic index (sAAIPI) (0 / 1 versus 2 / 3). Patients in the Breyanzi study arm were to receive lymphodepleting chemotherapy consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day for 3 days followed by Breyanzi infusion (target dose of 100×10^6 CAR+ viable T cells) 2 to 7 days after completion of lymphodepleting chemotherapy. In the Breyanzi arm, bridging chemotherapy was permitted between leukapheresis and the start of lymphodepleting chemotherapy with 1 cycle of immunochemotherapy (i.e., rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin, and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R-GDP]). All patients randomized to the SOC arm were to receive 3 cycles of salvage immunochemotherapy (i.e., R-DHAP, R-ICE, or R-GDP). Patients responding (complete response [CR] or partial response [PR]) after 3 cycles were eligible to proceed to HDCT and autologous HSCT. Patients receiving SOC treatment were allowed to receive Breyanzi (cross-over) if they failed to achieve CR or PR after 3 cycles of salvage immunochemotherapy, or had disease progression at any time, or if the patient needed to start a new treatment due to efficacy concerns.
Of 92 patients randomised to Breyanzi, 89 (97%) received Breyanzi and 1 (1%) patient received nonconforming product. Two patients did not receive Breyanzi. Of these 2 (2%) patients, 1 (1%) did not receive Breyanzi due to manufacturing failure, and 1 (1%) patient withdrew consent prior to treatment. Breyanzi was administered in a qualified Breyanzi treatment centre in an inpatient or

outpatient setting. 70 (79%) patients received Breyanzi in an inpatient setting and 19 (21%) patients in an outpatient setting. The median dose of Breyanzi was 99.9 × 10^6 CAR+ viable T cells (range: 97-103 × 10^6 CAR+ viable T cells). Out of 92 patients randomised to the SOC arm, 91 (99%) patients started treatment. One (1%) patient withdrew consent before starting treatment. Forty-three (47%) patients completed immunochemotherapy, HDCT, and HSCT treatment. Forty-eight (53%) patients received salvage immunochemotherapy but did not proceed to receive HDCT and HSCT. Fifty-eight (63%) patients went on to receive Breyanzi after failing SOC treatment.
The efficacy analyses were based on the ITT analysis set (n=184), which was defined as all patients randomised to a treatment arm.
The median time from leukapheresis to product availability was 26 days (range: 19 to 84 days), and the median time from leukapheresis to infusion was 36 days (range: 25 to 91 days).

Table 3 summarizes the baseline patient and disease characteristics in the TRANSFORM trial.

Table 3: Baseline demographic and disease-related characteristics for TRANSFORM (intention-to-treat [ITT] analysis set)

Characteristic	**SOC (N=92)**	**Breyanzi arm (N=92)**
Median age, years (range)	58.0 (26, 75)	60.0 (20, 74)
≥ 65 years, n (%)	23 (25.0)	36 (39.1)
≥ 75 years, n (%)	2 (2.2)	0
Sex, n (%) Male Female	 61 (66.3) 31 (33.7)	 44 (47.8) 48 (52.2)
ECOG Performance Status (at Screening) ECOG 0, n (%) ECOG 1, n (%)	 57 (62.0) 35 (38.0)	 48 (52.2) 44 (47.8)
Disease histology subtype, n (%)		
DLBCL, NOS	50 (54.3)	53 (57.6)
DLBCL transformed from indolent lymphoma	8 (8.7)	7 (7.6)
HGBCL	21 (22.8)	22 (23.9)
PMBCL	9 (9.8)	8 (8.7)
T cell rich/histiocyte rich large B-cell lymphoma	4 (4.3)	1 (1.1)
Chemorefractory[a], n (%)	18 (19.6)	25 (27.2)
Refractory[b], n (%)	68 (73.9)	67 (72.8)
Relapsed[c], n (%)	24 (26.1)	25 (27.2)
Confirmed CNS involvement, n (%)	3 (3.3)	1 (1.1)
Never achieved CR from prior therapies, n (%)	64 (69.6)	62 (67.4)

[a] Chemorefractory is defined as experiencing stable disease (SD) or progressive disease (PD) to last chemo-containing regimen
[b] The status was refractory if a patient achieved SD, PD, PR or CR with relapse before 3 months.
[c] The status was relapsed if a patient with a CR relapsed between 3 and 12 months after CR.

