swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Tecartus

International non-proprietary name: brexucaptagene autoleucel

Pharmaceutical form: dispersion for infusion

Dosage strength(s): a single dose of Tecartus contains a target of 1×10^6 CAR-positive viable T cells per kg of body weight, or a maximum of 1×10^8 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag.
Route(s) of administration: for autologous and intravenous use only

Marketing authorisation holder: Gilead Sciences Switzerland Sàrl

Marketing authorisation no.: 67884

Decision and decision date: extension of therapeutic indication approved on 12.01.2023

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

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALL	Acute lymphoblastic leukaemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CR	Complete remission
CRi	Complete remission and incomplete haematological recovery
CRS	Cytokine release syndrome
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FAS	Full analysis set
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MCL	Mantle cell lymphoma
Min	Minimum
mITT	Modified intention-to-treat
MRD	Minimum residual disease
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
OCR	Overall complete remission
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics

PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SCT	Stem cell transplant
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 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 22 June 2021.

2.2 Indication and dosage

2.2.1 Requested indication

Tecartus is indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

2.2.2 Approved indication

Tecartus is indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL) after 2 or more systemic therapies.

2.2.3 Requested dosage

A single dose of Tecartus contains a target of 1 × 10^6 CAR-positive viable T cells per kg of body weight, or a maximum of 1 × 10^8 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	3 December 2021
Formal control completed	15 December 2021
List of Questions (LoQ)	13 April 2022
Response to LoQ	13 July 2022
Preliminary decision	20 September 2022
Response to preliminary decision	21 November 2022
Final decision	12 January 2023
Decision	approval

3 Medical context

ALL is a heterogeneous group of lymphoid disorders resulting from the clonal proliferation of immature lymphocytes of B or T cell lineage in the blood, bone marrow, and other organs, with the majority of these lymphocytes being of B cell lineage. The disease occurs with a bimodal age distribution, with 55% of cases diagnosed in patients < 20 years of age and 28% of cases diagnosed in adult patients ≥ 45 years of age. In the US, approximately 6,000 new cases of ALL are diagnosed and approximately 1,500 deaths from ALL occur each year. In the EU, the estimated overall incidence of ALL is 1.28 per 100,000 persons per year, with a higher incidence (1.45 per 100,000 persons per year) in adults aged 75-99 years. While the 5-year overall survival (OS) rate for children is 89%, survival rates for adults remain low (~20% to 40%), and the majority of ALL-related deaths occur in adults.

Treatment strategies for ALL are largely determined by the origin of leukemic cells (B or T cell) and risk factor status, such as the Philadelphia chromosome (Ph) rearrangement. ALL can be classified into 3 major subtypes: B-cell precursor ALL, mature B-cell ALL, and T-cell ALL. B-ALL is the most common form of ALL in adult patients. Furthermore, 25% of adult patients with ALL have Ph-positive (Ph+) disease. Ph+ status confers a very poor prognosis, with 5-year OS and relapse-free survival (RFS) rates of 8% and 0%, respectively.

Standard first-line treatment involves the use of several antineoplastic agents. Treatment for ALL typically involves the following: induction, consolidation, and maintenance. The goals of treatment are to reduce the tumoral population, restore normal haematopoiesis, prevent treatment-resistant disease, eliminate minimal residual disease (MRD), and provide prophylaxis. Allogeneic stem cell transplant (allo-SCT) plays a role in the management of ALL, and tyrosine kinase inhibitors (TKIs) are added to chemotherapy and transplant regimens in patients with Ph+ disease. Given the poor outcomes achieved with chemotherapy in the adult population, the salvage setting represents the area of greatest unmet need in adult patients who have r/r B-ALL. Second-line chemotherapy yields remissions in approximately 20% to 40% of patients, with the remission rate being lower in patients who relapse within 12 months of an initial response. The poor prognosis for r/r B-ALL has been improved by the development of the novel targeted agents blinatumomab and inotuzumab.

With each subsequent relapse, the prognosis gets progressively worse, and the majority of remissions are short-lived. A retrospective analysis of 1,706 adult subjects with Ph− r/r B-ALL found that the CR rates after first, second, and third or greater salvage therapy were 40%, 21%, and 11%, respectively. Median OS decreased with each subsequent line of therapy; median OS after first, second, and third or greater salvage therapy was 5.8, 3.4, and 2.9 months, respectively.

There is an unmet medical need for adult patients with r/r B-ALL. Among those with primary refractory or primary relapsed ALL, patients with short first remissions (< 12 months) have worse outcomes than patients who relapse after a longer first remission (CR rates of 22% vs 41%, respectively). Survival rates for patients with r/r B-ALL 1 year after the second, third, and fourth or higher lines of therapy are 26%, 18%, and 15%, respectively. Furthermore, CR rates decline with each subsequent line of treatment.

For elderly patients, treatment remains challenging due to the high morbidity and mortality associated with intensive chemotherapy regimens and allogenic SCT. In Switzerland, there is an effective CAR T-cell product available for patients with r/r B-ALL. Tisagenlecleucel, an autologous anti-CD19 CAR T-cell therapy, is approved for the treatment of r/r B-ALL in paediatric and young adult patients up to 25 years of age. Patients must have refractory B-ALL, be in relapse following transplant, or be in second or later relapse to receive tisagenlecleucel therapy for B-ALL. For subjects over 25 years of age, there is no other effective CAR-T cell product approved for r/r B-ALL in Switzerland.

4 Nonclinical aspects

No new preclinical data were submitted. Based on the active substance and the newly applied for indication, this was accepted.

5 Clinical aspects

5.1 Clinical pharmacology

Pharmacokinetics

The following dose levels of KTE-X19 were evaluated in Phase 1 of the ZUMA-3 study: 0.5 x 10^6 anti-CD19 CAR T cells/kg (68 mL), 0.5 x 10^6 anti-CD19 CAR T cells/kg (40 mL), 1 x 10^6 anti-CD19 CAR T cells/kg, 1 x 10^6 anti-CD19 CAR T cells/kg (with modified toxicity management), and 2 x 10^6 anti-CD19 CAR T cells/kg.

After the initial single dose infusion of KTE-X19, KTE-X19 cells exhibited an initial rapid expansion phase followed by bi-phasic decline. KTE-X19 achieved peak levels in the blood between 8 to 15 days post-infusion in subjects with B-ALL. Across the dose levels evaluated, there is no clear dose response for KTE-X19 exposure (C_{max} and $AUC_{0\text{-}28d}$). Median peak anti-CD19 CAR T-cell levels were highest in subjects treated at the 1.0 x 10^6 dose level with modified toxicity management (37.7 cells/µL), followed by subjects treated at the following dose levels (from the highest to the lowest): 1.0 x 10^6 cells/kg with original toxicity management (26.5 cells/µL); 0.5 x 10^6 cells/kg (68 mL; 23.1 cells/µL); 2.0 x 10^6 cells/kg (8.6 cells/µL); and 0.5 x 10^6 cells/kg (40 mL; 4.7 cells/µL). A similar pattern was observed for the median $AUC_{0\text{-}28d}$.

The dose chosen for the Phase 2 part of the study was 1x10^6 cells/kg and all subjects in Phase 2 were treated at the 1 x 10^6 anti-CD19 CAR T cells/kg dose according to the modified toxicity management guidance. The PK profiles of KTE-X19 in Phase 2 were similar to Phase 1 1 x 10^6 dose cohorts. Median peak anti-CD19 CAR T-cell levels and $AUC_{0\text{-}28d}$ for subjects in Phase 2 were 20.6 cells/µL and 220.60 cells/µL*days, respectively. Median T_{max} was 15 days post-dose. IFN-γ levels in co-culture showed a potential positive association with the post-infusion peak level of anti-CD19 CAR T cells. At the dose level of 1.0 x 10^6 cells/kg (n=78), levels of percentage of blast at screening were negatively associated with KTE-X19 expansion.

Tocilizumab and corticosteroids were used in management of CRS and neurologic events after treatment with KTE-X19. Subjects who received both tocilizumab and corticosteroids had higher KTE-X19 exposure than subjects who received either medication alone or neither medication. These observations are confounded by the fact that the need for tocilizumab and/or corticosteroids was triggered by toxicity, which was associated with higher KTE-X19 exposures.

