15 October 2020
EMA/588798/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Tecartus

Usual common name: autologous anti-CD19-transduced CD3+ cells

Procedure No. EMEA/H/C/005102/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ASCT/allo-SCT	autologous stem cell transplant
AST	aspartate aminotranferase
AUC0-28	area-under-the-curve from Day 0 to Day 28
BEAM	carmustine/etoposide/cytarabine/melphalan
BED	business-enabling documents
BM aspirate/biopsy	bone marrow aspirate/biopsy
BTKI	bruton's tyrosine kinase inhibitor
BR	bendamustine/rituximab
CAR	chimeric antigen receptor
CHMP	committee for medicinal products for human use
CI	confidence interval
CCR7	chemokine receptor 7
CLL	chronic lymphatic/lymphocytic leukemia
CR	complete response
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CSR	clinical study report
CTAE	common terminology criteria for adverse events
CRS	cytokine release syndrome
CXCL	C-X-C motif chemokine
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
DSMB	data safety monitoring board
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	eastern cooperative oncology group
EEG	electroencephalogram
ELISA	enzyme-linked immunosorbent assay
EQ-5D/VAS	european quality of life-5 dimensions/ visual analogue scale (for health/pain assessment)
EOS	end of study
EOT	end of trial

FAS	full analysis set
FL	follicular lymphoma
FU	follow-up
GM-CSF	granulocyte macrophage colony stimulating factor
HIV	human immunodeficiency virus
HLH	haemophagocytic lymphohistiocytosis
IAS	inferential analysis set
IB	investigator brochure
ICAM	intercellular adhesion molecule
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
IFN	interferon
IL	interleukin
IL-1RA	interleukin-1 receptor antagonist
IL-2Rα	interleukin-2 receptor alpha
IP	investigational product
IRB/IEC	institutional review board/independent ethics committee
IV	intravenous
IWG	international working group
Ki-67	protein as marker for cell proliferation in humans
KM	Kaplan-Meier
LLOQ	lower limit of quantification
LTFU	long term follow-up
LTRs	long terminal repeats
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAS	macrophage activating syndrome
MCL	mantle cell lymphoma
MCP	monocyte chemoattractant protein
MIP	macrophage inflammatory protein
MIPI	mantle cell lymphoma prognostic index
mITT	modified intend to treat
MMSE	minimal mental status exam
MRI	magnetic resonance imaging
MSD®	MesoScale Discovery®
NCI	national cancer institute

NHL	non-Hodgkin lymphoma
ORR	overall/objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PET-CT	positron emission tomography-computed tomography
PFS	progression free survival
PK/PD	pharmacokinetic/pharmacodynamic
PMBCL	primary mediastinal B-cell lymphoma
PO	per os
PR	partial response/partial remission
qPCR	quantitative polymerase chain reaction
R-CHOP	rituximab/cyclophosphamide/doxorubicin/vincristine/prednisolone
RCR	replication competent virus
R-DHAP	rituximab/dexamethasone/highdose-cytarabine/cisplatin/ rituximab maintenance
r/r	relapsed/refractory
SAE	serious adverse event
scFv	single chain variable fragment
sFASL	soluble FAS ligand
SCT	stem cell transplantation
SD	stable disease
s-MIPI	simplified mantle cell lymphoma international prognostic index
SOP	standard operating procedure
SPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TBI	total body irradiation
TCR	T-cell receptor
TEAE	treatment emerged adverse event
THAM	total body irradiation/cytarabine/melphalan
TNF	tumour necrosis factor
TLS	tumour lysis syndrome
TSS	transcription start site
ULOQ	upper limit of quantification
URMC	university of rochester medical center
UTI	urinary tract infection

VCAM-1	vascular cell adhesion molecule-1
VIS	vector integration site
WBC	white blood cells, also called leucocytes (unit: 10E9/L)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Kite Pharma EU B.V. submitted on 9 January 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Tecartus, through the centralised procedure falling within the Article 3(1) and point 1a of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 May 2018.

Tecartus, was designated as an orphan medicinal product EU/03/19/2220 on 13 November 2019 in the following condition: Treatment of mantle cell lymphoma.

Tecartus was granted eligibility to PRIME on 1 June 2018 in the following indication: Treatment of adult patients with relapsed or refractory mantle cell lymphoma.

Eligibility to PRIME was granted at the time in view of the following:

- Mantle cell lymphoma is an aggressive and incurable subtype of B-cell non-Hodgkin lymphoma. Although most cases are initially sensitive to chemotherapy, relapse and progressive chemoresistance are the rule in advanced stages. Currently available therapy for patients with relapsed MCL results in CR rates of 19% in patients who had failed ibrutinib therapy. Although the introduction of novel agents (e.g. IMiDs, temsirolimus and, in particular, BTK inhibitors such as ibrutinib and acalabrutinib) has improved the outcomes of subjects with relapsed or refractory (r/r) MCL, the available therapies (with the possible exception of HSCT) do not have a curative intent, and prolonging PFS and symptoms palliation remain the main goals of treatment. The unmet medical need can therefore be agreed.
- Despite the overall limited data and models' limitations, the non-clinical data package may be overall considered a sufficient proof-of-concept to address the product potential to treat CD19 expressing onco-haematological malignancies such as r/r MCL.
- Limited but promising clinical data have been provided from 28 subjects treated with KTE-C19 (XLP process) in Cohort 1 in ZUMA-2 after failing a BTK inhibitor. In particular, the reported ORR (86%), CR rate (54%) and estimated 9-month DoR and OS rates (69.9% and 83.7%, respectively) observed in a heavily pre-treated population already exposed to ibrutinib should be regarded with interest, since the currently available literature data seem to point toward median OS ranging from 2.9 to 5.8 months after failure of BTK inhibitors (Martin P et al, Blood 2016).

The applicant applied for the following indication: Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL)

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Tecartus as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Tecartus.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that autologous anti-CD19-transduced CD3+ cells was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies)

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0433/2019 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

Conditional marketing authorisation

The applicant applied for a full marketing authorisation, but during the assessment, in response to CAT and CHMP concerns on the comprehensiveness of the data, requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above mentioned Regulation.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14(9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance autologous peripheral blood t cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific recommendation on Classification

The applicant Kite Pharma EU B.V. submitted on 8 May 2019 an application for Scientific recommendation on Classification to the European Medicines Agency (EMA) for Tecartus, which was designated as an Advanced Therapy Medicinal Product on 1 July 2019. Tecartus was classified as a gene therapy medicinal product.

PRIME support

Upon granting of eligibility to PRIME, Jan Müller-Berghaus was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 30 October 2018. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

to seek further scientific advice namely multiplicity of infection, vector impurities and drug substance specification for quality and historical control rate and bridging therapy for clinical and significant benefit for the maintenance of the orphan designation. In addition, the Agency asked the Company to consider seeking EMA/HTA parallel advice with regards to the historical control.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
29 May 2019	EMEA/H/SA/3117/7/2019/PA/ADT/PR/III	Dr Ole Weis Bjerrum and Dr Jan Mueller-Berghaus

The protocol assistance pertained to the following quality and clinical aspects of the dossier:

- The process characterisation studies addressing several parameters of the viral transduction step; the acceptability of the developmental activities to improve the quality of the retroviral vector used to genetically modify the autologous T-cells in KTE-X19; the appropriateness of the release specifications for the KTE-X19 final product.
- The acceptability of an assumed historical control rate of 25% ORR, based on ORRs observed with salvage therapies after progressing on a BTK inhibitor.
- The use of bridging therapy in ZUMA-2 and the impact it may have on the assessment of KTE-X19 benefit in r/r MCL.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Rune Kjeken

Accelerated Assessment procedure was agreed-upon by CAT and CHMP on	12 December 2019
The application was received by the EMA on	9 January 2020
The procedure started on	28 January 2020
The Rapporteur's first Assessment Report was circulated to all CAT and	23 April 2020

CHMP members on	
The Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	21 April 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	1 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The CAT agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 May 2020
The applicant submitted the responses to the CAT consolidated List of Questions on	12 August 2020
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at two sites (sponsor site in the US and CRO site in Germany) between 23 April 2020 and 03 July 2020. Please note that the sponsor site was inspected remotely. The outcome of the inspection carried out was issued on	23 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CAT and CHMP members on	29 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	04 September 2020
The CAT agreed on a list of outstanding issues in writing to be sent to the applicant on (TT reverted back to normal timetable)	11 September 2020
The applicant submitted the responses to the CAT List of Outstanding Issues on	17 September 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	29 September 2020
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tecartus on	09 October 2020
The CAT adopted a report on similarity of Tecartus with Imbruvica on (Appendix 1)	09 October 2020

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tecartus on	15 October 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The present centralised marketing authorisation application concerns the treatment of adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL).

The agreed indication for the product is: *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's tyrosine kinase (BTK) inhibitor.*

Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin lymphoma (NHL) with distinctive clinical, biological, and molecular characteristics {Fakhri 2017, National Comprehensive Cancer Network 2018}

2.1.2. Epidemiology

MCL accounts for approximately 6% of all new cases of NHL in the United States (US) (Leukemia & Lymphoma Society 2014) and 5% to 7% of malignant lymphoma in Western Europe (Dreyling 2017b). The estimated annual incidence of MCL is approximately 1 to 2 per 100,000 persons in the US and Europe (Dreyling 2017b, Fu 2017). MCL is more likely to affect men than women (Vose 2017), and the median age at diagnosis is 68 years (Fakhri 2017)

2.1.3. Biologic features

The lymphoma cells in MCL are thought to originate from antigen-naive pre-germinal centre B cells within the mantle zone of the lymph node and typically express the surface markers CD19, CD20, CD22, CD43, CD79a, FMC7, CD5, surface immunoglobulin (Ig) M, and surface IgD (Dreyling 2014) but not CD11c and CD10 (Kraus 2010). The molecular hallmark of MCL is the chromosomal translocation t(11;14)(q13;q32), which results in overexpression of the cell cycle regulator cyclin D1. In addition to cell cycle dysregulation, aberrant cyclin D1 expression also results in alterations in the DNA damage response pathway and activation of cell survival pathways, both of which contribute to MCL pathogenesis (Jares 2012). Independent of cyclin D1 expression, the transcription factor sex determining region Y-box 11 (SOX11) may be used as a diagnostic marker for the rare cases of MCL that are cyclin D1-negative (Narurkar 2016, Sander 2016).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

According to the WHO 2016 update, MCL has been categorised in two major subgroups with distinct clinical and molecular features: Nodal MCL and leukemic non-nodal MCL.

Prognosis varies based on clinical and laboratory parameters. Early stage disease (Staged I-II) is defined by involvement of one or two lymph node regions (or extranodal sites) localised on the same side of the diaphragm. Patients are often diagnosed with advanced disease (Stage III or IV). Stage III-IV disease is characterised by involvement of lymph nodes or lymphoid regions on both sides of the diaphragm or diffuse extralymphatic organ involvement. Often, the primary diagnosis is advanced disease (Stage III/IV), present with lymphadenopathy and extranodal involvement of the blood, bone marrow, and spleen; the gastrointestinal tract is also reported to be involved in 15% to 30% of patients.

Prognostic indexes help predict long-term outcomes for this disease in treatment-naive patients. The Mantle Cell Lymphoma International Prognostic Index (MIPI) uses 4 independent factors (age, Eastern Cooperative Oncology Group [ECOG] performance status, blood lactate dehydrogenase, and leukocyte count) to stratify front-line patients into low-, intermediate-, and high-risk prognostic groups based on their overall survival (OS) status. After a median follow-up of 32 months, these groups had median OS values of not reached, 51 months, and 29 months, respectively (Hoster 2008). The authors who developed the MIPI also created the simplified MIPI (s-MIPI), which can be derived without a calculation. The MIPI and s-MIPI can be supplemented with the Ki-67 proliferative index, which offers additional discriminatory power (Geisler 2010, Hoster 2008).