This study demonstrated statistically significant improvements in the primary endpoint of event free survival (EFS), and key secondary endpoints of complete response (CR) rate, and progression-free survival (PFS) for patients randomized to Breyanzi compared to SOC. Efficacy was based on EFS as determined by an independent review committee (IRC) using 2014 Lugano criteria. EFS was defined as the time from randomization to death from any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization (meaning after 3 cycles of salvage immunochemotherapy and 5 weeks after Breyanzi infusion) or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first.
At a pre-specified interim analysis at 80% of the information fraction with a median on-study follow up time of 6.2 months (range 0.9 to 20 months), Breyanzi demonstrated a statistically significant improvement in EFS compared to the SOC arm (HR = 0.349 [95% CI: 0.229, 0.530], one-sided p-value <0.0001). The p-value was compared with 0.012 of the allocated alpha for the pre-specified interim analysis.

The results of the subsequent primary analysis (shown in Table 4), with a median on-study follow-up time of 17.5 months (range 0.9 to 37 months), were consistent with the interim analysis. Of the 92 patients in the Breyanzi arm, 80 (68 CR, 12 PR) had a response with an overall response rate of 87%. Figure 1 shows the Kaplan-Meier plot of OS based on IRC assessment at the time of the primary analysis and includes 58 (63%) patients in the SOC-Arm who received Breyanzi after failing SOC treatment.

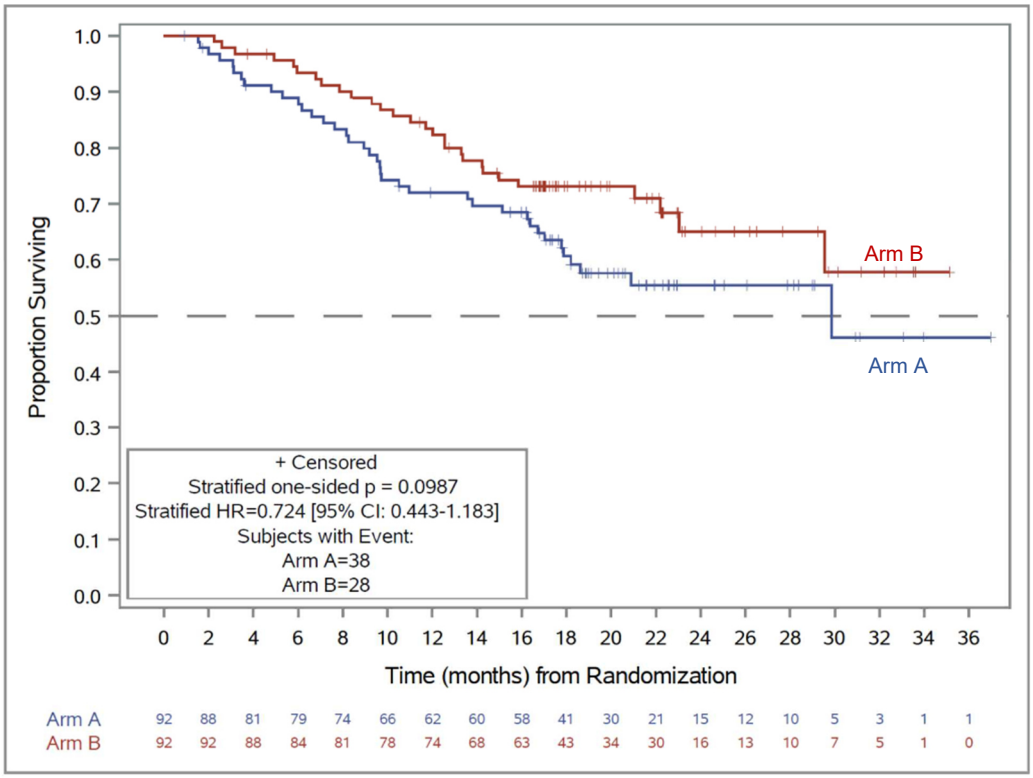
Table 4: TRANSFORM study: Response rate, event-free survival, progression-free survival (ITT analysis set)