After KTE-X19 infusion, substantially higher expansion (median values of C_{max} and $AUC_{0\text{-}28d}$) was observed in responders (CR+CRi) compared to non-responders. Among subjects in the efficacy analysis set (ZUMA-3 Phase 2, N=54), median peak anti-CD19 CAR T-cell levels over time by best overall response per independent review were 38.35 cells/µL (range: 1.31 to 1,533.40 cells/µL; n = 32) in subjects who had OCR, and 0.49 cells/µL (range: 0.00 to 183.50 cells/µL, n = 17) in subjects who had non-complete remission. The median $AUC_{0\text{-}28}$ in subjects who had OCR was 424.03 cells/µL*days (range: 14.12 to 19,390.42 cells/µL*days; n = 32) vs 7.9 cells/µL*days in subjects who had non-complete remission (range: 0.00 to 889.0 cells/µL*days; n=17).

Higher KTE-X19 exposure (C_{max} and $AUC_{0\text{-}28d}$) was associated with a higher incidence of Grade 2 and above CRS and NT.

At the dose level of 1.0 x 10^6 cells/kg (n=78), the median C_{max} and $AUC_{0\text{-}28d}$ of KTE-X19 in subjects with Grade 2 or higher CRS were 6.9-fold and 5.3-fold, respectively, compared to those in subjects with Grade 1 or no CRS. The median C_{max} and $AUC_{0\text{-}28d}$ of KTE-X19 in subjects with Grade 2 or higher NT were 2.5-fold and 2.6-fold, respectively, compared to those in subjects with Grade 1 or no NT.

Pharmacodynamics

After KTE-X19 infusion, the majority of subjects had B-cell aplasia. B-cell recovery was observed at Month 3. At Month 12, B-cell recovery was observed in all evaluable subjects.

Serum analytes (cytokines, chemokines, and other molecules) generally peaked between 7-8 days after KTE-X19 infusion and decreased to near-baseline levels by Week 4. The following associations were observed between serum analyte levels and severe adverse events (CRS and neurologic events):

- After KTE-X19 infusion, a substantial elevation in serum levels was observed in subjects with Grade 3 or higher CRS compared to subjects with Grade 2, Grade 1, or no CRS for the following biomarkers: ferritin, granzyme B, INF-γ, IL-2Rα, IL-6, IL-8, IL-10, IL-15, TNF-α, and GM-CSF.

- After KTE-X19 infusion, a substantial elevation in serum levels was observed in subjects with Grade 3 or higher neurologic event compared to subjects with Grade 2, Grade 1, or no neurologic event for following biomarkers: IL-1RA and IL-6.

5.2 Dose finding and dose recommendation

In ZUMA-3 Phase 1, 45 subjects were enrolled and treated at 0.5 x 10^6, 1 x 10^6, or 2 x 10^6 anti-CD19 CAR T cells/kg. The dose of 1 x 10^6 anti-CD19 CAR T cells/kg showed the highest efficacy, a manageable safety profile, and the most favourable benefit-risk profile across the doses evaluated. Therefore, the dose of 1 x 10^6 anti-CD19 CAR T cells/kg (maximum dose of 1 x 10^8 anti-CD19 CAR T cells for subjects ≥ 100 kg) was considered the recommended Phase 2 dose. On the basis of these data, the decision for a RP2D of 1 x 10^6 anti-CD19 CAR T cells/kg can be reproduced and accepted.

5.3 Efficacy

The efficacy and safety of KTE-X19 were evaluated in adult subjects with relapsed/refractory B-cell precursor acute lymphoblastic leukaemia (r/r B-ALL) in a single Phase 2, multicentre, open-label study (KTE-C19-103; ZUMA-3). ZUMA-3 allowed enrolment of subjects previously treated with blinatumomab and/or inotuzumab. No comparator treatment was used as there is no fully established standard of care for adult patients with r/r B-ALL. Study enrolment was completed on 1 November 2019. ZUMA-3 is currently ongoing.

A total of 71 patients with r/r ALL were enrolled (i.e. underwent leukapheresis) and 55 patients were treated with KTE-X19 in Phase 2 of ZUMA-3. Of the 55 patients treated with KTE-X19, 45 patients received KTE-X19 after 2 or more systemic therapies. The FAS included all patients who underwent leukapheresis, and the modified intent-to-treat (mITT) analysis set included all patients who were underwent leukapheresis in Phase 2 and were treated with KTE-X19 after 2 or more systemic therapies.

The median time from leukapheresis to KTE-X19 infusion was 29 days (range: 20 to 60 days). The median dose was 1.0 × 10^6 anti-CD19 CAR T cells/kg. All patients received the KTE-X19 infusion on Day 0 and remained hospitalised for at least 7 days.

The primary endpoint was the rate of overall complete remission (OCR) (complete remission [CR] + complete remission and incomplete haematological recovery [CRi]) in patients treated with KTE-X19, as determined by independent review. In the 45 treated patients (mITT) who received KTE-X19 after 2 or more systemic therapies, the OCR rate was 66.7%, with a CR rate of 51.1%, which was significantly higher than the pre-specified control rate of 40%. Among the 30 patients who achieved a CR or CRi, the median time to response was 1.1 months (range: 0.85 to 2.99 months). Among all assessable subgroups, OCR rates were generally consistent with the OCR rate observed for all patients, including patients previously treated with blinatomumab (63%; 95% CI: 41.0; 81.0), inotuzumab (67%; 95% CI: 35.0; 90.0); allo-SCT (68%; 95% CI: 45.0; 86.0); patients who were Ph+ (77%; 95% CI: 46.0; 95.0); patients with primary refractory disease (71%; 95% CI: 42.0; 92.0); and patients who had a first relapse with a first remission ≤12 months (64%; 95% CI: 31.0; 89.0).

A retrospective matched cohort study of adult patients with r/r B-ALL was conducted with samples from historical clinical trials. The analysis included patients with r/r B-ALL who were matched with patients enrolled in ZUMA-3. The OCR rate was 35% [95% CI (15.4; 59.2)] in patients not previously treated with blinatomumab or inotuzumab, compared to 85% [95% CI (62.1; 96.8)] in the matched ZUMA-3 patients. The median OS for patients treated with the standard of care was 5.49 months [95% CI (3.32; 9.23)] for the overall population. The comparison of OS between the matched patients from ZUMA-3 and historical control patients showed a statistically significant benefit for patients treated in ZUMA-3 (mOS 25.43 months vs. 5.49; HR 0.32; $p < 0.0001$).

For further details, please consult the “Properties/effects” and “Clinical efficacy” sections of the Information for healthcare professionals.

5.4 Safety

Safety data on the pooled Phase 1 and 2 data of ZUMA-3, based on 100 subjects with relapsed/refractory B-cell ALL treated with a single dose of CAR-positive viable T cells (0.5×10^6, 1×10^6 or 2×10^6 anti-CD19 CAR-T cells/kg) were provided. According to this analysis, the most frequently occurring adverse events were CRS (91%), encephalopathy (56%), and infections (41%). Serious adverse events occurred in 70% of patients. The most common serious adverse events included CRS (25%), infections (22%), and encephalopathy (21%). Grade 3 or higher adverse events were reported in 76% of patients. The most common non-haematological Grade 3 or higher adverse event included infections (27%), CRS (25%), and encephalopathy (22%).

Among the 55 subjects treated in Phase 2, all subjects had at least 1 AE, 52 subjects (95%) had worst Grade 3 or higher AEs, and 41 subjects (75%) had SAEs. Forty-nine subjects (89%) had CRS and 13 subjects (24%) had worst Grade 3 or higher CRS. No subject had Grade 5 CRS. Thirty-three subjects (60%) had at least 1 neurologic AE; 14 subjects (25%) had worst Grade 3 or higher neurologic AEs and 14 subjects (25%) had serious neurologic AEs. One subject had a Grade 5 neurologic AE of brain herniation. As of the data cutoff date, 10 subjects (18%) in Phase 2 had died due to AEs, including 4 subjects (7%) who died due to disease progression within 3 months after the KTE-X19 infusion (reported as Grade 5 ALL) and 6 subjects (11%) who died due to AEs other than disease progression.

