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 3
2 Background information on the procedure 4
2.1 Applicant's request(s) 4
2.2 Indication and dosage 4
2.2.1 Requested indication 4
2.2.2 Approved indication 4
2.2.3 Requested dosage 4
2.2.4 Approved dosage 4
2.3 Regulatory history (milestones) 4
3 Medical context 5
4 Clinical aspects 7
4.1 Clinical pharmacology 7
4.2 Dose finding and dose recommendation 7
4.3 Efficacy 8
4.4 Safety 9
4.5 Final clinical benefit risk assessment 11
5 Risk management plan summary 12
6 Appendix 13

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.

swissmedic

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

Swiss Public Assessment Report

Extension of therapeutic indication

Breyanzi

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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:

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Table of contents

1 Terms, Definitions, Abbreviations 3
2 Background information on the procedure 4
2.1 Applicant's request(s) 4
2.2 Indication and dosage 4
2.2.1 Requested indication 4
2.2.2 Approved indication 4
2.2.3 Requested dosage 4
2.2.4 Approved dosage 4
2.3 Regulatory history (milestones) 4
3 Medical context 5
4 Clinical aspects 7
4.1 Clinical pharmacology 7
4.2 Dose finding and dose recommendation 7
4.3 Efficacy 8
4.4 Safety 9
4.5 Final clinical benefit risk assessment 11
5 Risk management plan summary 12
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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.