	SOC arm (N=92)	**Breyanzi arm (N=92)**
Event-free survival,[a] **(months)** Median (months)[b] [95% CI] Hazard ratio [95% CI][c]	 2.4 (2.2, 4.9) -	 NR (9.5, NR) 0.356 [0.243, 0.522]
Complete response rate,[a] **n (%)** [95% CI] One sided p-value[d,e]	40 (43.5) [33.2, 54.2] -	68 (73.9) [63.7, 82.5] <0.0001
Progression-free survival,[a] **(months)** Median (months)[b] [95% CI] Hazard ratio [95% CI][c] One-sided p-value[d]	 6.2 (4.3, 8.6) - -	 NR (12.6, NR) 0.400 [0.261, 0.615] <0.0001
Overall survival (OS), (months) Median[b] [95% CI] Hazard ratio [95% CI][c] One-sided p-value[d]	 29.9 (17.9, NR) -	 NR (29.5, NR) 0.724 [0.443, 1.183] 0.0987

NR=not reached; CI=confidence interval.
[a] Per the Lugano criteria, as assessed by an IRC.

[b] Kaplan-Meier estimate
[c] Based on a stratified Cox proportional hazards model.
[d] p-value is compared with 0.021 of the allocated alpha for this pre-specified interim analysis
[e] Cochran-Mantel-Haenszel test.

Figure 1: TRANSFORM study: Kaplan-Meier Plot of OS Based on IRC Assessment (ITT analysis set)



Abbreviations: Arm A = SOC arm subjects; Arm B = Breyanzi arm subjects; CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intent-to-treat; OS = overall survival.

PILOT

The efficacy and safety of Breyanzi was evaluated in a phase 2, open-label, multicenter, single arm trial (PILOT, 017006) in adult patients who have relapsed from, or are refractory to, front-line chemotherapy for diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS; de novo or transformed from follicular lymphoma [tFL]), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (DHL/THL), or FL3B per WHO 2016 classification and were not intended for transplant. The study included patients who met at least one of the following criteria; Age ≥ 70 years, gender-specific adjusted diffusing capacity of the lung for carbon monoxide (DLCO) ≤ 60%; LVEF < 50%; creatinine clearance < 60mL/min; aspartate or alanine aminotransferase (AST/ALT) > 2 × ULN, or with ECOG performance status = 2. Patients with secondary CNS lymphoma involvement were eligible. The study excluded patients who had prior HSCT, ECOG performance status of 3, a creatinine clearance of ≤ 30 mL/min, AST/ALT > 5 times the ULN, or left ventricular ejection fraction < 40%. 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.
Bridging anticancer therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy. Of the 61 patients treated with Breyanzi, 32 (53%) received anticancer therapy for disease control.

Treatment consisted of lymphodepleting chemotherapy, fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day for 3 days, followed by Breyanzi 2 to 7 days later. The target dose of Breyanzi was 100 × 10^6 CAR-positive viable T cells. The median dose of Breyanzi was 99.9 × 10^6 CAR-positive viable T cells (range: 64-103 × 10^6 CAR-positive viable T cells).

Of 74 patients who underwent leukapheresis, 61 (82%) received Breyanzi and 1 patient received nonconforming product. 12 (16%) patients did not receive Breyanzi. Of these 12 patients, 5 patients died, 1 patient had disease-related complications, 5 no longer met the eligibility criteria and 1 for other reasons.
Breyanzi was administered in the inpatient (67%) and outpatient (33%) setting. Safety and efficacy for patients treated in the outpatient setting were consistent with the overall population. The number of patients who were evaluable for efficacy was 61 (Efficacy set), confirmed by an IRC to have baseline PET-positive disease including after bridging anticancer therapy. The median time from leukapheresis to product availability was 35 days (range: 25 to 187 days), and the median time from leukapheresis to infusion was 36 days (range: 25 to 188 days).

The baseline patient and disease characteristics in the PILOT study are summarized in Table 5.