2.1.5. Management

Current frontline therapy options

The current standard of care for first-line treatment depends on the stage of MCL, the patients' age, the symptoms and the tumour burden. Frontline therapy includes autologous stem cell therapy, mainly reserved for patients ≤ 65 years of age, and different therapy regimens such as R-CHOP, R-DHAP and BR. Frontline therapy for MCL has evolved over the past decade, and overall response rates (ORR) of up to 94% and complete response (CR) rates of up to 40% have been achieved with first-line therapies. However, despite high ORR, the majority of patients will relapse, and outcomes in the relapsed setting are much poorer. Recent studies have shown a median OS of 5 to 7 years in patients with earlier stages of disease (Martin et al, 2009; Herrmann et al, 2009), but median OS of approximately 10 to 13 months in patients who have progressed after chemotherapy and targeted agents (Martin et al, 2014).

Current treatment options in the relapsed and refractory situation

In the r/r situation in MCL, a repeated biopsy is recommended to identify important prognostic features and individual therapy options (Dreyling et al, Annals of Oncology, 2017). The treatment concepts comprise immunochemotherapy followed by autologous/allogeneic SCT, BTK inhibitors (ibrutinib and acalabrutinib; both approved in the US; only ibrutinib is approved in the EU), the immunomodulatory (and thalidomide analogue) agent lenalidomide, the m-TOR inhibitor temsirolimus and the BCL-2 antagonist venetoclax. Bortezomib is approved in the EU for use in combination with R-CHOP for the treatment of newly diagnosed MCL, and it has also been investigated as a monotherapy in relapsed/refractory MCL.

Responses to ASCT in relapse are inferior to those in first-line and there is no consensus on the benefit of its use in relapsed/refractory disease (Ketterer et al, 1997; Robinson et al, 2015). By contrast, allo-SCT has the potential to be curative in relapse/refractory MCL (Vose 2015). In a recent review of 7 single-institution and

registry studies of patients with relapsed or refractory MCL, Rajabi and colleagues (Rajabi and Sweetenham 2015) reported that approximately 25% of patients could achieve durable remissions with allo-SCT treatment if their disease was demonstrated to be chemosensitive prior to transplant. These studies included patients who had previously undergone ASCT. However, they also reported high treatment-related mortality rates of up to 40% following allo-SCT, primarily due to graft-versus host disease, and the majority of patients still did not achieve durable remissions.

Maintenance regimens with rituximab in the r/r situation have a favourable safety profile and prolong PFS and OS, however, second-line maintenance in patients relapsing after front-line maintenance is not recommended which implies a restriction of a therapeutically approach in the r/r situation of MCL a priori.

Despite promising high rates of ORR (68%) for BTK inhibitors (ibrutinib SmPC) in the relapsed setting, they are not considered as curative treatments since all patients will eventually have progressive disease after receiving a BTK inhibitor. Subsequent to the approval of ibrutinib in the US, Rule and colleagues published a pooled analysis of 370 subjects with r/r MCL who received ibrutinib across 3 studies after 2 to 5 prior therapy lines (Phase 2 SPARK, Phase 3 RAY, and Phase 2 PCYC-1104). Collectively, these subjects initially had a median follow-up of 24 months (Rule 2017) and later of 3.5 years in a follow-up study (Rule 2019). The ORR and CR rates for all subjects were 70% and 27%, respectively, but the median range for DOR was 3 to 5.8 months, and for OS 2.5 to 9 months (Dreyling et al on behalf of ESMO Guidelines Committee, Annals of Oncology, Volume 28, Jul 2017).

Although the clinical outcome at MCL generally improved in the last years, the r/r situation and disease progress during or after treatment with BTK inhibitors mean a rather limited further treatment options for the patient. Thus, novel therapy strategies resulting in durable response rates are required.

About the product

Tecartus is a gene therapy medicinal product containing autologous T cells genetically modified whereby a patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction using an MSCV based gamma-retroviral vector to express a CAR comprising an anti-CD19 single chain variable fragment (scFv) linked to CD28 co-stimulatory domains and CD3-zeta signalling domain . The transduced anti-CD19 CAR T cells are expanded ex vivo and infused back into the patient, where they can recognise and eliminate CD19 expressing target cells.

Tecartus binds to CD19 expressing cancer 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 signaling 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 apoptosis and necrosis of CD19 expressing target cells.

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's tyrosine kinase (BTK) inhibitor.

Type of Application and aspects on development

The CHMP and CAT agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the fact that currently patients with r/r MCL have only limited treatment options with insufficient clinical outcome. An unmet medical need was substantiated

by the applicant and is acknowledged. Data were presented to support that Tecartus may address that unmet need. Though limited clinical data were available at the time of the accelerated assessment request, yet the promising ORR and CR rate observed so far, and the possibility for long-term disease control suggest that Tecartus might indeed represent a major therapeutic advantage over existing therapies.

However, during assessment the CAT and CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as the proposed indication did not fully correspond to the patients treated in clinical trials and since the data set was not considered comprehensive and the applicant had to provide a justification to support consideration of the application for conditional approval.

In light of the concerns raised during assessment on the comprehensiveness of the data set, the applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the fulfilment of following requirements, as presented by the applicant:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data by post-approval measures:
    - Long-term follow-up data from ZUMA-2: In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from the mITT population enrolled in the pivotal study ZUMA-2. Expected date for submission of the final data is 31 March 2022
    - A registry-based study:In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol. Expected date for submission of the final data is 30 September 2025. These post authorisation studies will provide further efficacy and safety information on important subgroups: elderly, females, patients with severe disease which are not fully represented in the pivotal study submitted for this procedure. The provision of this data post authorisation will complement the dossier in order have a more comprehensive understanding of efficacy, safety and benefit risk balance of the product.
- An existing unmet medical need will be addressed, as an additional and novel therapeutic option is given for patients with r/r MCL after having received at least two prior lines of systemic therapy including a BTK-inhibitor. Patients with mantle cell lymphoma who are refractory or who relapsed after two or more lines of approved systemic therapy including Bruton's kinase inhibitors have an overall poor prognosis as few authorised treatment options with established efficacy and safety remain. Usually, patients are treated by therapy regimens or modifications thereof, they have already received and on which they have relapsed at some point. Tecartus provides a treatment option for which a significant clinical benefit was demonstrated with respect to complete response, overall response rate and duration of response. Thus, the availability of Tecartus represents a major therapeutic advantage.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. As benefit-risk on basis of the current data is regarded positive, an additional therapeutic option for Mantle cell lymphoma patients with two or more previous systemic therapies is considered beneficial.

The development programme/Compliance with CHMP Guidance/Scientific advice

The clinical development programme for Tecartus consists of four ongoing, uncontrolled clinical studies. The primary data for this marketing authorisation application come from one single, uncontrolled, open label multicentre Phase 2 clinical study, KTE-C19-102 (ZUMA-2) evaluating safety and efficacy of Tecartus in patients whose disease had relapsed or progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTK inhibitor (ibrutinib and/or acalabrutinib). The remaining three ongoing studies are phase I/II trials, intended to provide clinical experience of Tecartus in the context of other indications.

The applicant received Protocol Assistance from the CHMP on:

23.07.2015 - focusing on quality and the clinical study design of ZUMA-2 [Procedure number: EMEA/H/SA/3117/1/2015/SME/ADT/II]

- The target patient population of adult subjects with r/r MCL was considered acceptable. The applicant was advised to also include some patients refractory to protease inhibitors (PI) and/or immune modulators (IMID). This advice was followed.
- The Objective Response Rate as a primary efficacy endpoint was considered acceptable in a non-comparative study. The use of independent endpoint assessment committee was recommended and implemented.

17.12.2015 - focusing on the quality and nonclinical development program [Procedure number: EMEA/H/SA/3117/4/2015/SME/ADT/III]

- Scientific advice considered that the manufacturing procedure for KTE-X19 is particular due to an enrichment of CD4 and CD8 cells.
- Scientific advice considered that the proposed potency assay could potentially be considered a relevant test of the potency of KTE-X19 at the present stage of development. However, additional validation, correlation and characterisation data would be needed to support the conclusion that the proposed potency assay could provide a quantitative measure of the biological activity.
- The provided RCR (replication competent retrovirus) testing has been performed on the MCB, WCB, and used vector stock, and the omission of RCR testing was clearly justified with data at marketing authorisation application. Scientific advice considered it might be acceptable not to perform RCR testing on the finished product.
- Scientific advice considered that the proposed release specifications should be considered expanded.

31.05.2018 - focusing on the nonclinical development program as well as the clinical study design of ZUMA-3 (investigating acute lymphoblastic leukemia [ALL]) [Procedure number: EMEA/H/SA/3117/6/2018/PA/ADT/III]

- *In vitro* data addressing the transduction efficiency and functionality of KTE-X19 were required for MAA. Such *in vitro* data conducted with axicabtagene ciloleucel (Yescarta)) were not considered as sufficient, since KTE-X19 and axicabtagene ciloleucel (Yescarta) use a different manufacturing process and therefore the two products were not considered the same.
- The assumed historical control rate of 25% ORR, was not considered sufficiently compelling. Furthermore, there were concerns that the cut-off could not be considered an a priori decision as the meta-analysis conducted to support the cut-off was finalised after the efficacy data for the first 28 patients had been analysed. For the MAA, the applicant was requested to provide information concerning the search protocol for the meta-analysis as well as information on how heterogeneity between studies affected the estimation of the pooled ORR. This request was not followed.

- The influence of both bridging therapy and conditioning therapy should be carefully considered in the evaluation of the data.
- The inferential analysis set was not endorsed as a primary analysis population. This advice was not followed. However, results for both the inferential- and the full analyses set were generally presented in the MAA.

29.05.2019 - focusing on the quality and clinical development program for the treatment of MCL [Procedure number: EMEA/H/SA/3117/7/2019/PA/ADT/PR/III]

The applicant received Scientific Advice given by CHMP with respect to vector quality and the transduction step. The data confirm that the specification of the vector titre is acceptable.

The applicant plans to introduce improvements to the vector process, i.e. after the planned submission of the Tecartus MAA. The overall strategy to improve vector quality was in essence endorsed, and the proposed timeline was considered acceptable.

Regarding quality aspects, the applicant has taken the recommendations given by CHMP into consideration.

During Protocol Assistance received in December 2015 and in May 2018 the process characterisation studies addressing several parameters of the viral transduction step, the acceptability of the developmental activities to improve the quality of the retroviral vector used to genetically modify the autologous T-cells in Tecartus, and the appropriateness of the release specifications for the Tecartus final product have been discussed.

2.2. Quality aspects

2.2.1. Introduction

Tecartus (autologous anti-CD19-transduced CD3+ cells), also referred to as KTE-X19, is a CD19-directed gene therapy medicinal product. To prepare Tecartus, patient's own T cells are harvested and genetically modified *ex vivo* by gamma-retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 co-stimulatory domain and CD3-zeta signalling domain. The anti-CD19 CAR T cells are expanded and infused back into the patient, where they can recognise and eliminate CD19-expressing target cells.

Each patient specific single infusion bag of Tecartus contains a suspension of anti-CD19 CAR T cells, strength 0.4 x 10^8 - 2 x 10^8 cells in approximately 68 mL.