In Phase 2, the most common AEs by system organ class (SOC) were general disorders and administration site conditions (54 subjects, 98%), vascular disorders (42 subjects, 76%), and blood and lymphatic system disorders (41 subjects, 75%). The most common AEs by PT were pyrexia (52 subjects, 95%), hypotension (37 subjects, 67%), and anaemia (29 subjects, 53%). The most common worst Grade 3 or higher AEs were anaemia (27 subjects, 49%), pyrexia (20 subjects, 36%), and platelet count decreased (17 subjects, 31%).

The most common KTE-X19-related AEs of any grade were pyrexia (46 subjects, 84%), hypotension (34 subjects, 62%), and sinus tachycardia (19 subjects, 35%). The most common KTE-X19-related AEs that were worst Grade 3 or higher were pyrexia (20 subjects, 36%), hypotension (16 subjects, 29%), and hypoxia (11 subjects, 20%).

Overall, KTE-X19 is rather toxic, but the rates of the identified risks were similar to the known safety profile of KTE-X19 in the already approved indication of MCL. During the rather short observation period to date, no secondary malignancies occurred in Phase 2 of ZUMA-3 that were attributable to KTE-X19, and no new safety signals were identified.

5.5 Final clinical benefit-risk assessment

Despite the limitations of the clinical data with regard to comparison to the historical controls, number of patients studied, and duration of observation period, evidence is provided to conclude that the risk-benefit assessment for KTE-X19 is positive for the treatment of adult patients with relapsed or

refractory (r/r) B-cell precursor acute lymphoblastic leukaemia (pre-B ALL) – in a recommended dosage of a target dose of 1 x 10^6 anti-CD19 CAR-positive viable T cells per kg body weight, with a maximum of 1 x 10^8 anti-CD19 CAR-positive viable T cells – after 2 or more systemic therapies. There is an unmet need in this patient population and KTE-X19 represents a new therapeutic option for these patients.

To further substantiate the advantage of therapy with KTE-X19, the submission of the results of the ongoing study KTE-C19-103 (ZUMA-3) and real-world evidence from US and EU register data must be submitted in due course.

6 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.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Tecartus 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.

TECARTUS®

Composition

Active substances

TECARTUS (brexucabtagene autoleucel) is a gene therapy medicinal product containing autologous T cells genetically modified ex vivo using a retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains.

Excipients

Cryostor CS10 (DMSO; Dextran 40), sodium chloride, human serum albumin (sodium chloride, N-acetyl-DL-tryptophan, caprylic acid, water), 5% DMSO.
TECARTUS contains 300 mg sodium per infusion.

Pharmaceutical form and active substance quantity per unit

Dispersion for infusion.
A clear to opaque, white to red dispersion of cells, supplied in an infusion bag individually packed in a metal cassette.

Mantle Cell Lymphoma

Each patient specific single infusion bag contains a dispersion of anti-CD19 CAR-positive viable T cells in approximately 68 mL for a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: $1.0 \times 10^6 – 2.0 \times 10^6$ cells/kg), with a maximum of 2×10^8 anti-CD19 CAR-positive viable T cells.

Acute Lymphoblastic Leukemia

Each patient specific single infusion bag contains a dispersion of anti-CD19 CAR-positive viable T cells in approximately 68 mL for a target dose of 1×10^6 anti-CD19 CAR-positive viable T cells/kg body weight with a maximum of 1×10^8 anti-CD19 CAR-positive viable T cells.

Indications/Uses

TECARTUS is a genetically modified autologous T-cell immunotherapy directed against CD19.

Mantle Cell Lymphoma

TECARTUS is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton tyrosine kinase (BTK) inhibitor.

Acute Lymphoblastic Leukemia

TECARTUS is indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) after two or more systemic therapies.

Dosage/Administration

TECARTUS must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with TECARTUS, including treatment of cytokine release syndrome (CRS) and neurotoxicity, with immediate access to appropriate intensive care units. A minimum of four doses of tocilizumab for use in the event of cytokine release syndrome (CRS) must be available prior to infusion of TECARTUS. Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of TECARTUS.

TECARTUS is a single infusion product, for autologous and intravenous use only (see “Warnings and precautions”).
The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen. There may be reasons why a patient cannot be treated with TECARTUS despite completing leukapheresis (for details see “Properties/Effects”).

Mantle Cell Lymphoma

Dosage

A patient specific single infusion bag of TECARTUS with a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2×10^6 CAR-positive viable T cells/kg body weight (range: $1.0 \times 10^6 – 2.0 \times 10^6$ cells/kg), with a maximum of 2×10^8 CAR-positive viable T cells for patients of 100 kg and above.

Pre-treatment (lymphodepleting chemotherapy) for MCL patients

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 should be administered intravenously on the 5th, 4th, and 3rd day before infusion of TECARTUS. An absolute neutrophil count (ANC) ≥ 1000/µL and a platelet count ≥ 75,000/µL before initiating lymphodepleting chemotherapy is recommended.

Acute Lymphoblastic Leukemia

Dosage

A single dose of TECARTUS contains a target of 1×10^6 CAR-positive viable T cells per kg of body weight, or maximum of 1×10^8 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag.

Pre-treatment (lymphodepleting chemotherapy) for ALL patients

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 900 mg/m^2 over 60 minutes should be administered intravenously on the 2nd day before infusion of TECARTUS and fludarabine 25 mg/m^2 over 30 minutes should be administered intravenously on the 4th, 3rd, and 2nd day before infusion of TECARTUS.

Mantle Cell Lymphoma and Acute Lymphoblastic Leukemia

Clinical evaluation prior to TECARTUS infusion

Treatment with TECARTUS should be postponed in certain high-risk patients (see “Warnings and precautions”).

Pre-medication

- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 500-1000 mg given orally and diphenhydramine 12.5-25 mg, intravenous or oral (or equivalent) approximately 1 hour prior to infusion.
- Prophylactic use of systemic steroids is not recommended (see “Interactions”).

Monitoring after infusion

- Patients should be monitored at a qualified treatment centre, daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient should be monitored at the physician’s discretion.
- Patients should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

Special dosage instructions

Patients with impaired hepatic function

Data from patients with hepatic impairment are insufficient to draw conclusions on this population.

Patients with impaired renal function

Data from patients with renal impairment are insufficient to draw conclusions on this population.

Elderly patients

No dose adjustment is required in patients ≥ 65 years of age.

Children and adolescents

The safety and efficacy of TECARTUS in children and adolescents aged less than 18 years have not yet been established. No data are available.

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)

There is no experience with manufacturing TECARTUS for patients with a positive test for HIV, active HBV, or active HCV infection. Therefore, the benefit/risk has not yet been established in this population.

Mode of administration

Intravenous use.
TECARTUS is solely intended for autologous use via intravenous infusion.
TECARTUS must not be irradiated. Do NOT use a leukodepleting filter.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified human blood cells. Standard precautions regarding handling of this type of product should be followed. For special precautions for disposal and other instructions for handling, see “Other information”.
Healthcare professionals handling TECARTUS should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation of TECARTUS

- Verify that the patient’s identity (ID) matches the patient identifiers on the TECARTUS metal cassette.
- The TECARTUS infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a sterile second bag or per local guidelines.

- Thaw TECARTUS at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. TECARTUS should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, TECARTUS is stable at room temperature (20°C - 25°C) for up to 3 hours. However, TECARTUS infusion should begin within 30 minutes of thaw completion.

Administration

- For autologous single use only.
- Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration of TECARTUS.
- Verify the patient ID again to match the patient identifiers on the TECARTUS bag.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the TECARTUS bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during infusion to prevent cell clumping.
- After the entire content of the bag is infused, rinse the tubing at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) to ensure all the treatment is delivered.

Contraindications

Hypersensitivity to the active substance, any of the excipients (see “Composition”).
Contraindications of the lymphodepleting chemotherapy must be considered.

Warnings and precautions

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years.

General

Warnings and precautions of lymphodepleting chemotherapy must be considered.

Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

Counsel patients to remain within the proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Monitoring of vital signs and organ functions should be considered depending on the severity of the reaction. The patient must also be made aware that although most CRS and neurological symptoms occur within the first 4 weeks after infusion, undesirable effects can occur at any time and may require treatment.