Table 5: Baseline demographic and disease-related characteristics for PILOT

Characteristic	**All leukapheresed (N=74)**	**Breyanzi-treated (N=61)**
Median Age, years (range)	72.8 (53, 84)	73.1 (53, 84)
≥ 65 years, n (%)	66 (89.2)	55 (90.2)
≥ 75 years, n (%)	32 (43.2)	28 (45.9)
Sex, n (%) Male Female	 45 (60.8) 29 (39.2)	 37 (60.7) 24 (39.3)
ECOG Performance Status (at screening) ECOG 0-1 n (%) ECOG 2 n (%)	 54 (73.0) 20 (27.0)	 45 (73.8) 16 (26.2)
Large B-cell lymphoma subtype, n (%)		
DLBCL, NOS	41 (55.4)	33 (54.1)
DLBCL transformed from follicular lymphoma	10 (13.5)	9 (14.8)

Characteristic	All leukapheresed (N=74)	Breyanzi-treated (N=61)
HGBCL	22 (29.7)	18 (29.5)
FL3B	1 (1.4)	1 (1.6)
Chemorefractory[a], n (%)	23 (31.1)	18 (29.5)
Refractory[b], n (%)	40 (54.1)	33 (54.1)
Relapsed[b], n (%)	34 (45.9)	28 (45.9)
Never achieved CR from prior therapies, n (%)	40 (54.1)	33 (54.1)

[a] Chemorefractory is defined as experiencing stable disease (SD) or progressive disease (PD) to last chemo-containing regimen
[b] The status was refractory if a subject achieved less than a CR to last prior therapy; otherwise the status was relapsed.

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 using Lugano 2014 criteria and overall survival (OS) (Table 6). The median on-study follow-up time was 12.3 months (range 1.2 to 26.5 months). The median time to first response (CR or PR) was 0.95 months (range: 0.8 to 2.7 months). The median time to first CR was 0.95 month (range 0.8 to 6.9 months). Response durations were longer in patients who achieved a CR, as compared to patients with a best response of PR.

Table 6: PILOT clinical study: Response rate, duration of response and overall survival

	All leukapheresed (N=74)	Patients treated with Breyanzi and evaluable for efficacy (N=61)
Overall response rate (ORR)[a], n [95% CI][b]	50 (67.6%) [55.7%, 78.0%]	49 (80.3%) [68.2%, 89.4%]
Complete response (CR), n [95% CI] [b]	34 (45.9%) [34.3%, 57.9%]	33 (54.1%) [40.8%, 66.9%]
Partial response (PR), n [95% CI] [b]	16 (21.6%) [12.9%, 32.7%]	16 (26.2%) [15.8%, 39.1%]
Duration of response (DOR)[a] (months) Median [95% CI][c] Range	 12.1 [5.82, NR] 0.0, 23.0	 12.1 [6.2, NR] 0.0, 23.0
DOR if Best Overall Response is CR[a] (months) Median [95% CI][c] Range	 21.7 [12.1, NR] 2.0, 23.0	 21.7 [12.1, NR] 2.1, 23.0
DOR if Best Overall Response is PR[a] (months) Median [95% CI][c] Range	2.1 [1.4, 3.3] 0.0, 8.6	2.1 [1.4, 3.3] 0.0, 8.6
Overall survival (OS) (months) Median [95% CI][c] Range	 NR [14.7, NR] 0.0, 36.5	 NR [17.3, NR] 1.2, 35.4

CI=confidence interval; NR=Not reached; DOR=duration of response; CR=complete response; PR=partial response

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

[b] 2-sided 95% exact Clopper-Pearson confidence intervals.

[c] Kaplan-Meier (KM) method is used to obtain 2-sided 95% confidence intervals

TRANSCEND

The efficacy and safety of Breyanzi were evaluated in an open-label, multicentre, single- arm trial TRANSCEND (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), 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, $\geq$ 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 tumour 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 7 summarizes the baseline patient and disease characteristics in the TRANSCEND trial.

Table 7: Baseline demographic and disease-related characteristics

Characteristic	**All leukapheresed (N=298)**	**Breyanzi-treated (N=229)**
Median Age, years (range)	62.0 (18, 82)	62.0 (18, 82)
≥ 65 years, n (%)	116 (38.9)	89 (38.9)
≥ 75 years, n (%)	25 (8.4)	19 (8.3)
Sex, n (%) Male Female	 197 (66.1) 101 (33.9)	 153 (66.8) 76 (33.2)
Prior HSCT, n (%) Autologous HSCT Allogeneic HSCT	106 (35.6) 100 (33.6) 11 (3.7)	87 (38.0) 84 (36.7) 8 (3.5)
ECOG Performance Status ECOG 0-1 n (%) ECOG 2 n (%)	 290 (97.3) 8 (2.7)	 225 (98.3) 4 (1.7)
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)

Characteristic	All leukapheresed (N=298)	Breyanzi-treated (N=229)
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 8).