Tecartus is presented as a clear to opaque, white to red dispersion of cells for infusion formulated with Cryostor CS10 containing dimethylsulfoxyde (DMSO), sodium chloride and human serum albumin.

Tecartus is supplied in an ethylene-vinyl acetate (EVA) cryostorage bag individually packed in a shipping metal cassette.

2.2.2. Active Substance

KTE-X19 is produced from leukapheresis material obtained from individual patients, and therefore the product is unique to each patient. The patient's T cells are engineered *ex vivo* to express the anti-CD19 CAR using a replication incompetent γ-retroviral vector containing the CAR transgene.

The section on the active substance is separated into two parts; part 1 for the gene therapy retroviral vector PG13-CD19-H3 and part 2 for the transduced cells resulting in the active substance KTE-X19.

The entire manufacturing process is covered by respective GMP certificates.

2.1. Part 1: PG13-CD19-H3 retroviral vector

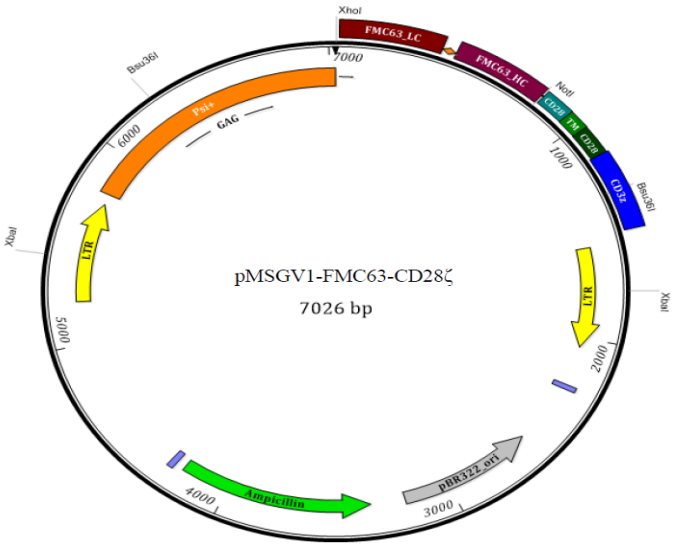
General Information (PG13-CD19-H3 retroviral vector)

The retroviral vector PG13-CD19-H3 is a murine stem cell virus (MSCV)-based vector pseudotyped with the gibbon ape leukemia virus (GaLV) envelope.

The MSCV vector is a long terminal repeat (LTR)-driven non-self-inactivating (non-SIN) retroviral vector that encompasses the 5'LTR as promoter for transgene expression, a packaging signal including the splice donor and splice acceptor sites, the FMC63-based (anti-CD19 FMC63-CD28-CD3ζ) CAR sequence containing a human GM-CSF receptor signal peptide, FMC63 light chain variable region, linker peptide, FMC63 heavy chain variable region, CD28 (hinge, transmembrane and cytoplasmic region), and CD3ζ (cytoplasmic region), followed by the MSCV 3'LTR.

Transfer of genetic material into T-cells occurs via retroviral transduction of autologous T-cells. The manufacturing of the vector is based on a stable packaging cell clone PG13-CD19-H3 from which a Master Cell bank (MCB)/Working Cell Bank (WCB) system has been established.

Figure 1. Elements of the retroviral transfer



Manufacture, process controls and characterisation (PG13-CD19-H3 retroviral vector)

Manufacturing process (PG13-CD19-H3 retroviral vector)

The applicant provided an adequate description of the vector manufacturing process. This includes the description of the manufacturing process steps, flow-charts and description of the in-process controls (IPCs) and operating ranges and/or acceptance limits.

The PG13-CD19-H3 vector is produced constitutively from a stably-transduced PG13 (ATCC CRL-10686) cell line. For the GMP-compliant production of the retroviral vector, cells from a single vial of WCB are expanded and the culture supernatant is harvested, filtered and filled into cryostorage bags.

Control of materials (PG13-CD19-H3 retroviral vector)

The packaging cell clone is based on a cell line that is commonly used to generate retroviral vector particles by introducing a γ-retroviral transfer vector of interest. These NIH3T3- derived cells stably express the Gibbon Ape Leukemia Virus (GALV) envelope and the Moloney murine leukemia virus (MoMLV) gag-pol proteins.

Stable transfer of the PG13-CD19 transfer vector and subsequent selection of the cell clone were conducted at the National Cancer Institute (NCI, Bethesda, Maryland, US). The respective MCB and the WCB are established in compliance with GMP. The MCB was tested and released based on ICH Q5A (R1). A single vial of the PG13-CD19-CAR-H3 MCB was used to produce vials of WCB. The WCB has been shown to be free of bacterial, fungal and mycoplasma contamination in compliance with ICH Q5A (R1) and Ph. Eur. (5.2.3). The WCB was also found to be negative for replication-competent retrovirus. The genetic stability of the WCB and end-of-production (EOP) has been investigated. The test method and results are adequately described. Overall the testing strategy and characterisation of the cell banks is considered adequate. Conformation for the presence of the vector sequence in the WCB is currently not specified as a release test, but respective PCR data confirming the presence of the vector sequences in the WCB have been provided and a respective test will be implemented for each new WCB that is established.

The sequence of the viral transfer vector has been determined for different genome regions at the level of plasmid DNA, MCB, WCB, EOP cells and vector particles. Overall the genetic stability of the vector construct is supported.

Adequate information and acceptance criteria are given for all listed ingredients used for vector manufacturing.

Manufacturing process development and validation (PG13-CD19-H3 retroviral vector)

For process validation of the commercial manufacturing process three manufacturing runs have been conducted, two at small-scale and one at full-scale level using 15 CS10 cell stacks. The rationale and the provided data show that the manufacturing at small-scale is representative for the commercial large-scale run and considered acceptable.

As terminal sterilisation is inapplicable for the vector starting material, aseptic manufacturing has been adequately established including requalification on a six-month interval in accordance with the requirements.

The ongoing process verification (OPV) run by the applicant is endorsed. The actions to be taken in the event of control rule violations are defined in the OPV program.

Characterisation (PG13-CD19-H3 retroviral vector)

Characterisation of the PG13-CD19-H3 vector included both structural and functional aspects. Studies demonstrated that the PG13-CD19-H3 vector encodes the transgene. Transduction results in integration of the vector genome into the genome of the T-cells. The transgene is transcribed to RNA and translated to anti-CD19 CAR. Anti-CD19 CAR T-cells bind to CD19 expressing cells. Upon engagement with CD19, T-cells are activated and secrete IFN-γ. t.

Impurities identified were host cell protein, HC-DNA, BSA and the viral vector protein p30. Additionally, vector purity was evaluated as a ratio of genome copies per transducing unit. Each harvest of PG13-CD19-H3 vector is considered a unique lot, and testing is conducted to assure sterility, while safety tests for mycoplasma, adventitious virus and replication competent retrovirus (RCR) are performed only on material in the last harvest from the production campaign. The last harvest is considered a worst-case condition and testing at this stage assures that the entire production campaign remains free of adventitious agents and that replication competent retrovirus is not present.

Specification, analytical procedures, reference standards, batch analysis, and container closure (PG13-CD19-H3 retroviral vector)

The applicant provided a justification for setting of specifications mainly based on manufacturing experience. With respect to infectious titre and impurities, the applicant confirmed with batch data from the different harvest days, that harvest day has no impact on vector quality with respect to the impurity profile.

The vector undergoes testing for adventitious agents prior to release for use in production of KTE-X19. and were shown to be negative up to date. In addition, a risk evaluation regarding potential generation of RCR during manufacture of the final product has been provided and the occurrence of RCR during manufacturing of Tecartus considered unlikely.

The analytical procedures used for release testing of PG13-CD19-H3 vector have been validated or verified as appropriate. Validation of the non-compendial analytical methods were performed in accordance with ICH Q2(R1). Verification of the compendial analytical methods for sterility, endotoxin and mycoplasma are performed in accordance with Ph. Eur. Summaries of the validation and verification reports for each method are provided.

Batch analysis data are available for lots of PG13-CD19-H3 vector manufactured and released in accordance with cGMP.

The analytical methods for PG13-CD19-H3 vector produce quantitative results.

Stability (PG13-CD19-H3 retroviral vector)

The stability of the PG13-CD19-H3 vector is being evaluated via long-term studies. In addition, the stability of PG13-CD19-H3 vector stored at either accelerated or stress (room temperature) conditions has been evaluated. All studies were conducted in accordance with ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products.

Long-term stability studies are ongoing with eight lots of PG13-CD19-H3 vector stored at the recommended storage temperature. These studies are being conducted with two lots used for clinical production, two lots used for process validation (PV) and potential commercial production, and four lots designated for commercial production. All of the PG13-CD19-H3 vector lots were manufactured by the commercial manufacturer.

PG13-CD19-H3 vector was exposed to elevated temperature to support potential temperature excursions that may occur during long term storage or during transportation. Samples from three lots of PG13-CD19-H3 vector were stored.

Based on available long-term and accelerated stability data for vector PG13-CD19-H3, the proposed shelf-life of and is considered acceptable. Updated stability results for the retroviral PG13-CD19-H3 vector are provided.

Stress testing of vector PG13-CD19-H3 at room-temperature was performed. This data confirm that the vector particles are sensitive to increased temperature. During the manufacturing of KTE-X19, the vector supernatant is incubated before adding of cells for the transduction step. The pre-incubation step does slightly lower the infectivity of the vector particles, as indicated by the calculation provided by the applicant considering a vector. The applicant provided data of a comprehensive binding study, confirming that the number of vector particles bound at or below the lower titre specification results in a sufficient transduction rate. These data confirm that the established transduction step results into the binding of a sufficient amount of vector particle. The applicant clarified that the vector is thawed, the maximal hold time after thawing, which is considered adequate.

2.2. Part 2: active substance KTE-X19

General Information (KTE-X19)

The active substance comprised in Tecartus contains autologous T-cells transduced *ex vivo* with a replication-deficient γ-retroviral vector containing an anti-CD19 chimeric antigen receptor (CAR). CD19 is a 95 kDa transmembrane protein selectively expressed in both normal and malignant B cells. CARs are fusion proteins with antigen binding, transmembrane, and T-cell activation domains that, when expressed in T-cells, can target tumour antigens through T-cell mediated killing.

The CAR target binding domain is a single chain variable region fragment (scFv) derived from the FMC63 monoclonal antibody (mAb). The antigen-binding domain of the anti-CD19 CAR construct encompasses the following domains:

- The FMC63 antibody light chain variable domain (complementary determining regions [CDR] 1 and 2);
- A peptide linker;
- the FMC63 antibody heavy chain variable domain (CDR1, CDR2, and CDR3).

Comparative analysis demonstrated that the specificity of the scFv was equivalent to that of the original FMC63 mAb.

A membrane proximal extracellular domain of the co-stimulatory receptor CD28 joins the scFv to a CD28 transmembrane domain and functions as a "hinge." An intracellular signalling domain of CD28 connects the extracellular scFv portion with the intracellular CD3ζ portion at the terminus of the CAR construct. The CD3ζ and co-stimulatory CD28 domains are signalling following CAR engagement to induce T-cell activation, proliferation, and acquisition of effector functions.

Details on the CAR protein construct within the transduced T-cells together with a description of the different CAR domains and their main function are provided in the dossier.

Manufacture, process controls and characterisation (KTE-X19)

Description of the manufacturing process

KTE-X19 is manufactured by Kite Pharma, Inc, (California, USA.

The manufacturing process of KTE-X19 starts with apheresis collection from a patient. The next steps in the manufacturing process include T-cell enrichment, T-cell activation, retroviral transduction and T-cell expansion.

