

## ***Swiss Public Assessment Report*** ***Extension of therapeutic indication***

### **Breyanzi**

**International non-proprietary name:** lisocabtagen maraleucel, 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).

**Pharmaceutical form:** dispersion for infusion

**Dosage strength(s):** The target dose is  $100 \times 10^6$  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.

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

**Marketing authorisation holder:** Bristol-Myers Squibb SA

**Marketing authorisation no.:** 67469

**Decision and decision date:** extension of therapeutic indication approved on 19.02.2026

#### **Note:**

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

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

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## 1 Terms, Definitions, Abbreviations

|          |                                                                                       |
|----------|---------------------------------------------------------------------------------------|
| 1L       | First-line                                                                            |
| 2L       | Second-line                                                                           |
| 3L       | Third-line                                                                            |
| BTK      | Bruton's tyrosine kinase                                                              |
| CI       | Confidence interval                                                                   |
| CNS      | Central nervous system                                                                |
| CRS      | Cytokine release syndrome                                                             |
| CSR      | Clinical study report                                                                 |
| DLBCL    | Diffuse large B-cell lymphoma                                                         |
| DOR      | Duration of response                                                                  |
| ECA      | External control arms (study)                                                         |
| FL       | Follicular lymphoma                                                                   |
| HGBCL    | High grade B-cell lymphoma                                                            |
| Ig       | Immunoglobulin                                                                        |
| INN      | International non-proprietary name                                                    |
| iiNT     | Investigator-identified neurologic toxicity                                           |
| IRC      | Independent review committee                                                          |
| LoQ      | List of questions                                                                     |
| MAH      | Marketing authorisation holder                                                        |
| MAIC     | Matching-adjusted indirect comparison                                                 |
| Max      | Maximum                                                                               |
| MCL      | Mantle cell lymphoma                                                                  |
| Min      | Minimum                                                                               |
| N/A      | Not applicable                                                                        |
| NHL      | Non-hodgkin lymphoma                                                                  |
| NR       | Not reached                                                                           |
| ORR      | Objective response rate                                                               |
| OS       | Overall survival                                                                      |
| PAS      | Primary analysis aet                                                                  |
| PBPK     | Physiology-based pharmacokinetics                                                     |
| PD       | Pharmacodynamics                                                                      |
| PFS      | Progression-free survival                                                             |
| PK       | Pharmacokinetics                                                                      |
| PMBCL    | Primary mediastinal large B-cell lymphoma                                             |
| PT       | Preferred term                                                                        |
| RMP      | Risk management plan                                                                  |
| r/r      | Relapsed or refractory                                                                |
| SOC      | System organ class                                                                    |
| SPM      | Secondary primary malignancies                                                        |
| 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)                |
| TP53     | Tumor Protein 53                                                                      |

## 2 Background information on the procedure

### 2.1 Applicant's request(s) and information regarding procedure

#### 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 adicies no. 2 TPA. Orphan drug status was granted on 30 July 2024.

### 2.2 Indication and dosage

#### 2.2.1 Requested indication

The applicant requested the addition of the following new therapeutic indication:

- relapsed or refractory (r/r) mantle cell lymphoma (MCL) after at least two lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

#### 2.2.2 Approved indications

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

#### 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                      | 15 April 2025    |
| Formal objection                 | 23 April 2025    |
| Response to formal objection     | 24 April 2025    |
| Formal control completed         | 27 April 2025    |
| List of Questions (LoQ)          | 25 August 2025   |
| Response to LoQ                  | 22 October 2025  |
| Preliminary decision             | 22 December 2025 |
| Response to preliminary decision | 22 January 2026  |
| Final decision                   | 19 February 2026 |
| Decision                         | approval         |

### 3 Medical context

MCL is an aggressive and relatively uncommon form of Non-Hodgkin Lymphoma (NHL) accounting for 5% to 7% of malignant lymphomas in Western Europe. The annual incidence of MCL has increased during recent decades to 1–2 cases per 100,000 individuals. MCL occurs more commonly among elderly people with a median age at diagnosis of 67 years, and has a striking sex imbalance, with approximately 70% of all cases reported in men. MCL is considered incurable with standard chemotherapy and is associated with a multiply-relapsing disease course and poor long-term survival. Across reported results from clinical trials, the median duration of remission from initial diagnosis is approximately 5 years, with median overall survival (OS) ranging from 3 to 10 years.

Patients with r/r MCL progressing after 2 or more lines of therapy, specifically after covalent BTKi treatment, have limited therapeutic options and outcomes. Development of resistance or intolerance to covalent BTKi therapies is common. In addition, toxicities from long-term use of BTKi therapies may not be tolerable for all patients, thus limiting their prolonged use for the treatment of r/r MCL.

### 4 Quality aspects

N/A

### 5 Nonclinical aspects

N/A

### 6 Clinical aspects

#### 6.1 Clinical pharmacology

##### 6.1.1 Pharmacokinetics

The Pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of liso-cel were evaluated in the MCL Cohort of Study TRANSCEND-MCL (CSR 017001). Results from the PK analyses in the MCL Cohort of Study 017001 were consistent with those observed for other indications (2L and 3L+ LBCL, 3L+ FL), and support the proposed dose range of  $44$  to  $120 \times 10^6$  CAR+ T cells, which is consistent with the dose range in 2L and 3L+ LBCL, and 3L+ FL.

##### 6.1.2 Pharmacodynamics

Results from the pharmacodynamic analyses of B-cell aplasia, soluble biomarkers, serum Ig, CRP, and ferritin in the MCL Cohort of Study 017001 were consistent with those observed for other indications (2L and 3L+ LBCL, 3L+ FL) and support the proposed target dose.