Table 8: 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]	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
DOR if best response is CR[a] (months) Median [95% CI][b] Range	n=128 26.1 [23.1, NR] 0.0, 27.4	n=115 26.1 [23.1, NR] 0.0, 27.4
DOR if best response is PR[a] (months) Median [95% CI][b] Range	n =51 2.1 [1.3-2.6] 0.0, 23.3	n = 42 1.9 [1.1-2.3] 0.0, 23.3
Median follow-up for DOR (months) Median [95% CI][c]	 23.0 [23. 0, 23. 2]	 23.0 [22.9, 23.2]
Overall survival (OS) (months) Median [95% CI][b] Range	 13.3 [10.2, 22.6] 0.1+, 56.7+	 27.3 [12.7, 45.2] 0.2, 53.4+

	Leukapheresed set (N=298)	Patients treated with Breyanzi and evaluable for efficacy (N=216)
Probability of OS, %		
≥ 6 months [95% CI][b]	69.2 [63.5-74.1]	73.1 [66.6-78.5]
≥ 12 months [95% CI][b]	53.0 [47.1-58.5]	57.5 [50.6-63.8]
≥ 24 months [95% CI][b]	43.0 [37.2-48.6]	50.1 [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.

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.

TRANSCEND-FL
The efficacy and safety of Breyanzi was evaluated in a Phase 2, open-label, multicenter, single-arm study (TRANSCEND-FL) in adult patients with relapsed or refractory FL grades 1, 2 and 3A after two or more lines of systemic therapy. The study enrolled patients with ECOG performance status of ≤ 1. The study excluded patients with a creatinine clearance of less than 30 mL/min, alanine aminotransferase > 5 times the upper limit of normal or, left ventricular ejection fraction (LVEF) ≤ 40%. 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 by Breyanzi 2 to 7 days later. The median dose of Breyanzi was 100.02 × 10^6 CAR-positive viable T cells (range: 93.4 - 109.2 × 10^6 CAR-positive viable T cells).

Anticancer therapy for disease control was permitted between apheresis and lymphodepletion. Of the 107 patients treated with Breyanzi, 44 (41%) received anticancer therapy for disease control at the discretion of the investigator.

Of 114 patients who underwent leukapheresis, 107 (93.8%) patients received Breyanzi and 4 (3.5%) patients received non-conforming product. Three patients did not receive Breyanzi. Of these 3 (2.7%) patients, 1 (0.9%) patient did not receive Breyanzi due to an adverse event, 1 (0.9%) patient did not meet study criteria and 1 (0.9%) patient for other reasons.

The number of patients who were evaluable for efficacy was 103 (primary efficacy analysis set). Four were not evaluable for efficacy, as those patients did not have baseline PET-positive disease, or confirmation of PET-positive disease after anticancer therapy for disease control by IRC.

The median time from leukapheresis to product availability was 29 days (range: 20 to 55 days), and the median time from leukapheresis to product infusion was 50 days (range: 31 to 313 days).

Table 9: Baseline demographic and disease-related characteristics for TRANSCEND-FL

Characteristic	**All leukapheresed (N=114)**	**Breyanzi-treated (N=107)**
Median Age, years (range) ≥ 65 to < 75 years, n (%) ≥ 75 years, n (%)	62.0 (23, 80) 36 (31.6) 10 (8.8)	62.0 (23, 80) 32 (29.9) 10 (9.3)
Male gender, n (%)	72 (63.2)	66 (61.7)
Prior HSCT, n (%) Autologous HSCT	 34 (29.8)	 33 (30.8)
High FLIPI score (3-5), n (%)	66 (57.9)	61 (57.0)
Stage III-IV disease at screening, n (%)	102 (89.4)	95 (88.7)
ECOG Performance Status (at screening) ECOG 0, n (%) ECOG 1, n (%)	 68 (59.6) 46 (40.4)	 65 (60.7) 42 (39.3)
Double refractory, n (%)	74 (64.9)	69 (64.5)
Progression within 24 months of first line therapy with anti-CD20 and alkylator, n (%) Yes No Not estimable	 63 (55.3) 50 (43.9) 1 (0.9)	 58 (54.2) 48 (44.9) 1 (0.9)
Median number of prior systemic treatments (range)	3 (2, 10)	3 (2, 10)

Efficacy was based on overall response rate (ORR), defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) after Breyanzi infusion as determined by an IRC (Table 10). The median on-study follow-up time was 30.0 months (range: 0.3 to 39.6 months).