Control of materials

All apheresis sites and personnel involved in handling and testing of the apheresis material are stated to be qualified by a competent authority for the purpose of those activities according to relevant Commission Directives in each member state. Testing of apheresis material is carried out using CE-marked testing kits where appropriate. The patient's serum or plasma is tested in accordance with the requirements described in Directive 2006/17/EC. Procurement of the apheresis starting material is performed using different standard apheresis equipment. Based on clinical studies, the minimal number of total viable cells in the apheresis material required to make dose is 2.8×10^8 total viable cells.

The reagents used in the manufacture of KTE-X19 are provided by approved suppliers qualified for use by the applicant; and the applicant performs incoming sampling, inspection and testing per approved specifications. The acceptance criteria provided for the raw materials seem appropriate. Certificate of analysis, certificate of conformance and product information files are provided. Control of the retroviral vector is provided in a separate active substance section, which is considered acceptable.

Consumables identified as high risk were tested for extractables and leachables. Studies simulated the conditions of use for the Yescarta manufacturing process. Toxicology assessments for the identified inorganic extractables (zinc and silicon) were found acceptable.

Control of critical steps

IPCs were established using a risk-based approach.

Process validation

The process validation, also referred to as process performance qualification (PPQ), consisted of PPQ batches using apheresis from independent healthy donors. The PPQ batches were split in groups to support the various process options

Data from KTE-X19 batches were used to establish the process validation acceptance criteria, of which were clinical batches and were healthy donor batches manufactured under GMP conditions or development batches. Criteria were based on healthy donor batches manufactured in the development laboratory. A summary of the subgroup analysis for the different process validation acceptance criteria (PVACs) dataset according to the different manufacturing streams has been provided.,

Apheresis material attributes, manufacturing steps, final product release tests, impurities, process parameters and two worst-case operations were validated.

Overall, the extent of validation data presented is considered adequate.

OPV is based on a monitoring and review programme established as part of the quality management system to define, collect, analyse, and respond to trends in process performance and product quality data.

Data on shipper qualification for transport of apheresis material have been provided regarding temperature and stress conditions.

Manufacturing process development

The manufacturing process for KTE-X19 is based on the Yescarta manufacturing process. The KTE-X19 manufacturing process uses the identical anti-CD19 CAR construct and PG13-CD19-H3 vector that are used in the Yescarta process. A detailed comparison of the Yescarta and KTE-X19 processes is provided.

For the KTE-X19 process, similar to the Yescarta process, activation is followed by transduction with a retroviral vector encoding the anti-CD19 CAR transgene

For manufacturing steps common to Yescarta, existing development data have been used and supplemented as needed with additional KTE-X19-specific studies using apheresis material from healthy donors and patients as appropriate.

Based on the Yescarta manufacturing experience, risk-based process characterisation studies were performed aiming to evaluate/classify critical and non-critical process parameters and to establish a control strategy for commercial manufacturing.

Development and characterisation studies were conducted using apheresis material from healthy donors and clinical subjects. It is appreciated that excess apheresis material from clinical subjects are also used. . The use of a small-scale model with material from healthy donor is not considered fully representative for the full-scale performance but is considered acceptable as part of DoE studies.

Apheresis starting material was analysed regarding use of different apheresis equipment, different apheresis storage temperatures and time and their impact on performance parameters as well as product quality attributes. From the single batches compared, apheresis equipment has no impact on the analysed parameters. Normal operating ranges (NORs) and various proven acceptable ranges (PARs) are proposed for different apheresis storage temperatures and times supported by data.

The T-cell labelling and enrichment process parameters were evaluated, and demonstrated to have no impact on critical quality attributes. Appropriate PARs have been established for the respective process parameters. With regard to the wash steps contained in the KTE-X19 manufacturing process, knowledge from the Yescarta process has been used where applicable and KTE-X19 specific studies evaluating impact of process times and extended hold times have been performed and PARs identified.

Cell culture media parameters were also evaluated, and none of the parameters was classified as critical within the characterised range.

Overall, manufacturing process development is considered satisfactory.

Characterisation

Elucidation of structure

Characterisation studies have been performed to analyse the impact of the physical and biological properties of KTE-X19 on the mechanism of action. This includes analysis of (i) CAR sequence integration into the host cell genome, (ii) CAR expression, antigen recognition and engagement, (iii) T-cell activation and proliferation, (iv) production of cytokines and chemokines, (v) killing of target cells and (vi) CAR-T-cell composition and phenotype.

Impurities

Process-related impurities were addressed by theoretical clearance calculations based on the individual wash steps as well as through analytical testing. Acceptance limits were defined risk-based from existing limits in literature and guidelines and from information on toxicological or adverse health effects associated with the individual impurity.

Experimental data on impurities related to reagents that have been introduced during the manufacturing process as well as impurities introduced with the retroviral vector have been presented from development runs. Individual data from the development and/or engineering runs analysed have been presented showing overall acceptable depletion-rates as well as residual quantities per dose. Absence of residual infectious retroviral particles in the final wash supernatant and shown to be below the limit of detection of the method. Clearance of is not monitored as the potential maximum amount per dose is considered to be.

A description of the methods employed for quantitation of impurities has been provided along with assay acceptance criteria and a summary of the analytical method´s qualification/validation status.

Specification, analytical procedures, reference standards, batch analysis, and container closure (KTE-X19)

As the manufacturing process for KTE-X19 is a continuous process, the transition from active substance to finished product does not include any hold steps. Therefore, specification, analytical procedures, validation of analytical procedures, batch analysis and justification of specifications, are provided in the final product section. Considering the nature of the product, the applicant's approach is considered acceptable.

No release of active substance is performed.

Stability (KTE-X19)

As no hold step is foreseen at active substance level before manufacturing of finished product, no stability studies have been performed at that level.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The transduced T-cells are formulated in a cryopreservation medium suitable for infusion. Each final product bag of Tecartus is filled to deliver a target dose of $1.0x10^6$ - $2.0x10^6$ anti-CD19 CAR-positive viable T-cells/kg of patient weight (maximum allowable dose: $2.0x10^8$ anti-CD19 CAR-positive viable T-cells/kg based on patient weight ≥100 kg). Tecartus is supplied cryopreserved at a temperature of ≤ -150°C in cryostorage EVA bags with sealed addition tube and two available spike ports. The cryostorage bag contains a nominal 68 mL of Tecartus. The composition of Tecartus consists of anti-CD19 CAR-positive viable T cells formulated with Cryostor CS10, sodium chloride and human albumin.

The excipients used in the formulation of finished product are sodium chloride injection (Ph. Eur.), albumin (human serum albumin, HSA) (Ph. Eur.), and CryoStor CS10 which is a cryopreservative agent containing DMSO (Ph. Eur.).

The final product composition is based on results from the Yescarta process development and characterisation and consists of the same excipients for formulation as well as the same cryopreservation programme.

A semi-automated formulation and filling method was developed for use as an alternative to manual formulation and filling in the Tecartus process. It consists of a single-use, sterile, closed-system fluid path and bag set which is loaded on a fluid transfer panel with active temperature and mixing control. The results demonstrated acceptable mixing homogeneity, fill volume and dose uniformity, closed-system integrity, and product quality attributes pre and post- cryopreservation, as compared to a manual process. Information on the custom-made bag system including specifications regarding microbiological safety, has been provided.

Following the formulation step, the final product bag containing Tecartus is aseptically sealed and transferred to a cassette for cryopreservation. For the cryopreservation process step, temperature profiles for Yescarta that showed consistency in the freeze cycle was used for Tecartus final products. In Tecartus stability studies, however, smaller bags of identical material are used. Cryopreservation of one or two product bags was comparable. Transfer between the CRF and storage in LN2 is performed using a CryoPod (portable LN2 vapor-based carrier). Comparable temperature profiles for freezing have been demonstrated.

Two primary container closure systems consisting of the same material (EVA) are used. Characterisation studies were performed with Yescarta material, which is acceptable taking into account the similarities of the two products. The suitability of both primary container closure systems was evaluated by extractable and leachable testing. The low amounts of silicon and zinc detected in the are not expected to have any toxicological impact.

Risks associated with elemental impurities in the KTE-X19 finished product were evaluated with respect to ICH Q3D guidance, and a summary was provided. All applicable sources of elemental impurities described in ICH Q3D were considered, including manufacturing process (equipment), final product container and excipients. All failure modes were assessed to be low risk and no further action is required. Finally, KTE-X19 is a parenteral single dose administration of 68 mL product, hence there is no risk of continuous exposure of elemental impurities over time.

Manufacture of the product and process controls

The names and addresses of the facilities involved in Tecartus manufacturing along with a description of the manufacturing activities for which each site is responsible, are provided.

A manufacturing license and a QP declaration concerning GMP compliance of the active substance manufacture have been provided. For the MIA for reference to EudraGMDP is made. This is acceptable.

The Tecartus process is continuous from active substance to finished product, with no intervening hold step. Process validation for the entire manufacturing process, from apheresis material to cryopreserved Tecartus, is described in the active substance section of the dossier.

Depending on the sufficient cells may be available to formulate two final product bags. Each bag of Tecartus is filled to deliver a target dose of 2.0×10^6 CAR T-cells/kg of patient weight in a nominal volume of 68 mL. Formulation of the Tecartus final product bags can be performed using a manual process or a semi-automated process. Manual or semi-automated filling will be performed. Comparability between the two processes has been demonstrated. The cell suspension is transferred to the final product bag. The cells are formulated with sodium chloride (NaCl), HSA, and CryoStor CS10, aseptically sealed, inspected for visible particulates, labelled and cryopreserved at ≤-150°C. Precise quantities of excipients, and values for the process parameters, normal operating range/target and proven acceptable range, have been included.

For the cryopreservation step, the same freeze cycle as used for Yescarta is established for Tecartus. A CryoPod (a portable liquid-nitrogen vapour-based carrier), is used in the process to transfer cryopreserved product bags between the controlled rate freezer and storage in liquid-nitrogen, and again during transfer from liquid-nitrogen storage to the liquid-nitrogen shipper. The transportation of cryopreserved Tecartus within the container closure in a dry-vapour liquid-nitrogen shipper at a temperature range of below ≤-150°C) was acceptably validated.

Product specification

Product release specifications have only been defined on the finished product level since the manufacturing process from receipt of the apheresis starting material through to finished product is continuous and no active substance is isolated. The finished product specifications include tests for identity, content, potency, purity and safety. The term "viable" was included in the acceptance criteria for commercial dose: $1.0x10^6$ – $2.0x10^6$ anti-CD19 CAR viable T-cells/kg, and maximum allowable dose: $2.0x10^8$ anti-CD19 CAR viable T-cells based on patient weight ≥100 kg.

The analytical methods, the corresponding pre-set acceptance criteria, and the sample points, have been provided in the specification table. The specification table was updated to include the unique identification numbers of the analytical method applied.

Analytical methods

Analytical methods have been described and are validated using Yescarta material. Some clarifications with regard to dose calculation and consistent operation of the flow cytometry and NucleoCounter method have been provided. Revalidation using Tecartus has been performed for a defined panel of parameters. The applicant provided also an updated validation documentation for each analytical method containing method validation summary for Tecartus with corresponding validation of the method.

The same microbiological sampling and testing strategy is applied as for Yescarta with all microbiological test results completed. The microbiological release control has been sufficiently qualified for the Tecartus matrix. The sample matrix for testing has been confirmed to be identical between Tecartus and Yescarta. In addition, a product-specific method qualification was successfully completed regarding parameter accuracy, repeatability and intermediate precision. This deems to further support absence of method interference for the Tecartus matrix.