Reasons to delay treatment

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

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection or inflammatory disease.
- Active graft-versus-host disease (GvHD).
- Development of clinically relevant worsening of lymphoma, that results in medically significant organ dysfunction or clinical deterioration, following chemotherapy for lymphocyte depletion.

In some cases, the treatment may be delayed after administration of the lymphodepleting chemotherapy regimen. If the infusion is delayed for more than 2 weeks after the patient has received the lymphodepleting chemotherapy, lymphodepleting chemotherapy regimen should be administered again (see "Dosage/Administration").

Serological testing

Screening for HBV, HCV, and HIV should be performed before collection of cells for manufacturing of TECARTUS (see section "Dosage/Administration").

Blood, organ, tissue and cell donation

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

Hypersensitivity reactions

Allergic reactions may occur with the infusion of TECARTUS. Serious hypersensitivity reactions including anaphylaxis may be due to DMSO or residual gentamicin in TECARTUS.

Concomitant disease

Patients with a history of or active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function and patients with thrombocytopenia or low fibrinogen levels are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention. In addition, there is no clinical experience with the use of TECARTUS in patients with moderate to severe organ function impairment.

Active central nervous system (CNS) lymphoma

There is no experience of use of TECARTUS in patients with active CNS lymphoma defined as brain metastases confirmed by imaging. In ALL, asymptomatic patients with a maximum of CNS-2 disease (defined as white blood cells <5/µL in cerebral spinal fluid with presence of lymphoblasts) without clinically evident neurological changes were treated with TECARTUS, however, data is limited in this population. Therefore, the benefit/risk of TECARTUS has not been established in this population.

Cytokine Release Syndrome

Nearly all patients experienced some degree of cytokine release syndrome (CRS). Severe CRS, which can be fatal, was observed with TECARTUS with a median time to onset of 3 days (range: 1 to 13 days) (see “Undesirable effects”). Patients should be closely monitored for signs or symptoms of these events, such as high fever, hypotension, hypoxia, chills, tachycardia and headache (see section “Undesirable effects”). CRS should be managed at the physician’s discretion, based on the patient’s clinical presentation and according to the CRS management algorithm provided in Table 1.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including active infection.
Management of cytokine release syndrome associated with TECARTUS
Ensure that a minimum of 4 doses of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, are available for each patient prior to infusion of TECARTUS.

Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on TECARTUS. These include the use of tocilizumab or /and corticosteroids, as summarised in Table 1 below. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS.

Low fibrinogen, especially in the setting of thrombocytopenia, may increase the risk of bleeding. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered. In some cases, macrophage activation syndrome (MAS) and haemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS.

TECARTUS continues to persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of TECARTUS -associated CRS.

Table 1: CRS grading and management guidance

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If not improving after 24 hours, administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement < 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity *(b).*	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS. If improving, discontinue tocilizumab.	If no improvement within 24 hours after starting tocilizumab, manage per Grade 3. If improving, taper corticosteroids, and manage as Grade 1.
Grade 3 Symptoms require and respond to aggressive intervention. 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.	Per Grade 2 If improving, discontinue tocilizumab.	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours) until Grade 1, then taper corticosteroids. If improving, manage as Grade 2. If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2 If improving, discontinue tocilizumab.	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, taper corticosteroids, and manage as Grade 3. If not improving, consider alternate immunosuppressants.

N/A = not available/not applicable
(a) Lee et al 2014
(b) Refer to Table 2 for management of neurologic adverse reactions
(c) Refer to tocilizumab product information for details

Neurologic adverse reactions

Severe neurologic adverse reactions (encephalopathy, confusional state or delirium, decreased level of consciousness, seizures, aphasia), also known as immune effector cell-associated neurotoxicity syndrome (ICANS), which could be fatal or life-threatening, were observed in patients treated with TECARTUS. The median time to onset was 7 days (range: 1 to 262 days) (see “Undesirable effects”). Cases of status epilepticus have been observed with TECARTUS. Patients with a history of CNS disorders such as seizures or cerebrovascular ischemia may be at increased risk. Serious cases of

cerebral oedema which may become fatal have occurred in patients treated with TECARTUS. Patients should be monitored for signs and symptoms of neurologic adverse reactions/ICANS (Table 2).

Patients who experience Grade 2 or higher neurologic toxicity/ICANS should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities/ICANS. Non-sedating, anti-seizure medicines should be considered as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on TECARTUS. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

Table 2: Neurologic adverse reaction/ICANS grading and management guidance

Grading Assessment	Concurrent CRS	No concurrent CRS
Grade 2	Administer tocilizumab as per Table 1 for management Grade 2 CRS. If not improving within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab. If still not improving, manage as Grade 3.	Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less. If improving, taper corticosteroids
	Consider non-sedating, anti-seizure medicines (e.g. levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab and manage as Grade 2. If still not improving, manage as Grade 4.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Infections and febrile neutropenia

Severe infections, which could be life-threatening, were very commonly observed with TECARTUS (see “Undesirable effects”).

Patients should be monitored for signs and symptoms of infection before, during and after TECARTUS infusion and treated appropriately. Prophylactic antibiotics should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after TECARTUS infusion (see section “Undesirable effects”) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

In immunosuppressed patients, life -threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation (e.g., HHV-6 and progressive multifocal leukoencephalopathy) have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations should be performed.

Viral reactivation

Viral reactivation, e.g. Heptitis B Virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and TECARTUS infusion and should be managed according to standard guidelines. Grade 3 or higher prolonged cytopenias following TECARTUS infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia (see section “Undesirable effects”). Patient blood counts should be monitored after TECARTUS infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with TECARTUS. Hypogammaglobulinaemia was very commonly observed in patients treated with TECARTUS (see section “Undesirable effects”). Hypogammaglobulinaemia predisposes patients to have infections. Immunoglobulin levels should be monitored after treatment with TECARTUS and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement in case of recurrent infections. Immunoglobulin replacement should be administered according standard guidelines.

Live vaccines

The safety of immunisation with live viral vaccines during or following TECARTUS 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 TECARTUS treatment, and until immune recovery following treatment with TECARTUS.

Secondary malignancies

Patients treated with TECARTUS may develop secondary malignancies or recurrence of their treated maligancy. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to TECARTUS infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines.

Prior stem cell transplantation (GvHD)

It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GvHD receive treatment because of the potential risk of TECARTUS worsening GvHD.

Prior treatment with anti CD19 therapy

TECARTUS is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Excipients

Tecartus contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

No pharmacokinetic or pharmacodynamic interaction studies have been performed with TECARTUS. Prophylactic use of systemic corticosteroids may interfere with the activity of TECARTUS. Prophylactic use of systemic corticosteroids is therefore not recommended before infusion (see section Dosage/Administration).

Administration of corticosteroids as per the toxicity management guidelines has not been demonstrated to impact the expansion and persistence of CAR T cells.

Pregnancy, lactation

Women of childbearing potential/Contraception in males and females

The pregnancy status of women of childbearing potential must be verified before starting TECARTUS treatment.

See the product information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with TECARTUS.

Pregnancy

There are no available data with TECARTUS use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with TECARTUS to assess whether it can cause foetal harm when administered to a pregnant woman (see section “Preclinical data”).

It is not known if TECARTUS has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced T cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, TECARTUS 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 foetus. Pregnancy after TECARTUS therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborn infants of mothers treated with TECARTUS should be considered.

Lactation

It is unknown whether TECARTUS is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women should be advised of the potential risk to the breast-fed child.

Fertility

No clinical data on the effect of TECARTUS on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

Effects on ability to drive and use machines

TECARTUS has major influence on the ability to drive and use machines.

Due to the potential for neurologic events, including altered mental status or seizures, patients should not drive or operate heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

Undesirable effects

Mantle Cell Lymphoma

The safety data described in this section reflect exposure to TECARTUS in ZUMA-2, a Phase 2 study in which a total of 82 patients with relapsed/refractory MCL received a single dose of CAR-positive viable T cells (2×10^6 or 0.5×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight-based.

Serious adverse reactions occurred in 56% of patients. The most common serious adverse reactions included infections (28%), encephalopathy (26%), and cytokine release syndrome (15%).