The median time to first response (CR or PR) and median time to first CR was 0.95 months (range: 0.6 to 3.3 months).

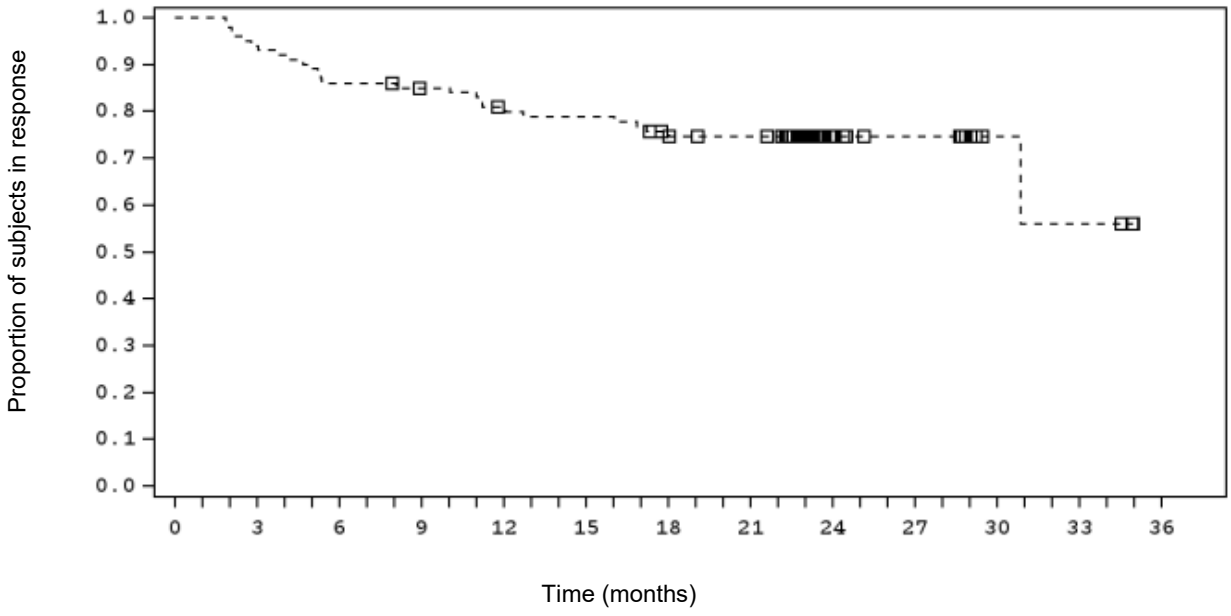
Table 10: TRANSCEND-FL study: Response rate, duration of response (IRC assessment)

	All leukapheresed (N=114)	**Efficacy set (N=103)**
Overall response rate (ORR)[a], n (%) [95% CI][b]	106 (93.0) [86.6, 96.9]	100 (97.1) [91.7, 99.4]
Complete response (CR), n (%) [95% CI][b]	103 (90.4) [83.4, 95.1]	97 (94.2) [87.8, 97.8]
Partial response (PR), n (%) [95% CI][b]	3 (2.6) [0.5, 7.5]	3 (2.9) [0.6, 8.3]

	All leukapheresed (N=114)	Efficacy set (N=103)
Duration of response (DOR) (months)		
Median [95% CI][c]	N.R [30.85, N.R]	N.R [30.85, N.R]
Range	1.9, 35.0+	1.9, 35.0+
Rate of continued response[d], % [95% CI]		
At 12 months	82.0 (73.2, 88.1)	80.9 (71.7, 87.4)
At 18 months	76.1 (66.7, 83.2)	75.7 (66.0, 83.0)
At 24 months	75.1 (65.6, 82.3)	74.6 (64.8, 82.1)
DOR if best response is CR (months)		
Median [95% CI][c]	N.R [30.85, N.R]	N.R [30.85, N.R]
Range	1.9, 35.0+	1.9, 35.0+
Rate of continued response[d], % [95% CI]		
At 12 months	84.4 (75.8, 90.1)	83.4 (74.3, 89.5)
At 18 months	78.3 (69.0, 85.2)	78.0 (68.3, 85.1)
At 24 months	77.3 (67.8, 84.3)	76.9 (67.1, 84.2)