Aseptic processing appears adequately controlled via aseptic process validation and aseptic operator qualification (AOQ). This includes relevant media simulation runs using tryptic soy broth in place of raw materials and product component. All runs were successfully completed including demonstration of media performance.

Batch analysis

Batch data are provided for a total of. Batch data for PPQ lots manufactured from healthy donor material have been provided. The applicant presented information about all initiated clinical manufacturing starts, including out-of-specification batches and terminated batches, for both including the identified root cause.

Stability of the product

The stability of Tecartus has been investigated in long-term, accelerated and stress testing studies.

PPQ lots, healthy donor lots and lots from clinical subjects have been placed in long-term stability studies. Lots from clinical subjects are derived from patients that have dropped off the clinical trial. Commercial and "protocol" acceptance criteria are intermittently used in the presentation of stability data due to evolving of the release acceptance criteria based on the progress made in process development.

The presented long-term stability results from clinical patient lots of Tecartus, stored at the recommended storage condition are within the "protocol" acceptance criteria for most of the results of the ten lots. The results suggest that clinical patient lots stored at the recommended storage condition remain viable for months.

PPQ and post-PPQ healthy donor stability studies have been tested at release to demonstrate product stability according to "protocol" acceptance criteria. All results met the acceptance criteria with the exception of four lots. Data on the investigation and corrective actions taken with regard to these lots have been provided. Overall, the results from the PPQ batches are complex to trend for the various conditions investigated. The applicant provided the results from the PPQ stability study in separate figures for each condition as requested. No trend in the results was detected.

The claimed shelf life of 12 months when stored in the vapour phase of liquid nitrogen (≤ -150°C) for the Tecartus final product in cryostorage bags is considered acceptable. Tecartus must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are available for patient administration.

All results from accelerated studies were within the proposed commercial acceptance criteria. Stress testing was performed on Tecartus lot with dose sourced from healthy donor material and stored. The suitability of tests to be stability-indicating was confirmed.

In-use stability testing revealed that post-thawed Tecartus lots are stable for 3 hours at room temperature (20°C to 25°C). Thawing instructions in the SmPC indicate that Tecartus infusion should begin within 30 minutes of thaw completion time and total Tecartus infusion time should not exceed 30 minutes. Thawed product should not be refrozen.

Cracked cryobags were reported for during long-term stability studies at the months' time point each. The applicant has identified the most probable root cause for the observed container defects and implemented respective CAPAs.

Adventitious agents

TSE compliance

Donors of the T-cells are of autologous origin, therefore, defined selection criteria with regard to Creutzfeldt-Jakob disease (CJD) do not apply according to Directive 2006/17/EC. Foetal bovine serum (FBS) is used during production of the retroviral vector PG13-CD19-CAR-H3 and has been used during production of the vector producing cell banks. For all FBS valid certificates of suitability issued by the EDQM are provided. The cells of the vector cell bank are of murine origin with no TSE relevance. HSA used as excipient and holds an EU marketing authorisation. All relevant marketing authorisation numbers in the EU are listed in a summary table for sources of adventitious viruses. In summary, compliance with the TSE guideline for all raw materials of animal origin and with EU Directives for human-derived materials has been demonstrated.

Virus safety

Due to the nature of the product, the manufacturing process of the PG13-CD19-H3 vector and of the Tecartus finished product does not contain any step that removes or inactivates viruses. In addition, the final finished

product is not tested for adventitious viruses. Control of adventitious agents is mainly based on selection and testing of starting materials and raw materials of biological origin and testing of the retroviral vector. In order to ensure safety of the product, procedural controls are followed for acceptance of material used in the manufacture of PG13-CD19-H3 vector and KTE-X19. These controls are as follows:

1. Safety testing of the PG13-CD19-CAR-H3 master cell bank and PG13-CD19-CAR-H3 working cell bank

2. Procedural controls, raw material controls, and safety testing of the PG13-CD19-H3 vector

3. Media and reagents used in the manufacturing of Tecartus are sourced from qualified vendors

This strategy is considered acceptable.

In summary, the virus safety of Tecartus is sufficiently shown.

GMO

The GMO are autologous T-cells genetically modified with a non-SIN retroviral vector based on MSCV pseudotyped with the GALV envelope protein and encoding the CAR consisting of a CD19-specific scFv and the CD28/CD3zeta costimulatory domains under control of the MSCV 5´LTR enhancer/promoter region (see non-clinical section for further information).

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, the quality part of the dossier is of an acceptable standard.

The manufacturing process for KTE-X19 is based on the Yescarta manufacturing process and uses the identical murine gamma retroviral PG13-CD19-H3. The use of existing development data from Yescarta for process steps common to both the Yescarta and Tecartus processes is considered acceptable.

Apart from minor deficiencies satisfactorily addressed during the procedure, the manufacturing process and the associated process controls have been adequately described. Critical process steps and parameters have been identified and PARs and NORs have been established in process characterisation studies using both knowledge from the Yescarta process as well as from KTE-X19 specific studies using both healthy donor and patient apheresis material.

For the retroviral transduction, differences between the Yescarta and KTE-X19 unit operations are considered significant, which required re-evaluation of the transduction process parameters. Data have been presented by the applicant, suggesting consistent T-cell transduction.

The process is validated appropriately against pre-established process validation acceptance criteria based on data from clinical and healthy donor lots and considering the different manufacturing scenarios. In addition, shipper qualification and validation of transport of the apheresis material has been performed.

The KTE-X19 process has been demonstrated to deplete both product-related as well as process-related impurities and hence no tests for impurities, neither at the level of the retroviral vector nor for the release of Tecartus finished product are included, which is acceptable

Due to the continuous nature of the Tecartus manufacturing process, no active substance specifications have been established which is considered acceptable.

The final product composition is based on results from the Yescarta process development and characterisation and consists of the same excipients for formulation.

The production process for final product is considered validated and results in a finished product of acceptable quality. The proposal to use a semi-automated formulation and filling method as an alternative to manual formulation and filling in the Tecartus process is acceptable.

The term "viable" was included in the acceptance criteria for commercial dose. Due to the nature of the product, the large variability of the cellular starting material from highly pre-treated patients and the complexity of the manufacturing process, the specification limits are set fairly wide.

The batches used in the clinical trials were manufactured with the commercial manufacturing process. Batch data have been provided for clinical batches and suggest a consistent manufacturing process. Information about manufacturing conditions for the PPQ lots has been provided.

Long-term stability data have been provided for a sufficient number of batches including lots from clinical subjects supporting the proposed shelf life of 12 months for Tecartus when stored at -150°C.

To avoid further cryobag defects during storage and handling in the cryopreserved status, the applicant implemented the use of foam inserts in the aluminium cassette as part of CAPAs. Data on the comparability of the cryopreservation process with or without foam insert and further information about the material and size of the foam insert have been provided.

In July 2020, CHMP extended the call for review of nitrosamines impurities to all biologics. As a consequence, the applicant committed to provide a risk evaluation on the potential presence of nitrosamine impurities in Tecartus within six months of the marketing authorisation. In the event that a risk of presence of nitrosamines is identified, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorisation or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented (Recommendation). Considering the low risk for this product, the unmet medical need and the fact that the CHMP call for review for biologics was made at a late stage of this accelerated assessment procedure, it is considered acceptable, in this specific case, to address this matter as a post-authorisation Recommendation.

The TSE and virus safety of Tecartus has been sufficiently shown.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Tecartus is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Tecartus is considered approvable from the quality point of view.

The CHMP endorse the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

The applicant agreed to the Recommendations as identified below.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT recommends several points for investigation:

The CHMP endorse the CAT assessment regarding the recommendations for future quality development as described above.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant provided non-clinical pharmacology data confirming the *in vitro* functionality of KTE-X19. Additional non-clinical data supporting the development of KTE-X19 are leveraged from data generated in support of axicabtagene ciloleucel, the applicant's first anti-CD19 CAR T-cell product. Both KTE-X19 and axicabtagene ciloleucel use the same retroviral vector, producer clone, and anti-CD19 CAR transgene.

2.3.2. Pharmacology

Primary pharmacodynamic studies

CD19 Expression Profile Summary

Targeting B-lineage haematologic malignancies via CD19 is based on earlier findings demonstrating that expression of CD19 is restricted to cells, both normal and malignant, of the B-lineage, including mantle cell lymphoma (MCL) (Leonard 2001). Early publications by Nadler and colleagues (Nadler et al, 1983; Anderson et al, 1984) showed that CD19 protein is expressed on all B-lineage lymphoid cells, from the pro-B-cell maturation stage to naïve and differentiated B cells. Uckun and colleagues (Uckun et al, 1988) confirmed and extended these findings by demonstrating that leukemic progenitor B cells also express CD19, and that erythroid, myeloid, megakaryocytoid, and multilineage normal bone marrow progenitor cells do not express CD19. More recently, Johnson and colleagues (Johnson et al, 2009) showed that primary lymphoma cells from patients with diffuse large B-cell lymphoma (DLBCL) expressed CD19, whereas reference T cells did not. Olejniczak and colleagues (Olejniczak et al, 2006) examined the expression pattern and levels of CD19 in peripheral blood, bone marrow, and lymph node tissue from patients with 6 different common B-cell malignancies (chronic lymphocytic leukemia [CLL], small lymphocytic lymphoma [SLL], B-lineage acute lymphoblastic leukemia [ALL], hairy cell leukemia [HCL], DLBCL, and follicular lymphoma [FL]). Nearly all samples within each type were considered positive for CD19. Expression levels of CD19 were variable across the different B-cell malignancies, but all B-cell malignancies examined showed consistently measurable levels of CD19 expression above reference $CD3^+$ T cells.

Other investigators have shown that CD19 is expressed in MCL (Leonard et al., 2001; Ginaldi et al. 1998; Cabezudo 1999; D'Arena et al., 2000; Marcondes et al., 2017; Yang et al., 2005; Argatoff et al., 1997). Demonstration of clinical activity of an anti-CD19 CAR in a chemotherapy-refractory MCL patient further highlights the applicability of CD19 as a CAR target in MCL (Chen et al., 2016).

In summary, evidence from key published literature demonstrates that CD19 is expressed on the surface of normal B-lineage cells as well as most B-cell malignancies, including MCL, a subtype of non-Hodgkin lymphoma (NHL).

In vitro characterisation of anti-CD19-transduced human T cells

For initial *in vitro* evaluation of specific activity against $CD19^+$ target cells, the applicant used CD19 CAR T cells from patients that were enrolled in clinical trials conducted by the National Cancer Institute (NCI). Specific activity of these anti-CD19 CAR T cells was evaluated and cytotoxicity upon binding of the CD19 CAR T cells to its target antigen CD19. Thereby, the specificity of the CD19-CAR T cells for its target antigen has been confirmed by inclusion of appropriate negative controls, such as $CD19^-$ target cells, untransduced T cells and T cells transduced with a CD19-unrelated CAR construct (SP6-28Z). CD19 CAR T cells from patients with advanced B-cell haematologic malignancies manufactured at NCI were used for evaluation of different cytokine, chemokine, and effector molecule release upon co-culture with $CD19^+$ and $CD19^-$ target cells. Therefore, a Luminex™ analysis involving 17 analytes comprising markers for immune cell homeostasis and proliferation (IL-2), pro-inflammatory activity (IL-6, IL-13, TNF-α, GM-CSF), immune-modulating activity (IL-4, IL-5, IL-10, IFN-γ, CD137), chemokines (MIP-1α, MIP-1β), and effector molecules (granzyme A, granzyme B, soluble FAS, sFASL, perforin) has been performed.