The most significant and frequently occuring adverse reactions were CRS (91%), infections (55%) and encephalopathy (51%).

Grade 3 or higher adverse reactions were reported in 67% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (34%) and encephalopathy (24%). The most common Grade 3 or higher haematological adverse reactions included neutropenia (99%), leukopenia (98%), lymphopenia (96%), thrombocytopenia (65%) and anaemia (56%).

Acute Lymphoblastic Leukemia

The safety data described in this section reflect exposure to TECARTUS in ZUMA-3, a Phase 1/2 study in which a total of 100 patients with relapsed/refractory B-cell ALL received a single dose of CAR-positive viable T cells (0.5×10^6, 1×10^6, or 2×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight based.

The most significant and frequently occurring adverse reactions were CRS (91%), encephalopathy (57%), and infections (41%).

Serious adverse reactions occurred in 70% of patients. The most common serious adverse reactions included CRS (25%), infections (22%) and encephalopathy (21%).

Grade 3 or higher adverse reactions were reported in 76% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (27%), CRS (25%) and encephalopathy (22%).

Summary of adverse reactions

Adverse reactions described in this section were identified in a total of 182 patients exposed to TECARTUS in two multi-centre pivotal clinical studies, ZUMA-2 (n=82) and ZUMA-3 (n=100). These reactions are presented by system organ class and by frequency. Frequencies are defined as follows:

very common (≥ 1/10); common (≥ 1/100, < 1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Infections and infestations:
Very common: Unspecified pathogen infections (34%), Bacterial infections (16%), Fungal infections (10%), Viral infections (10%).

Blood and lymphatic system disorders:
Very common: Leukopenia[a] (99%), Neutropenia[a] (98%), Lymphopenia[a] (97%), Thrombocytopenia[a] (79%), Anaemia[a] (69%), Febrile Neutropenia[a] (12%).
Common: Coagulopathy.

Immune system disorders:
Very common: Cytokine Release Syndrome[b] (91%), Hypogammaglobulinaemia (12%).
Common: Hypersensitivity, Haemophagocytic lymphohistiocytosis.

Metabolism and nutrition disorders:
Very common: Hypophosphataemia[a] (41%), Decreased appetite (23%), Hypomagnesaemia (20%), Hyperglycaemia[a] (17%).
Common: Hypoalbuminaemia[a], Dehydration.

Psychiatric disorders:
Very common: Delirium (19%), Anxiety (15%), Insomnia (15%).

Nervous system disorders:
Very common: Encephalopathy (54%), Tremor (32%), Headache (27%), Aphasia (21%), Dizziness (14%), Neuropathy (10%).
Common: Seizure, Ataxia, Increased intracranial pressure.
Uncommon: Status Epilepticus.

Cardiac disorders:
Very common: Tachycardias (19%), Bradycardias (12%).
Common: Non-ventricular arrhythmias.

Vascular disorders:
Very common: Hypotension (21%), Hypertension (15%), Haemorrhage (12%).
Common: Thrombosis.

Respiratory, thoracic and mediastinal disorders:
Very common: Cough (25%), Dyspnoea (15%), Pleural effusion (13%), Hypoxia (11%).
Common: Respiratory failure, Pulmonary oedema.

Gastrointestinal disorders:
Very common: Nausea (29%), Diarrhoea (26%), Constipation (25%), Abdominal pain (25%), Vomiting (16%), Oral pain (14%).
Common: Dry mouth, Dysphagia.

Hepatobiliary disorders:
Very common: Alanine aminotransferase increased [a] (24%), Blood uric acid increased [a] (23%), Hypocalcaemia [a] (20%), Aspartate aminotransferase increased [a] (20%), Hyponatraemia [a] (18%), Direct bilirubin increased [a] (14%), Hypokalaemia [a] (13%).
Common: Bilirubin increased [a].

Skin and subcutaneous tissue disorders:
Very common: Rash (21%), Skin disorder (18%).

Musculoskeletal and connective tissue disorders:
Very common: Muscoloskeletal pain (35%), Motor dysfunction (29%).

Renal and urinary disorders:
Very common: Renal insufficiency (11%).
Common: Urine output decreased .

General disorders and administration site conditions:
Very common: Oedema (35%), Fatigue (34%), Pyrexia (29%), Pain (23%), Chills (12%).

Eye disorders:
Common: Visual impairment.

[a] Frequency based on Grade 3 or higher laboratory parameter.
[b] See section “Description of selected undesirable effects”.

Description of selected undesirable effects from ZUMA-2 and ZUMA-3

Cytokine release syndrome

CRS occurred in 91% of patients. Twenty percent (20%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was 9 days (range: 1 to 63 days). Ninety-seven percent (97%) of patients recovered from CRS.

The most common signs or symptoms associated with CRS among the patients who experienced CRS included pyrexia (94%), hypotension (64%), hypoxia (32%), chills (31%), tachycardia (27%), sinus tachycardia (23%), headache (22%), fatigue (16%) and nausea (13%). Serious adverse reactions that may be associated with CRS included hypotension, pyrexia, hypoxia, tachycardia, dyspnoea, and sinus tachycardia. See “Warnings and precautions” for monitoring and management guidance.
In addition, serious adverse reactions that have been observed with similar treatments and which may occur with TECARTUS treatment include: haemophagocytic lymphohistiocytosis/macrophage activation syndrome, cardiac failure, cardiac arrhythmia (including supraventricular tachycardia, atrial fibrillation, ventricular extrasystoles).

Neurologic events and adverse reactions

Neurologic adverse reactions occurred in 69% of patients. Thirty-two percent (32%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 7 days (range: 1 to 262 days). Neurologic events resolved for 113 out of 125 patients with a median duration of 12 days (range: 1 to 708 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. Ninty-four percent (94%) of all treated patients experienced the first CRS or neurological event within the first 7 days after TECARTUS infusion.

The most common neurologic adverse reactions included tremor (32%), encephalopathy (27%), headache (27%), confusional state (27%), aphasia (21%), delirium (19%), dizziness (14%) and agitation (11%). Serious adverse reactions including encephalopathy (15%), aphasia (6%), confusional state (5%) and seizure including status epilepticus (2%) have been reported in patients administered TECARTUS. Serious cases of cerebral oedema which may become fatal have occurred in patients treated with TECARTUS. Serious cases of muscular weakness suggestive of spinal cord involvement, including myelitis and paralysis syndromes, have occurred in patients treated with TECARTUS and/or similar treatments. See “Warnings and precautions for monitoring and management guidance.

ICANS, including status epilepticus was reported in the context of neurologic toxicity.

In addition, serious neurologic adverse reactions that have been observed with similar treatments and which may occur with TECARTUS treatment include: depressed level of consciousness and restlessness

Febrile neutropenia and infections

Febrile neutropenia was observed in 12% of patients after TECARTUS infusion. Infections occurred in 48% of the 182 patients treated with TECARTUS in ZUMA-2 and ZUMA-3. Grade 3 or higher (severe, life-threatening or fatal) infections occurred in 31% of patients including unspecified pathogen, bacterial, fungal and viral infections in 23%, 8%, 2% and 4% of patients respectively. See “Warnings and precautions” for monitoring and management guidance.

Prolonged Cytopenias

Cytopenias are very common following prior lymphodepleting chemotherapy and TECARTUS therapy.
Prolonged (present on or beyond Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher cytopenias occurred in 48% of patients and included neutropenia (34%), thrombocytopenia (27%), and anaemia (15%). See “Warnings and precautions” for management guidance.

Hypogammaglobulinaemia

Hypogammaglobulinaemia occurred in 12% of patients. Grade 3 or higher hypogammaglobulinemia occurred in 1% of patients. See “Warnings and precautions” for management guidance.

Immunogenicity

The immunogenicity of TECARTUS has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. To date, no anti-CD19 CAR T cell antibody mediated immunogenicity has been observed in MCL patients. Based on an initial screening assay, 17 patients in ZUMA-2 at any time point tested positive for antibodies; however, a confirmatory orthogonal cell-based assay demonstrated that all 17 patients in ZUMA-2 were antibody negative at all time points tested. Based on an initial screening assay, 16 patients in ZUMA-3 tested positive for antibodies at any timepoint. Among patients with evaluable samples for confirmatory testing, two patients were confirmed to be antibody-positive after treatment. One of the two patients had a confirmed positive antibody result at Month 6. The second patient had a confirmed antibody result at retreatment Day 28 and Month 3. There is no evidence that the kinetics of initial expansion, CAR T-cell function and persistence of TECARTUS, or the safety or effectiveness of TECARTUS, were altered in these patients.