CI = confidence interval; CR = complete response; NR = not reached;
+ indicates a censored value
[a] Per the Lugano criteria, as assessed by an IRC
[b] Two-sided 95% confidence interval based on exact Clopper-Pearson method.
[c] Median, Q1, Q3 are estimated from KM product-limit estimates
[d] Based on KM estimates of duration of response

Figure 2: Duration of response by IRC assessment, TRANSCEND-FL Efficacy set



Number of subjects at risk (censored)

3L+	100 (0)	94 (0)	86 (0)	83 (2)	78 (1)	76 (0)	71 (2)	68 (2)	14 (54)	10 (4)	4 (6)	3 (0)	0 (3)

Efficacy in elderly patients

No clinically important differences in efficacy of Breyanzi were observed between elderly and younger patients.

Pharmacokinetics

Absorption

DLBCL, PMBCL, HGBCL:
In TRANSCEND, in patients who received two or more prior lines of therapy, 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.

In TRANSCEND, responders (N=150) had a 2.85-fold higher median C_{max} than non-responders (N=45) (33,766.0 vs.11,846.0 copies/µg). Responders had a 2.22-fold higher median $AUC_{0\text{-}28d}$ than non-responders (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 $AUC_{0\text{-}28d}$, respectively, compared to patients who did not receive corticosteroids (N=199).

Among patients who received one prior line of therapy in TRANSFORM, the median C_{max} in responders (N=76) and non-responders (N=7) were 33,285 and 95,618 copies/ µg, respectively. The median $AUC_{0\text{-}28d}$ in responders and non-responders were 268,887 and 733,406 day*copies/ µg, respectively. No apparent relationship was observed between pharmacokinetics and response.

FL:
In TRANSCEND-FL, in patients who received two or more prior lines of therapy for FL, the median time of maximal expansion in peripheral blood occurred 10 days after the first infusion. Breyanzi was present in peripheral blood for up to 3 years.

Among patients who received Breyanzi for FL in TRANSCEND-FL, the median C_{max} in responders (N=100) and non-responders (N=2) were 31,336 and 15,568 copies/µg, respectively. The median $AUC_{0\text{-}28d}$ in responders (N=96) and non-responders (N=2) were 245,730 and 161,935 day*copies/µg, respectively.

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 $AUC_{0\text{-}28d}$.

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 $AUC_{0\text{-}28d}$, respectively, compared to patients ≥ 65 years old (N=101).

Children and adolescents

No conclusive data are available on the pharmacokinetics of Breyanzi in patients under 18 years of age.

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.**

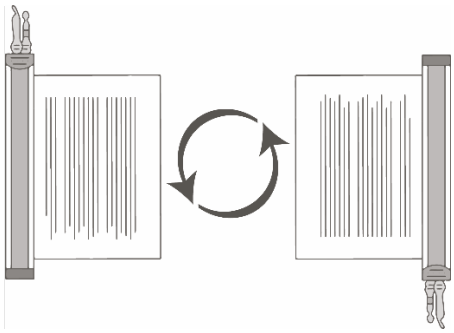
Dose preparation

- 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.

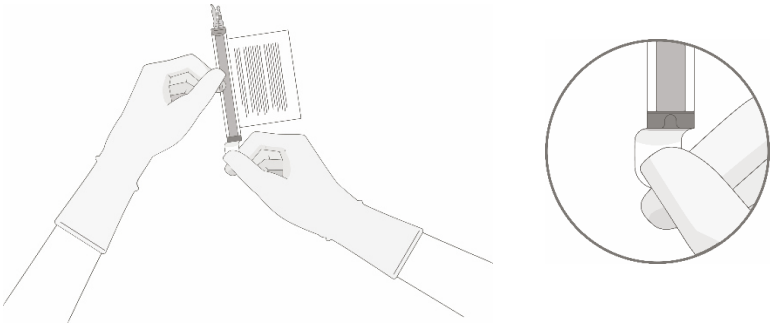
Withdrawal of the required volume of cells from each vial into a separate syringe should be carried out using the following instruction:

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.