The manufacturing processes used to generate the CD19 CAR T cells at NCI, and subsequently axicabtagene ciloleucel, are similar, but not equivalent, to the process used to manufacture KTE-X19.

In vitro characterisation of anti-CD19 T cells generated by the KTE-X19 manufacturing process

Using apheresis material from two healthy human donors, anti-CD19 CAR T cells were produced by a scaled-down KTE-X19 manufacturing process and were characterised *in vitro*. $CD4^+$ and $CD8^+$ T-cell activation, as measured by cell expansion (total number of cells), diameter, and viability were assessed on Days 0, 1, 6, 9, and 13. Most of the cells were frozen on Day 9 for subsequent functional characterisation studies while a small proportion of cells were kept in culture for additional phenotypic CAR characterisation over time. Upon activation, T cells from both donors increased in mean cell diameter from Day 0 to Day 1 and expanded 393- and 155-fold for T cells from Donor 1 and Donor 2, respectively, between Days 1 and 13. Mean T-cell viability ranged from 76.9% to 91.7% on all days measured (spanning Days 0 to 13). Transduction efficiency was monitored on Days 6, 9, 13, and 16 by flow cytometry using fluorophore-labelled, custom-made antibodies (KIP-1 and KIP-3) that bind to the scFv region of the engineered CAR T cell. Transduction was stable over time for T cells from both donors.

In a separate study, anti-CD19 CAR T-cell products generated from apheresis material from 2 healthy human donors from a scaled-down KTE-X19 manufacturing process (described in the study above; harvested on Day 9) as well as an additional anti-CD19 CAR T-cell product generated by the at-scale KTE-X19 manufacturing process from apheresis material from another healthy human donor (harvested on Day 6) were assessed functionally. Each of the 3 anti-CD19 CAR T-cell products were co-cultured with $CD19^+$ B-lineage acute lymphoblastic leukaemia (Nalm6) target cells, $CD19^+$ B-cell lymphoma (Raji) target cells, and CD19-knockout (Raji CD19KO) target control cells. CAR T cells derived from all 3 donors proliferated approximately 80% in response to co-culture with $CD19^+$ target cells at Day 4 after co-culture initiation. By comparison, only homeostatic proliferation (approximately 10% to 20%) was observed with nontransduced T cells co-cultured with $CD19^+$ target cells. All 3 donor-derived anti-CD19 CAR T-cell products co-cultured overnight with $CD19^+$ target cells resulted in measurable levels of TNF-α, IFN-γ, and IL-2 cytokine production. All three donor-derived anti-CD19 CAR T-cell products tested were cytotoxic to $CD19^+$ target cells in a dose-dependent manner. Results with

controls (nontransduced T cells and/or CD19⁻ target cells) demonstrated that proliferation, cytokine production, and cytotoxicity were specific to anti-CD19 CAR T cells and dependent on CD19 antigen engagement.

In vitro and in vivo activity of surrogate anti-murine CD19 CAR T cells

Since the anti-CD19 scFv utilised for KTE-X19 does only recognise human CD19, a murine surrogate model was engineered for non-clinical proof-of-concept studies in immune competent mice. This surrogate model used an anti-murine CD19 CAR construct that was similar to KTE-X19 with the exception of the scFv, which has been derived from the 1D3 mAb recognizing murine CD19. Murine T cells were transduced with the anti-murine CD19 CAR construct and adoptively transferred into syngeneic mice which underwent TBI at 5 Gy for lymphodepletion and were challenged with a CD19-expressing 38c13 lymphoma cell line to investigate the anti-lymphoma effect of the anti-murine CD19 CAR T cells.

The administration of the anti-murine CD19 CAR T cells into the syngeneic mouse lymphoma model revealed both the ability of the CD19 CAR T cells to prevent establishment of a lymphoma and to eradicate already established lymphoma masses including metastasis. Administration of the anti-murine CD19 CAR T cells in both the prophylactic and the therapeutic setting resulted in prolonged survival of the mice while control animals became rapidly moribund due to lymphoma and were euthanised. Using the syngeneic mouse lymphoma model, the applicant also investigated the influence of total body irradiation (TBI) prior to the administration of the lymphoma cells and the CD19 CAR T cells which revealed the importance of the TBI-induced lymphodepletion for prolonged survival of these animals and thus for a successful outcome of the CAR T cell therapy.

In addition, the surrogate murine CD19 CAR T cells were investigated *in vitro* for CD19-specific activation in co-cultures of the anti-murine CD19 CAR T cells and $CD19^+$ and $CD19^-$ target cells.

Secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interaction studies

No secondary pharmacodynamics studies, safety pharmacology studies and pharmacodynamic drug interaction studies were conducted.

2.3.3. Pharmacokinetics

No formal non-clinical pharmacokinetic studies were conducted. Absence of absorption, distribution, metabolism and excretion (ADME) studies is justified, since in accordance with the regulatory guidance for gene therapy medicinal products (GTMPs) (Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products, EMA/CAT/80183/2014) conventional ADME studies are not required.

Although no formal non-clinical pharmacokinetic studies of KTE-X19 were conducted, the persistence of anti-murine CD19 CAR T cells was examined in the syngeneic mouse lymphoma model using flow cytometry analysis. Results from this experiment showed that $CD4^+$and $CD8^+$anti-murine CD19 CAR T cells remained in the spleens of treated mice up to 1 week following injection. Anti-murine CD19 CAR T cells were not detected in the spleens of treated mice at Day 63 after injection of CAR T cells; longer follow-up for anti-murine CD19 CAR T cells was not examined. However, findings from other experiments showed that mice treated with anti-murine CD19 CAR T cells remained free of leukaemia up to 209 days (the last time point examined) after receiving the injection, suggesting that the anti-lymphoma effect was maintained long term.

No other non-clinical pharmacokinetic analyses were performed.

2.3.4. Toxicology

Formal single-dose study in animals was not performed for KTE-X19. KTE-X19 is intended to be administered as a single infusion treatment therefore no repeat-dose toxicities study was conducted. In addition, due lack of suitable animal model and applicability of traditional toxicology tests, non-clinical studies on safety pharmacology, reproductive and developmental toxicity, and genotoxicity/carcinogenicity were also not conducted.

The only safety aspects that were included in the non-clinical evaluation were:

- on-target/off-tumour toxicity of CD19 CAR T cells in the syngeneic mouse lymphoma model, and,
- analysis of Vector Integration Sites (VIS) in CAR T cells at the end of the manufacturing process have been conducted with KTE-X19

On-target/off-tumour toxicity of CD19 CAR T cells in the syngeneic mouse lymphoma model has been evaluated during the pharmacology study in parallel with the anti-lymphoma effect and the persistence of the anti-murine CD19 CAR T cells. Results showed that normal B cells (which are $CD19^+$), were eliminated in mice treated with anti-murine CD19 CAR T cells, but could be detected at Day 8 in mice treated with control CAR T cells. The inhibition of normal B-cell development persisted in mice treated with anti-murine CD19 CAR T cells; lack of normal splenic B cells was observed 63 days, 143 days, and 209 days (the last time point examined) after anti-murine CD19 CAR T-cell infusion, whereas T cells had recovered to normal levels at the time point of 143 days from infusion. Notably, this complete and prolonged absence of B cells was not accompanied by any evidence of overt toxicity. The prolonged absence of B cells was unique to mice that were treated with anti-murine CD19 CAR-transduced T cells, as control mice that received either 5 Gy of TBI alone or 5 Gy of TBI followed by infusions of T cells expressing the SP6-28Z.1-3 negative control CAR had detectable splenic B cells 4 to 8 days after irradiation. The observed prolonged depletion of normal B cells known to express CD19 confirmed the expected on-target/off-tumour effect of the CD19 CAR T cells on normal B cells. Additional toxicities of the anti-murine CD19 CAR T cells did not become evident in the pharmacology studies.

VIS were assessed in CAR T cells manufactured from healthy donor T cells transduced with the retroviral vector used for the manufacture of KTE-X19. The data of this study were re-evaluated during the procedure using an improved bioinformatics analysis method. Thereby, the re-evaluation of the data revealed a considerably increased number of total VIS in all donors compared to the initial analysis, as well as lower numbers and percentages of VIS that were detected in more than 2 out of 5 aliquots analysed per Donor. The VIS analysis revealed an even distribution across the chromosomes and the number of VIS paralleled the number of transcription start sites (TSS) on each chromosome. Thereby, the vector integrated non-randomly near active TSS of T-cell-related genes. 10.2% to 10.6% of the identified VIS occurred within exons. The applicant concluded from the VIS analysis that no predominance of a single VIS was apparent. This conclusion is based on the probability of detecting a given VIS in 3 or more aliquots investigated per donor, which ranged between 0.115%, 0.0403, and 0.0368% for Donor 1, 2, and 3, respectively. The number of unique identified VIS per donor ranged between 51684 and 91093 sites. Similarly, also the abundance of the top 100 VIS by chromosomal genomic coordinate per donor has been interpreted by the applicant as not revealing signs of over-representation of single VIS.

2.3.5. Ecotoxicity/environmental risk assessment

The risk for the environment in general and for transmission to third parties associated with the genetically modified T cells is considered negligible, as genetically modified cells cannot survive in the environment. If transmitted to third parties through direct contact the genetically modified cells are expected to be recognised by the immune system and cleared rapidly. A residual risk for the environment and third parties might only be associated with residual infectious viral particles present in the final cell suspension and/or replication-competent retroviruses (RCR) contaminating the viral vector suspension or being generated following mobilisation of the integrated provirus. However, the applicant showed that the amount of residual infectious particles in KTE-X19 will be reduced to negligible concentrations during manufacturing. Moreover, the absence of RCR has been confirmed at different stages of the manufacturing process. The applicant showed that in clinical studies with KTE-X19 no RCR has been detected in the blood of patients.

2.3.6. Discussion on the non-clinical aspects

Pharmacology

Some of the presented non-clinical *in vitro* pharmacology studies were conducted with CD19 CAR T cells that were generated at the NCI with a manufacturing process similar, but not fully equivalent to the KTE-X19 process. In order to complete the pharmacology data package, additional non-clinical *in vitro* pharmacology studies were conducted with CD19 CAR T cells manufactured using the KTE-X19 process. Thereby, the applicant followed the recommendation of the CHMP provided in a former protocol assistance of KTE-X19. In addition to the non-clinical *in vitro* data that were conducted with cells from healthy donors generated using the KTE-X19 manufacturing process, additional characterisation data for KTE-X19 has been included in the quality part of the dossier. These additional characterisation data revealed a similar transduction efficiency of KTE-X19 cells generated from healthy donors as compared to MCL patients. Moreover, poly-functionality of KTE-X19 has been demonstrated in the quality part by measuring secretion of multiple cytokines and chemokines upon binding of KTE-X19 to $CD19^+$ target cells.
Overall, the provided non-clinical *in vitro* data sufficiently demonstrate specific activity of KTE-X19 against its target antigen CD19. Moreover, poly-functionality of the CAR T cells at the end of the manufacturing process has been demonstrated for the cells manufactured at NCI using Luminex™ analysis and for KTE-X19 using MesoScale Discovery® (MSD®) analysis. Although these data are rather considered as characterisation data of the final product than non-clinical pharmacology data, they are still important as they support the versatile capability of KTE-X19 with regard to lymphocyte activation and effector mechanisms.