Other Serious Adverse Reactions

Serious adverse reactions that have been observed with similar treatments and which may occur with TECARTUS treatment include: deep vein thrombosus, embolism (including pulmonary embolism), muscle spasms, syncope, and weight decreased.

Reporting of suspected undesirable effects

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

There are no data regarding the signs of overdose with TECARTUS.

Properties/Effects

ATC code

Not yet assigned.

Mechanism of action

TECARTUS, a CD19-directed genetically modified autologous T cell immunotherapy, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 co-stimulatory domain and CD3-zeta signalling domain activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

Pharmacodynamics

In both ZUMA-2 and ZUMA-3, after TECARTUS infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, interferon-gamma (IFN-γ) and IL-2 receptor alpha were analysed. Peak elevation was generally observed within the first 8 days after infusion and levels generally returned to baseline within 28 days.

Due to the on target, off-tumour effect of TECARTUS a period of B-cell aplasia may occur following treatment. From 25 patients with MCL, who had evaluable samples at basline at the 24-month follow-up analysis and were in ongoing response, 80% had detectable B cells, whereas the B cell aplasia observed in 20% of patients was attributed to prior therapies. Following TECARTUS treatment, the proportion of patients in ongoing response with detectable B cells decreased with 39.1% of evaluable patients having detectable B cells at Month 3, 15% had detectable B cells at Month 6 and 41.7% had

detectable B cells at month 12. By Month 24, 53.3% of evaluable subjects in ongoing response had detectable B cells.

From 49 patients with ALL, who had evaluable samples at baseline and were in ongoing response, 96% had detectable B cells, whereas the B cell aplasia observed in 4% was attributed to prior therapies. Following TECARTUS treatment, the proportion of patients ongoing response with detectable B cells decreased with 25% of evaluable patients having detectable B cells at Day 28, 62.5% had detectable B cells at Month 3, 93% had detectable B cells at Month 6, 100% had detectable B cells at Month 12 and 80% of evaluated patients had detectable B cells at Month 15. By Month 18, 100% of evaluable subjects in ongoing response had detectable B cells.

Clinical efficacy

Relapsed or refractory MCL: ZUMA-2

The efficacy of TECARTUS in adult patients with relapsed or refractory (r/r) MCL who had previously received anthracycline or bendamustine-containing chemotherapy, an anti CD20 antibody, and a Bruton's tyrosine kinase inhibitor (BTKi) (ibrutinib or acalabrutinib), was evaluated in a phase 2 single-arm, open-label, multicenter trial. Eligible patients also had disease progression after last regimen or refractory disease to the most recent therapy. Patients with active or serious infections, prior allogeneic haematopoietic stem cell transplantation (HSCT), detectable cerebrospinal fluid malignant cells or brain metastases, and any history of central nervous system lymphoma or CNS disorders were ineligible. Also, patients with a serum creatinine > 1.5 mg/dL, cardiac ejection fraction of less than 50%, or room air oxygen saturation of less than 92%, or autoimmune disease requiring systemic immunosuppression were excluded. In ZUMA-2 a total of 74 patients were enrolled (*i.e.* leukapheresed) and 68 of these patients (modified intent to treat (mITT) analysis set) were treated with TECARTUS. Three patients did not receive TECARTUS due to manufacturing failure. Two other patients were not treated due to progressive disease (death) following leukapheresis. One patient was not treated with TECARTUS after receiving lymphodepleting chemotherapy due to ongoing active atrial fibrillation. The full analysis set (FAS) was defined as all patients who underwent leukapheresis. A summary of the patient baseline characteristics is provided in Table 3.

Table 3: Summary baseline characteristics for ZUMA-2

Category	All leukapheresed (FAS) (N=74)
Age (years)	
Median (min, max)	65 (38, 79)
≥ 65	58%
Male gender	84%
Median number of prior therapies (min, max)	3 (1; 5)
Relapsed/refractory subgroup	
Relapsed after auto-SCT	42%
Refractory to last MCL therapy	39%
Relapsed after last MCL therapy	19%
Patients with disease stage IV	86%
Patients with bone marrow involvement	51%
Morphological characteristics	
Classical MCL	54%
Blastoid MCL	26%
Other	1%
Unknown	19%
Received bridging therapy	
Yes	38 %
No	62%
Ki-67 IHC by central laboratory	
N	49
Median	65%

Auto-SCT, autologous stem cell transplant; IHC, immunohistochemistry; Max, maximum; MCL, mantle cell lymphoma; Min, minimum.

TECARTUS was administered to patients as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 2×10^8 cells) after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously, both given on the 5th, 4th, and 3rd day before TECARTUS. Bridging therapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden.

For patients treated with TECARTUS, the median time from leukapheresis to product release was 13 days (range: 9 to 20 days) and the median time from leukapheresis to TECARTUS infusion was 27 days (range: 19 to 74 days, with the exception of one outlier of 134 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. All patients received TECARTUS infusion on day 0 and were hospitalized until day 7 at the minimum.

The primary endpoint was objective response rate (ORR) as determined by Lugano 2014 criteria by an independent review committee. Secondary endpoints included duration of response (DOR), overall survival (OS), progression free survival (PFS) and severity of adverse events.

For the primary analysis, the analysis set was defined a priori which consisted of the first 60 patients treated with TECARTUS who were evaluated for response 6 months after the Week 4 disease assessment after TECARTUS infusion. In this analysis set of 60 patients the ORR was 93% with a CR rate of 67%. The ORR was significantly higher than the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ($p < 0.0001$).

At an updated ad-hoc descriptive efficacy analysis (median follow-up time of 25.5 months (range: 1.21 to 49.6 months), among the 68 patients (mITT) who received a single infusion of TECARTUS, the OOR was 91% with a CR rate of 68%. The median DOR was 24.8 months with a median follow-up time of 23.1 months (95% CI: 22.6, 35.9 months) and median OS was not reached after a median follow-up time of 25.5 months (range: 1.2 to 49.6 months).

At the updated 24-month follow-up analyses (median follow-up time of 35.6 months (range: 25.9 to 56.3 months)) of efficacy among the 68 patients who received TECARTUS (mITT), the ORR was 91% with a CR rate of 68%. In the FAS, the ORR was 84% with a CR rate of 62%. The 24-month analysis showed that for the 46 subjects who achieved a CR, the KM median DOR was 46.7 months (95% CI: 24.8 months, NE). Among all responders with first objective response (CR or PR), the 24-month follow-up analysis showed a KM median DOR (measured from the date of first objective response to the date to disease progression or death) of 28.2 months (95% CI: 13.5, 47.1 months). The KM estimates of the proportion of all responders who remained in response at 12 months, 18 months, and 24 months from first response were 64.6%, 57.6%, and 57.6% respectively.

Results in the FAS from both the ad-hoc analysis and the 24-month follow-up analysis are shown in Table 4.