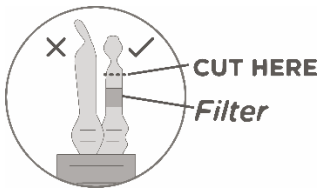
Vial upright Vial inverted

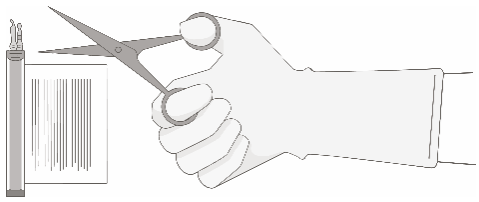
2. Visually inspect the thawed vial(s) for damage or leaks. Do not use if the vial is damaged or if the clumps do not disperse; contact the company. The liquid in the vials should be slightly opaque to opaque, colourless to yellow, or brownish-yellow.
3. Remove the polyaluminium cover (if present) from 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.

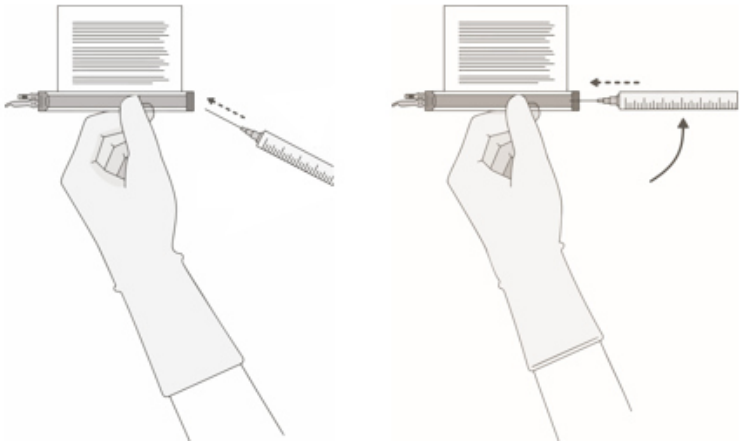
4. Keeping the vial(s) upright, cut the seal on the tubing line on the top of the vial immediately above the filter to open the air vent on the vial.
   NOTE: Be careful to select the correct tubing line with the filter. Cut ONLY the tubing with a filter.



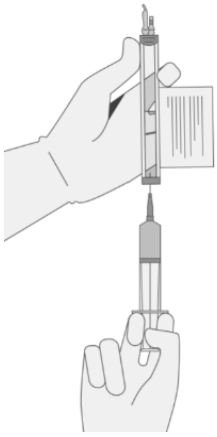


5. Hold a 20 gauge, 1-1 ½ inch needle, with the opening of the needle tip away from the retrieval port septum.
   a. Insert the needle into the septum at a 45-60° angle to puncture the retrieval port septum.
   b. Increase the angle of the needle gradually as the needle enters the vial.

a. b.

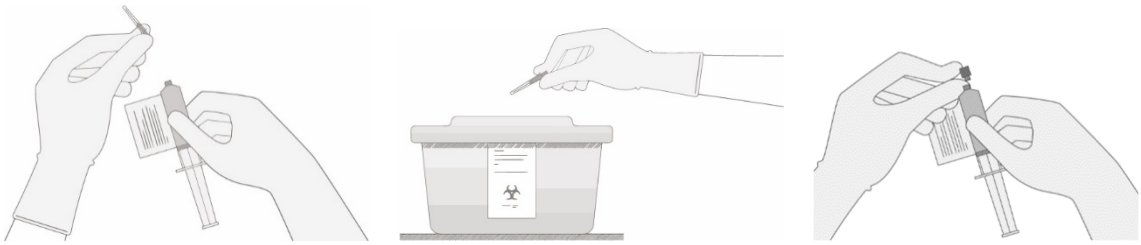


6. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the RFI Certificate).



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.

Bristol-Myers Squibb SA, Steinhausen

Date of revision of the text

May 2025