In addition to the *in vitro* evaluation of KTE-X19, the applicant established murine surrogate CD19 CAR T cells for *in vivo* evaluation in a syngeneic mouse lymphoma model. This approach provided important proof-of-concept for the overall design of the chosen CD19 CAR construct including for example the choice of the co-stimulatory domain. Such a surrogate model may also be considered as the most appropriate non-clinical model for investigating the persistence of the CD19 CAR T cells and for evaluating potential on-target/off-tumour effects of the CAR T cells. On the other hand, it is evident that crucial parameters of the CAR T cell may differ between the murine surrogate CD19 CAR T cells and the human CD19 CAR T cells. This includes for example the binding affinity of the scFv, the manufacturing of the transduced cells, and the composition of T cell subsets. Despite these expected differences, the use of murine surrogate CD19 CAR T cells

in immunocompetent mice is an acceptable approach that overcomes some of the limitations of the *in vivo* testing of KTE-X19 in immunocompromised animals (e.g. unspecific xenogeneic immune responses of KTE-X19 in mice, lack of complex interactions of the CAR T cells with other components of the immune system). Since both models do have clear, although differing, limitations with regard to the translation of the non-clinical pharmacology data to human, additional non-clinical *in vivo* pharmacology data (e.g. testing of KTE-X19 in immunocompromised animals transplanted with human $CD19^+$ tumour cells) would not add significant value to the available non-clinical and clinical pharmacology data sets.

Absence of secondary pharmacodynamics studies, safety pharmacology studies and pharmacodynamic drug interaction studies is acceptable based on the nature of the product and the limitations of the available animal models, respectively.

Pharmacokinetics

The provided non-clinical pharmacokinetic investigations focused on the *in vivo* persistence of the murine surrogate CAR T cells in the syngeneic mouse lymphoma model, which is acceptable for this type of product. The chosen model provides all necessary stimuli that are considered important for a specific activation, expansion, and survival of the CD19 CAR T cells (e.g. $CD19^+$ target tumour cells, endogenous cytokines, chemokines and cellular interactions of a fully functional immune system). Despite these ideal preconditions, the anti-murine CD19 CAR T cells could only be detected in spleen at Day 8, but no longer at Day 63 post-infusion. Thus, persistence of CD19 CAR T cells could only be demonstrated for a short time period, despite a prolonged anti-lymphoma effect and B-cell aplasia, which were evident for up to 209 days (the latest time point investigated).

Toxicology

Similar as the pharmacology evaluation, also the non-clinical safety evaluation of KTE-X19 has been severely limited due to the lack of a relevant animal model. Therefore, no GLP-compliant formal toxicology studies were performed. Instead, the on-target/off-tumour effect on normal B cells was confirmed during the pharmacology studies in the syngeneic mouse lymphoma model. This effect on normal B cells was expected based on the expression pattern of CD19 and resulting B cell aplasia has been observed in both the syngeneic mouse lymphoma model and in study participants that were treated with either axicabtagene ciloleucel or KTE-X19 in clinical trials. Consequently, B cell aplasia leading to hypogammaglobulinaemia has been included in Section 4.4 of the summary of product characteristics (SPC). Other toxic effects of anti-murine CD19 CAR T cells were not evident in the mouse lymphoma model. However, off-target toxicities are also not expected to be reliably detected in the surrogate mouse model, since off-target recognition of other antigens may differ between the anti-human and anti-murine CD19 CAR T cells due to the different scFvs that were used in the CD19 CAR constructs. Similarly, the use of KTE-X19 in immunocompromised mice would also not be expected to reliably predict off-target effects, since potential differences of cross-recognition of unrelated antigens, differences of antigen expression patterns, and differences in the *in vivo* survival, activation and expansion of KTE-X19 are expected to hamper detection of potential off-target effects in such a model.
In addition to these potential toxicities of the CD19 CAR T cells that are either dependent on the expression pattern of the chosen target antigen (on-target/off-tumour toxicities) or on the cross-reactivity of the chosen ScFv with other non-target antigens (off-target toxicities), there are also expected risks that are associated with the general mode of action of CAR T cells, such as uncontrolled T cell proliferation, tumour lysis syndrome (TRS), cytokine release syndrome (CRS), neurotoxicity, and macrophage activation syndrome (MAS). These toxic effects have also not been investigated in non-clinical studies which is fully acceptable considering that these effects are general effects of CAR T cells and that the extent of these expected toxicities are largely based on patient-specific parameters such as the individual tumour load.

The combination of both the use of a γ-retroviral vector with full-length viral long terminal repeats (LTRs) and the high proliferative potential of the transduced T cells provides a certain risk of insertional oncogenesis, which has not been addressed beyond the analysis of VIS in CAR T cells at the end of the manufacturing process. The lack of additional data on insertional oncogenesis has been sufficiently justified by the applicant. The applicants' line of argumentation involves the following key arguments: 1) an exceptional high resistance of mature mouse T cells against transformation induced by genomic integration of γ-retroviral vectors as reported in the literature; and 2) lack of reported cases of insertional oncogenesis in the clinical evaluation of KTE-X19 itself, axicabtagene ciloleucel, or T cells that were transduced with γ-retroviral vectors encoding other transgenes. Thereby, clinical experience with study participants that were treated with γ-retrovirally transduced T cells engineered to express either a T cell receptor (TCR) or a CAR included up to 11 years of follow-up. Taken together, the experience so far with mouse and human T cells suggests that T cell transformation due to genomic integration of γ-retroviral vectors is a very rare event which cannot be completely ruled out, but may be expected to occur at a particularly low frequency.
The non-clinical VIS data revealed the expected vector integration pattern of γ-retroviral vectors, which are known to preferentially integrate within close proximity of TSS and near transcriptionally active genes due to the open chromatin structure. In contrast, integration of the γ-retroviral vector into exons is relatively rare. In addition, the applicant concluded that no signs of predominance of single VIS have been observed. This conclusion has been supported by re-evaluation of the data using an improved bioinformatics analysis method.

The lack of non-clinical reproductive and developmental toxicity studies is acceptable based on the type of product, the expression pattern of the target antigen and the lack of a relevant animal model. The risk of inadvertent germline transmission of the CD19 CAR construct has not been addressed by the applicant. However, the *Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors, EMEA/273974/2005* indicates that the risk of germline transmission associated with the administration of genetically modified human cells is considered to be low and, as animal testing of human cells may be difficult or not meaningful, non-clinical germline transmission studies of human genetically modified cells are not recommended.

The SmPC appropriately indicates the lack of non-clinical toxicology studies, carcinogenicity and genotoxicity studies, and reproductive and developmental toxicity studies (see Section 5.3. of the SmPC).

Ecotoxicology/environmental risk assessment

The risk of RCR formation during manufacturing is considered negligible due to the absence of the majority of the parental retroviral sequence in the vector and the necessity of several independent recombination events for the generation of a functional RCR. In addition, the applicant confirmed the lack of RCR in the vector harvest using a suitable test method with an acceptable sensitivity. Finally, the applicant provided data on RCR testing from samples of patients treated with KTE-X19 in order to demonstrate that no RCR has been detected in treated patients. Thus, the likelihood that RCR is administered to study participants and released into the environment or transmitted to third parties is considered negligible.

The CHMP endorse the CAT discussion on the non-clinical aspects as described above

2.3.7. Conclusion on the non-clinical aspects

A limited non-clinical development package was provided for KTE-X19. However, the type of product and the limitations of available animal models for investigating pharmacodynamics, pharmacokinetics and safety of KTE-X19 do not allow meaningful non-clinical investigation of many of the aspects that are usually required for a GTMP. Therefore, the presented non-clinical *in vitro* and *in vivo* data demonstrating CD19 CAR expression on transduced T cells, specific activation of CD19 CAR T cells, *in vivo* anti-lymphoma activity and persistence of the surrogate CD19 CAR T cells, B cell aplasia as an expected on-target/off-tumour effect, and the integration sites analysis of the retroviral vector conducted at the end of the manufacturing process of the CD19 CAR T cells, can be considered sufficient for marketing approval of KTE-X19.

The product is considered as approvable from a non-clinical point of view. Moreover, the risk for the environment and human health is regarded as negligible.

The CHMP endorse the CAT conclusions on the non clinical aspects as described above.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A routine GCP inspection was conducted for the clinical trial: A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in Subjects with Relapsed/ Refractory Mantle Cell Lymphoma (ZUMA-2). The purpose of the inspection was to evaluate compliance with GCP and applicable regulations, in particular where it has impact on the validity of the data or the ethical conduct of the trial.

The original inspection request included the sponsor and an investigator site in the US. The planned inspections on site in the US were cancelled due to travel restrictions caused by Covid-19 pandemic. The sponsor inspection was conducted remotely and as a follow-up to the findings at sponsor, a CRO inspection was included in the procedure. The CRO inspection was conducted on site in Germany and partly remotely.

Despite the findings observed by the inspection team, overall the trial was conducted ethically and the level of compliance with GCP was sufficient to conclude that the data are of acceptable quality.

It is the general conclusion of the inspectors that the data reported in the CSR submitted to the agency are reliable and can be used for the assessment of the MAA.

Tabular overview of clinical studies

Table 1: Clinical Trials with KTE-X19

Study	Indication	Product/dosage	Number of subjects	Study Design	Primary Objectives	Status
ZUMA 2 (Phase II): KTE-C19- 102	Adult r/r MCL and confirmation of overexpression of cyclin D1 or presence of t (11;14) after≤5 prior therapy lines (anthracyclineor bendamustine, anti CD20 mABs, ibrutinib or acalabrutinib must be included)	Conditioning therapy KTE-X19: Cohort 1: 2x10Exp6 cells/kg Cohort 2: 0.5x10Exp6 cells/kg Axicabtagene ciloleucel: 2x10Exp6 cells/kg	Planned: 130 Enrolled: 105 Treated with KTE-X19: 82 Treated with axicabtagene ciloleucel: 10	multicentre; open label; safety and efficacy trial with 2 dose cohorts	ORR and PR per Lugano Classification (Cheson et al. 2014)	Primary Analysis: Data cutoff: 24 July 2019 Ongoing 15-year Safety-FU
ZUMA 3 (Phase I/II): KTE-C19-103	Adult r/r B-precursor acute lymphoblastic leukemia	Conditioning therapy KTE-X19: 2x10Exp6 cells/kg 1xExp6 cells/kg 0.5x10Exp6 cells/kg/68 mL 0.5x10Exp6 cells/kg/40 mL	Planned: 100 Enrolled: 107 Treated with KTE-X19: 82	multicentre; open label; safety and efficacy trial	Phase I: Incidence of AEs defined as DLTs: completed Phase II: CR	Phase II Ongoing
ZUMA 4 (Phase I/II): KTE-C19-104	Pediatric and adolescent r/r B-precursor acute lymphoblastic leukemia or r/r B-cell NHL	Conditioning therapy KTE-X19: 2x10Exp6 cells/kg 1x10Exp6 cells/kg/68	Planned: 116 Enrolled: 40 Treated with KTE-X19: 29	multicentre; open label; safety and efficacy trial	Phase I: Incidence of AEs defined as DLTs: completed Phase II:	Phase II: Ongoing

		mL 1x10Exp6 cells/kg/40 mL			all cohorts: CR NHL cohort: ORR	
ZUMA 8 (Phase I/II): KTE-C19-108 (on temporary hold since Jan 2020)	Adult r/r chronic lymphatic leukemia after≥2 prior therapy lines	Conditioning therapy KTE-X19: 0.5x10Exp6 cells/kg 1x10Exp6 cells/kg 2xExp6 cells/kg	Planned: 108 Enrolled: 7 Treated with KTE-X19: 5	multicentre: open label; safety and efficacy trial	Phase I: Incidence of AEs defined as DLTs Phase II: CR	Phase I enrolling
ZUMA 18 (expanded access): KT-US-472-0118	Per Zuma 2	Per ZUMA 2		multicentre; open label; expanded access;		Planned

Evaluation of pharmacokinetics and pharmacodynamics of KTE-X19 were included as secondary endpoints in the pivotal ZUMA-2 study with the primary analysis based on cut-off date of 24 July 2019. Analyses presented are based on data from 68 subjects in Cohort 1 treated with KTE-X19 at the target dose 2 x 106 anti-CAR T cells/kg and on supportive data from 14 subjects in Cohort 2 receiving a dose of 0.5 x 106 anti-CAR T cells/kg.