Table 4: Summary of efficacy results for ZUMA-2

Category	**All leukapheresed[a] (FAS) (N=74)**	
	Ad-hoc Analysis	**24-month follow-up Analysis**
Objective Response Rate (ORR), n (%) [95% CI]	**62 (84%)** [73.4, 91.3]	**62 (84%)** [73.4, 91.3]
CR n (%) [95% CI]	46 (62%) [50.1, 73.2]	46 (62%) [50.1, 73.2]
PR n (%) [95% CI]	16 (22%) [12.9, 32.7]	16 (22%) [12.9, 32.7]
Duration of Response [b]		
Median in months [95% CI]	24.8 [13.5, NE]	28.2 [13.5, 47.1]
Range [c] in months	0.0+, 47.0+	0.0+, 53.0+
Ongoing Responses, CR+PR, CR, n (%) [d]	27 (36.5%), 27 (36.5%)	25 (34%), 25 (34%)
Progression Free Survival		
Median, months [95% CI]	19.1 [9.9, 38.2]	24.0 [10.1, 48.2]
Overall Survival		

Category	All leukapheresed[a] (FAS) (N=74)	
	Ad-hoc Analysis	24-month follow-up Analysis
Median, months [95% CI]	NR [25.9, NE]	47.4 [24.6, NE]
6 month OS (%) [95% CI]	83.6 [72.9, 90.3]	83.6 [72.9, 90.3]
12 month OS (%) [95% CI]	76.7 [65.3, 84.8]	76.7 [65.3, 84.8]
24 month OS (%) [95% CI]	64.4 [52.3, 74.2]	63.0 [50.9, 73.0]
30 month OS (%) [95% CI]	58.1 [45.7, 68.6]	56.2 [44.1, 66.7]
36 month OS (%) [95% CI]	55.0 [41.9, 66.4]	53.9 [41.5, 64.8]
Actual follow-up time from TECARTUS infusion (months)[e]		
N	68	68
Median	25.5	32.2
Min, max	1.2, 49.6	1.2, 56.3

Data cutoff date for ad hoc analysis (18-months follow-up analysis after initial response) = 31Dec2020, data cuttoff date for the 24-month follow-up analysis = 24Jul2021
CI, confidence interval; CR, complete remission; FAS, full analysis set; NE, not estimable; NR, not reached; OS, overall survival; PR, partial remission.
a. Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received conditioning chemotherapy, and 68 patients received TECARTUS.
b. Among all responders. DOR is measured from the date of first objective response to the date of progression or death.
c. A + sign indicates a censored value.
d. At the data cutoff date. Percentages are calculated using the total number of patients in the analysis set as the denominator.
e. Actual follow-up time from TECARTUS infusion is calculated as time from first dose of TECARTUS to date of death or the last date known alive. (Death date or last known alive date – TECARTUS treatment date +1)/(365.25/12)

At an updated 36-month follow-up analyses mOS in the mITT population was 46.4 months (95% CI: 24.9, 58.7 months), and in the FAS 44.2 months (95% CI: 24.6, 50.2 months).

Relapsed or refractory B-cell precursor ALL: ZUMA-3

A Phase 2, open-label, multicenter trial evaluated the efficacy and safety of TECARTUS in adult patients with r/r B-cell precursor ALL. Relapsed or refractory was defined as one of the following: primary refractory; first relapse following a remission lasting ≤ 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogeneic stem cell transplant (allo-SCT) (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment). The study excluded patients with active or serious infections, active graft-vs-host disease, and any history of CNS disorders. Patients with CNS-2 disease without clinically evident neurologic changes were eligible. In ZUMA-3 Phase 2, a total of 71 patients were enrolled (i.e. leukapheresed) and 55 patients were treated with TECARTUS. Six patients did not receive TECARTUS due to manufacturing failure. Eight other patients were not treated, primarily due to AEs following leukapheresis. Two patients who underwent leukapheresis and received lymphodepleting chemotherapy were not treated with TECARTUS; one patient experienced bacteremia and neutropenic fever and the other patient did not meet eligibility criteria after lymphodepleting chemotherapy. From the 55 patients treated with TECARTUS, 45 patients received TECARTUS after two or more systemic therapies. The FAS included all patients who underwent leukapheresis and the modified intent to treat (mITT) analysis set included all patients leukapheresed and treated with TECARTUS after two or more systemic therapies in Phase 2. This mITT analysis set

is Swiss specific and aligned with the Swiss ALL indication. A summary of patient baseline characteristics is provided in Table 5.

Table 5: Summary of baseline characteristics for ZUMA-3

Category	All leukapheresed (FAS) (N=71)	All treated (mITT) # (N=45)
Age (years) Median (min, max)	44 (19, 84)	41(19, 84)
Male gender	58%	60%
White ethnicity	72%	64%
Primary refractory disease	30%	31%
Relapsed/refractory disease after ≥ 2 lines of therapy	76%	96%
Relapse within first remission ≤ 12 months	28%	24%
Number of Lines of Prior Therapy		
Median (min, max)	2 (1, 8)	3 (2, 8)
≥ 3	48%	58%
Prior Therapies		
Allo-SCT	39%	49%
Blinatumomab	46%	53%
Inotuzumab	23%	27%
Philadelphia chromosome (Ph+)	27%	29%

Auto-SCT, autologous stem cell transplant; Max, maximum; Min, minimum

This mITT analysis set is Swiss specific and aligned with the Swiss ALL indication.

Following lymphodepleting chemotherapy, TECARTUS was administered to patients as a single intravenous infusion at a target dose of 1×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 1×10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 900 mg/m^2 intravenously over 60 minutes on the 2nd day before TECARTUS infusion and fludarabine 25 mg/m^2 intravenously over 30 minutes on the 4th, 3rd, and 2nd day before TECARTUS infusion. Of the 45 patients who received TECARTUS after two or more systemic therapies, 41 patients received bridging therapy between leukapheresis and lymphodepleting chemotherapy to control disease burden.

The median time from leukapheresis to product delivery was 16 days (range: 11 to 42 days) and the median time from leukapheresis to TECARTUS infusion was 29 days (range: 20 to 60 days). The median dose was 1.0×10^6 anti-CD19 CAR T cells/kg. All patients who received TECARTUS infusion on day 0 were hospitalized until day 7 at a minimum.

The primary endpoint was overall complete remission rate (OCR) (complete remission [CR] + complete remission with incomplete hematologic recover [CRi]) in patients treated with TECARTUS as determined by an independent review. In the 45 patients treated with TECARTUS (mITT) after two or more systemic therapies, the OCR rate was 66.7% with a CR rate of 51.1% (Table 6), which was significantly greater than the prespecified control rate of 40%. Among the 30 patients who achieved a CR or CRi, the median time to response was 1.1 months (range: 0.85 to 2.99 months). Across all

evaluable subgroups, OCR rates were generally consistent with the OCR rate observed for all subjects, including patients previously treated with blinatumomab (63%; 95% CI: 41.0, 81.0), inotuzumab (67%; 95% CI: 35.0, 90.0); allo-SCT (68%; 95% CI: 45.0, 86.0); patients who were Ph^+ (77%; 95% CI: 46.0, 95.0); primary refractory disease patients (71%; 95% CI: 42.0, 92.0), and patients who had first relapse with first remission ≤ 12 months (64%; 95% CI: 31.0, 89.0).

All treated patients had potential follow-up ≥ 30 months with a median actual follow-up time of 20.5 months (95% CI: 7.5, 34.7 months) and a median follow-up time for OS of 35.5 months (95% CI: 31.0, 36.5).

Table 6: Summary of efficacy results for ZUMA-3 Phase 2

Category	**FAS (N=71)**	**mITT[a#] (N=45)[b]**
OCR rate (CR + CRi), n (%) [95% CI]	39 (54.9) [43.0, 67.0]	30 (66.7) [51.0, 80.0]
CR rate, n (%) [95% CI]	31 (43.7) [32.0, 56.0]	23 (51.1) [36.0, 66.0]
Minimal Residual Disease (MRD) negative rate among OCR (CR or CRi) patients, n(%)	n=39 38 (97%)	n=30 30 (100%)
Duration of Remission, median in months [95% CI] Range in months	14.6 [9.4, 24.1][c] (0.03+, 37.91)	14.6 [9.4, 24.1][c] (0.03+, 37.91)
Relapse-Free Survival, median in months [95% CI]	3.7 [0.0, 12.9]	11.0 [1.8, 15.5]
OS, median in months [95% CI]	23.1 [10.4, 40.5]	25.6 [14.2, 38.9]
6 month OS (%) [95% CI]	70.2 [57.6, 79.6]	79.4 [64.2, 88.7]
12 month OS (%) [95% CI]	62.4 [49.5, 72.8]	69.8 [53.7, 81.2]
18 month OS (%) [95% CI]	55.9 [43.0, 66.9]	60.2 [43.9, 73.1]
24 month OS (%) [95% CI]	49.3 [36.5, 60.8]	52.8 [36.8, 66.5]
36 month OS (%) [95% CI]	41.7 [29.1, 53.7]	41.5 [26.0, 56.3]

CI, confidence interval; CR, complete remission; NE, not estimable; OS, overall survival; "+" indicates censoring

a. Of the 71 patients that were enrolled (*i.e.* leukapheresed), 57 patients received conditioning chemotherapy, and 55 patients received TECARTUS.

b. One patient in the mITT analysis lacked presence of BM blast at baseline disease assessment post-bridging chemotherapy.

c. The duration of remission was defined only for subjects achieving an OCR, therefore the results of the anylsis in the FAS and mITT were identical.