#### 6.2 Efficacy and safety

##### 6.2.1 Pivotal study TRANSCEND-MCL

The efficacy of Breyanzi was established based on a single-arm clinical study (TRANSCEND-MCL) in adult subjects with r/r MCL. The primary endpoint, objective response rate (ORR), was 86.7% in the primary analysis set (PAS), by the independent review committee (IRC) assessment, of which 74.7% were reported as achieving complete response. Median duration of response was 11.3 months (5.7, 24). Subgroup analysis was consistent across all prespecified subgroups in the PAS, in terms of ORR and DOR (Duration of Response; including patients with high-risk features such as high Ki-67 proliferation fraction, TP53 (Tumor Protein 53) mutation, blastoid morphology, secondary CNS (Central Nervous System) lymphoma, and extra-nodal disease.)

In the PAS, the median IRC-assessed PFS was 8.6 months, and the median OS was 18.4 months (95% CI: 13.5, NR). However, due to the single arm design of the phase 1 study, the small sample size and the lack of comparators, uncertainties remain especially in relation to the interpretation of time to event endpoints such as PFS and OS.

### 6.2.2 Safety

Safety data for the r/r MCL liso-cel-treated analysis set from study TRANSCEND-MCL were consistent with the known liso-cel safety profile for r/r LBCL Treated Set and for r/r FL. No new safety concerns or new types of clinically important events were identified with liso-cel in the MCL Cohort. TEAEs were experienced by 100% of patients in the r/r MCL treated set. Grade 3 or 4 TEAEs were experienced by 81.8% of patients in the r/r MCL set, of which 45.5% were considered related to liso-cel. Serious TEAEs were experienced by 53.4% of patients in the r/r MCL set.

These safety data were compared with the 2L/3L+ LBCL total liso-cel set (n=608). Overall, the adverse events observed with liso-cel monotherapy in study 017001 were consistent with the total liso-cel set and the known safety profile of the other liso-cel indications.

The most frequently occurring TEAEs by System Organ Class (SOC) were blood and lymphatic system disorders (77.3%), general disorders and administration site conditions (67.0%), and immune system disorders and metabolism and nutrition disorders (63.6%, each). The most frequently occurring TEAEs by Preferred Term (PT) were Cytokine Release Syndrome (CRS; 61.4%), neutropenia (59.1%), and anaemia (44.3%).

The most frequently occurring Grade  $\geq 3$  TEAEs by SOC were blood and lymphatic disorders (72.7%), metabolism and nutrition disorders (23.9%) and infection and infestations (14.8%). The most frequently occurring Grade  $\geq 3$  TEAEs by PT were neutropenia (55.7%), anaemia (37.5%), and thrombocytopenia (25.0%).

In the r/r MCL treated Set, 52.3% of subjects died any time after the first liso-cel infusion compared with 42.4% of subjects in the r/r LBCL treated set. In both datasets, most of the deaths reported after the first liso-cel infusion were due to disease progression, 33% in the r/r MCL treated set and 33.9% in the r/r LBCL population. The safety profile of liso-cel in r/r MCL is consistent with the liso-cel safety profile in LBCL and FL indications, with a similar rate of Grade  $\geq 3$  CRS and Grade  $\geq 3$  Investigator-identified Neurologic Toxicity (iiNT).

During the post-treatment-emergent period, the data suggest the frequency of Secondary Primary Malignancies (SPMs) was higher in the r/r MCL liso-cel-treated analysis set compared with the r/r LBCL treated set and comparators, although interpretation is limited by the absence of a direct comparison.

### 6.2.3 Other relevant efficacy/safety data

To compare these efficacy results with those of two recently approved treatments (pirtobrutinib and brexu-cel) for the same indication, a supportive study was submitted: non-interventional Matching-Adjusted Indirect Comparison (MAIC) study using indirect treatment comparison methods to estimate the comparative efficacy and safety of liso-cel versus brexu-cel and comparative efficacy of liso-cel vs pirtobrutinib in patients with 3L+ r/r MCL.

Moreover, in response to the LoQ, and to further contextualize findings from the single-arm TRANSCEND MCL Cohort, and to compare the efficacy of liso-cel vs currently used standard regimens for 3L+ r/r MCL in the real-world setting, the Marketing Authorisation Holder (MAH) conducted an external control arms (ECA) study.

Whether it be the matching-adjusted indirect comparative study (MAIC) or the real-world data study (ECA), several methodological limitations have been identified that preclude the possibility of drawing a conclusion. The results are only exploratory and do not allow the previously identified uncertainties regarding efficacy and safety to be resolved.

### 6.3 Final clinical benefit/risk assessment

The single-arm clinical study TRANSCEND-MCL (CSR 017001) in adult subjects with r/r MCL showed significant and clinically meaningful responses to treatment.

The evidence supporting the efficacy of liso-cel in the target population comes from one single uncontrolled, open-label study with clinically relevant rates of deep and durable responses observed in an advanced setting of r/r MCL associated with the known risks associated with anti-CD19 CAR T cell therapy. However, uncertainties remain as to whether this effect will translate into significant benefit in PFS and OS with respect to comparators with the same indication.

Moreover, during the post-treatment-emergent period, the data suggest an increased risk of SPM compared to comparators in the same indication.

Overall, the benefit/risk balance can be considered positive, but uncertainty remains and should be clearly stated in professional information.

## 7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

## 8 Appendix

### Approved Information for healthcare professionals

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

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see [www.swissmedicinfo.ch](http://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.