This mITT analysis set is swiss specific and aligned with the swiss ALL indication.

SCHOLAR-3

A retrospective, matched cohort study of adult patients with r/r B-ALL sampled from historical clinical trials was conducted to provide confirmation of the prespecified control response rate of 40% and historical context for interpreting the ZUMA-3 results. The analysis included patients with r/r B-ALL which were matched to patients entrolled into ZUMA-3. Response and survival after treatment with available standard of care therapy was evaluated. The OCR rate was 35% [95% CI (15.4, 59.2)] in patients not previously treated with blinatumomab or inotuzumab versus 85% [95% CI (62.1, 96.8)] in the matched ZUMA-3 patients. Median OS patients treated with standard of care was 5.49 months

[95% CI (3.32, 9.23)] for the overall population. The comparison of OS between matched ZUMA-3 and historical control patients demonstrated a statistically significant benefit for patients treated in ZUMA-3 (mOS 25.43 mo vs. 5.49, HR 0.32, p < 0.0001).

Pharmacokinetics

Absorption

Mantle Cell Lymphoma

Following infusion of 2 × 10^6 anti-CD19 CAR T cells/kg of TECARTUS in ZUMA-2, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7 to 15 days after the TECARTUS infusion.

Among patients with MCL, the number of anti-CD19 CAR T cells in blood was associated with objective response (CR or PR).

The median peak anti-CD19 CAR T-cell level in responders vs nonresponders was 97.52 cells/µL (range: 0.24 to 2589.47 cells/µL; n=62), and 0.39 cells/µL (range: 0.16 to 22.02 cells/µL, n=5; Wilcoxon rank rank-sum test p=0.0020), respectively. The median $AUC_{0\text{-}28}$ in subjects with an objective response was 1386.28 cells/µL•days (range: 3.83 to 2.77E+04 cells/µL•days; n=62) vs 5.51 cells/µL•days in nonresponders (range: 1.81 to 293.86 cells/µL•days; Wilcoxon rank-sum p=0.0013; n=5). The median T_{max} was 15 days for both responders and non-responders.
Some patients required tocilizumab and corticosteroids for management of CRS and neurologic toxicity/ICANS. Patients who received tocilizumab (n=10) alone had 230% and 250% higher anti-CD19 CAR T-cell levels and patients who received tocilizumab and corticosteroids (n=38) had 577% and 454% higher anti-CD19 CAR T-cell levels measured by C_{max} and $AUC_{Day\ 0\text{-}28}$ respectively, as compared to patients who did not receive these medications (n=18).

Acute Lymphoblastic Leukemia

Following infusion of a target dose of 1 × 10^6 anti-CD19 CAR T cells/kg of TECARTUS in ZUMA-3 (Phase 2), anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Median time to peak levels of anti-CD19 CAR T cells was within the first 15 days after TECARTUS infusion.

Among patients with ALL, the median peak anti-CD19 CAR T-cell levels over time by best overall response per independent review was 38.35 cells/µL (range: 1.31 to 1533.40 cells/µL; n=36) in patients who had overall complete remission (CR+CRi), and 0.49 cells/µL (range: 0.00 to 183.50 cells/µL, n=14) in patients who had non-complete remission. The median $AUC_{Day\ 0\text{-}28}$ in patients who

had overall complete remission (CR+CRi) was 424.03 cells/µL•days (range: 14.12 to 19390.42 cells/µL•days; n=36) vs 4.12 cells/µL•days in patients who had non-complete remission (range: 0.00 to 642.25 cells/µL•days; n=14).

Distribution

No data available.

Metabolism

No data available.

Elimination

TECARTUS comprises human autologous T cells, the anticipated metabolic products are typical cellular degradation products resulting from normal cellular clearance mechanisms. Thus, the infused CAR T cells are expected to be cleared over time. Anti-CD19 CAR T-cell levels decreased toward near background levels by Month 3 in ZUMA-2 (range: < LLOQ to 10.86 cells/µL) and ZUMA-3 (range: 0.00 to 1.73 cells/ µL) . In ZUMA-2,100% (30 of 30) of evaluable subjects who were in ongoing response had detectable CAR at Month 3, 88% (28 of 32) of subjects had detectable CAR at Month 6, 85% (11 of 13) of subjects had detectable CAR at Month 12 and 56% (5 of 9) of subjects had detectable CAR at Month 24. In ZUMA-3, 52% (16 of 31) of subjects with evaluable samples, had detectable CAR at Month 3, 21% (6 of 28) of subjects had detectable CAR at Month 6, 10% (2 of 21) of subjects had detectable CAR at Month 12 and 0% (0 of 13) of subjects had detectable CAR at Month 18. No secondary expansion of CAR T-cells was observed.

Kinetics in specific patient groups

Age, gender and ethnicity

Median peak anti-CD19 CAR T cell values were 74.08 cells/µL in MCL patients ≥ 65 years of age (n=39) and 112.45 cells/µL in MCL patients < 65 years of age (n=28). Median anti-CD19 CAR T cell AUC values were 876.48 cells/µL·day in MCL patients ≥ 65 years of age and 1640.21 cells/µL·day in MCL patients < 65 years of age.
Median peak anti-CD19 CAR T-cell values were 34.8 cells/µL in ALL patients ≥ 65 years of age (n=8) and 17.4 cells/µL in ALL patients < 65 years of age (n=47). Median anti-CD19 CAR T-cell AUC values were 425.0 cells/µL in ALL patients ≥ 65 years of age and 137.7 cells/µL in ALL patients < 65 years of age.
In MCL and ALL patients, gender had no significant impact on $AUC_{Day\ 0\text{-}28}$ and C_{max} of TECARTUS.

Hepatic impairment

Studies of TECARTUS in patients with hepatic impairment were not conducted.

Renal impairment

Studies of TECARTUS in patients with renal impairment were not conducted.

Preclinical data

TECARTUS comprises engineered human T cells; therefore, there are no representative in vitro assays, ex vivo models, or in vivo models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

Genotoxicity

No genotoxicity studies have been conducted with TECARTUS.

Carcinogenicity

No carcinogenicity studies have been conducted with TECARTUS.

Reproductive toxicity

No studies have been conducted to evaluate the effects of this treatment on fertility, reproduction, and development.

Other information

Incompatibilities

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

Shelf life

TECARTUS is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ −150°C).

TECARTUS is stable at room temperature (20°C to 25°C) for up to 3 hours after thawing. However, TECARTUS infusion should begin within 30 minutes of thaw completion and the total infusion time should not exceed 30 min. Thawed product should not be refrozen.

Do not use TECARTUS after the expiry date (“EXP”) stated on the container.

Special precautions for storage

TECARTUS must be stored in the vapor phase of liquid nitrogen (≤ −150˚C) and must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are available for patient administration.

For storage conditions after thawing of the medicinal product, see “Shelf life”.

Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken for the transport and disposal of the medicinal product

TECARTUS should be transported within the facility in closed, break-proof, leak-proof containers.

TECARTUS contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal products or waste material. All material that has been in contact with TECARTUS (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material.

Accidental exposure to TECARTUS must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with TECARTUS must be decontaminated with appropriate disinfectant.

Authorisation number

67884 (Swissmedic)

Packs

TECARTUS, maximum of 2 x 10^8 cells/68 mL dispersion for infusion [A]
TECARTUS is supplied in an ethylene-vinyl acetate cryostorage bag with sealed addition tube and two availble spike ports.
One cryostorage bag is individually packed in a shipping metal cassette.

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug

Date of revision of the text

January 2023

Revision history

Application ID	Milestone	Created on	Change	Initials
102667309	Approval	12 January 2023	Type II: Indication extension ALL incl. new dosage recommendation	FVO
102679663	Approval	11 January 2023	Type II: CCDS v4.0 – ICANS_SE	FVO
102657747	Approval	16 December 2022	PAM: Update with 24 month follow-up for MCL	FVO
102635994	Approval	25. August 2021	Initial MAA	CVA