2.4.2. Pharmacokinetics

Methods

Table 2:

Category/Method	Description
Pharmacokinetics	
Sampling times	At enrollment/leukapheresis (prior to conditioning chemotherapy), Day 0a, after infusion on Days 7, 14, 28, Month 3, then every 3 months through Month 24 and annually thereafter; day of unscheduled hospital re- admission with any KTE-X19 related adverse event (AE), then weekly, and on day of discharge; at the time of disease progression
Assay for anti-CD19 CAR T cells in PBMC	Validated qPCR method adapted from NCI method (Kochenderfer 2012), see m5.3.1.4
Pharmacodynamics	

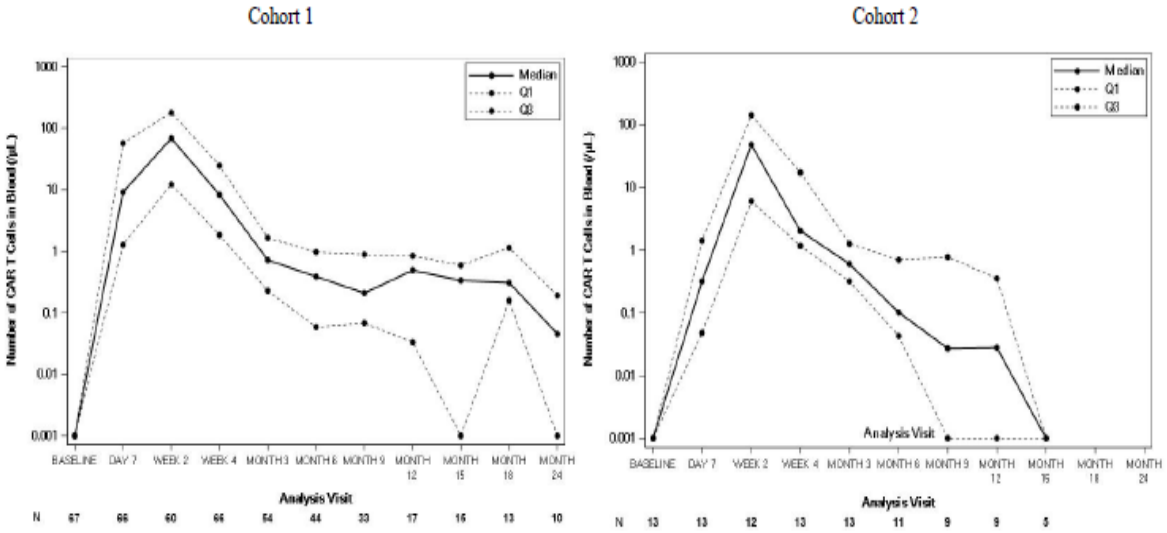
Serum sampling times	At enrollment/leukapheresis (prior to conditioning chemotherapy), Day 0a, after infusion on Days 3, 7, 14, 28; day of unscheduled hospital
CSF sampling times	• Subjects with new onset Grade ≥ 2 neurologic events after KTE-X19 infusion • Subjects who sign the optional portion of the consent: at baseline
Methods	
Luminex® MILLIPLEX® MAP human CD8+ T-cell panel (EMD Millipore®)	Granzyme B, perforin (SOP-00332)
Meso Scale Discovery® (Rockville, MD)	IL-7, IL-15 (SOP-00326, REP-00255) CRP, ICAM-1, VCAM-1 (BED-01484, REP-00256) TNF-α, IL-2, IL-10, IL-6, IFN-γ, IL-8 (SOP-00328, REP-00257)
Quantikine® ELISA (R&D Systems®; Minneapolis, MN) ProteinSimple® Simple Plex™	IL-1RA (SOP-00330, REP-00259; SOP-00572, REP-00380) IL-2Rα (SOP-00331, REP-00260; BED-02157, REP-17900)
Abcam® ELISA (Abcam®; Cambridge, MA) ProteinSimple® Simple Plex™	Ferritin (SOP-00453; SOP-00476)

a The Day 0 time point is after chemotherapy, but before CAR T-cell infusion.

Results

The following graphical comparison demonstrates parallels and differences in the curve characteristics of Cohort 1 and Cohort 2.

Anti-CD19 CAR T cells were measurable in peripheral blood within the first 7 days after the KTE-X19 infusion in all evaluable subjects in both study cohorts. For subjects in Cohort 1, median peak anti-CD19 CAR T-cell levels were 88.64 cells/μL (range: 0.16 to 2589 cells/μL), with median time to peak levels of 15 days. The median AUC0-28 was 1136 cells/μL•days (range: 1.81 to 2.77 x 10^4 cells/μL•days). Anti-CD19 CAR T-cell levels decreased to near baseline but still detectable levels at Month 3 after the infusion in most subjects with evaluable samples. Anti-CD19 CAR T cells were still detectable at 24 months in 6 of 10 subjects with evaluable samples at the time of the data cut-off. For subjects in Cohort 2, peak and total exposure was approximately 60% that of subjects treated in Cohort 1, and had decreased to undetectable levels in 4 of 5 subjects by 15 months.



Summary of anti-CD19 CAR T-cell pharmacokinetics (Cohort 1, safety analysis set)

Table 3:

	ZUMA-2 Cohort 1 (N = 68)
AUC_{0-28} (cells/µL•days), n	67[b]
Mean (StD)	3212.34 (5605.97)
Median (Q1, Q3)	1136.61 (218.99, 3049.87)
Min, Max	1.81, 2.77E+04
Peak, n	67[b]
Mean (StD)	316.90 (589.71)
Median (Q1, Q3)	88.64 (17.18, 267.10)
Min, Max	0.16, 2589.47
Time to peak (days), n	67[b]
Mean (StD)	14.07 (5.86)
Median (Q1, Q3)	15 (8, 15)
Min, Max	8, 31
Baseline, n	67[b]
Mean (StD)	< LLOQ
Median (Q1, Q3)	< LLOQ

Min, Max	< LLOQ
Day 7, n	66[b]
Mean (StD)	163.00 (423.95)
Median (Q1, Q3)	9.15 (1.27, 57.07)
Min, Max	0.01, 2241.62
Week 2, n	60[b]
Mean (StD)	206.55 (486.33)
Median (Q1, Q3)	68.57 (12.25, 179.94)
Min, Max	0.16, 2589.47
Week 4, n	66[b]
Mean (StD)	16.72 (21.89)
Median (Q1, Q3)	8.31 (1.84, 24.64)
Min, Max	< LLOQ, 113.02
Month 3, n	54[b]
Mean (StD)	1.48 (2.03)
Median (Q1, Q3)	0.72 (0.23, 1.65)
Min, Max	< LLOQ, 10.86
Month 6, n	44[b]
Mean (StD)	0.91 (1.84)
Median (Q1, Q3)	0.39 (0.06, 0.97)
Min, Max	< LLOQ, 11.79
Month 9, n	33[b]
Mean (StD)	0.93 (2.34)
Median (Q1, Q3)	0.21 (0.07, 0.89)
Min, Max	< LLOQ, 13.32
Month 12, n	17[b]
Mean (StD)	1.12 (2.19)
Median (Q1, Q3)	0.49 (0.03, 0.84)
Min, Max	< LLOQ, 8.06

Month 15, n	15[b]
Mean (StD)	0.56 (1.09)
Median (Q1, Q3)	0.34 (< LLOQ, 0.59)
Min, Max	< LLOQ, 4.36
Month 18, n	13[b]
Mean (StD)	0.73 (0.91)
Median (Q1, Q3)	0.31 (0.16, 1.14)
Min, Max	< LLOQ, 3.17
Month 24, n	10[b]
Mean (StD)	0.15 (0.23)
Median (Q1, Q3)	0.05 (< LLOQ, 0.19)
Min, Max	< LLOQ, 0.62

Data cutoff date = 24 July 2019

Abbreviations: AUC0-28, area-under-the-curve from Day 0 to Day 28; CAR, chimeric antigen receptor; LLOQ, lower limit of quantification; Max, maximum; Min, minimum; PBMC, peripheral blood mononuclear cell; Q, quartile; StD, standard deviation.

Notes: All data have units of cells/µL except AUC0-28 is cells/µL•days and time to peak is measured in days. Peak is defined as the maximum number of CAR T cells measured after infusion. Time to peak is defined as the number of days from KTE-X19 infusion to the date when the CAR T cells in blood first reached the maximum postbaseline level. AUC0-28 is defined as the area-under-the-curve in a plot of number of CAR T cells against scheduled visit from Day 0 to Day 28. Due to the timing of samples collected immediately after infusion (Day 7, Day 14, and Day 28), the calculated values for peak, AUC0-28, and time to peak are considered estimates.

[a] The number of anti-CD19 CAR T cells in blood (per µL) was calculated as (1,000 x white blood cell count/µL) x ([% monocyte + % lymphocyte count]/100) x (qPPB/100), where qPPB is the percentage of PMBCs that express the anti-CD19 CAR.

[b] At some time points, subject numbers were lower than the total number of subjects; reasons include sampling error, low PBMC count, or PBMC count below the LLOQ. Complete blood counts were used to normalise data presented in cells/µL.

Effect of Intrinsic and Extrinsic Factors

The influence of intrinsic and extrinsic factors has been assessed in an explorative manner. For cohort 1 a number of subgroup analysis where performed. These were not designed to test for differences between subgroups and should be considered descriptive only.

PK by Age: 39 subjects were ≥ 65 years of age, and 29 subjects were < 65 years of age. A conspicuous difference is the median peak anti-CD19 CAR T level between the two age groups of< 65 years and ≥65 years as presented in the following table:

PK in ZUMA-2 Cohort 1 (*Notes:adults only; no details on age categories; 1 subject was missing in the analysis;*)	Age < 65 years (total number/percentage) 39 of 68 (=57%)	Age ≥ 65 years (total number/percentage) 28 of 68 (43%)

Median Peak anti-CD19 CAR T cells	112.45 cells/µL (range: 0.39 to 2589.47 cells/µL)	74.08 cells/µL (range: 0.16 to 2565.84 cells/µL)

PK by Sex: Fifty-seven subjects were male, and 11 subjects were female. No major trends toward differences in Median peak anti-CD19 CAR T or Median anti-CD19 CAR T-cell AUC0-28 values were observed. However, median anti-CD19 CAR T cell values were about 20% higher in female subjects.

PK by Race: the predominantly white patient population (62 out of 68) precluded comparisons across race.

PK according to Baseline Tumour Burden

Tumour burden was measured per the revised guidelines from the International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson 2014) and as the sum of the cross-products of target lesions. The association of anti-CD19 CAR T-cell expansion with baseline tumour burden was assessed according to quartiles of tumour burden. Median anti-CD19 CAR T-cell peak values were 42.18 cells/µL in the first (lowest) tumour burden quartile, 135.82 cells/µL in the second quartile, 133.00 cells/µL in the third quartile, and 48.11 cells/µL in the fourth (highest) quartile. Were 458.99 cells/µL•days in the first quartile, 1486.96 cells/µL•days in the second quartile, 2168.29 cells/µL•days in the third quartile, and 566.27 cells/µL•days in the fourth quartile. Thus, a trend towards lower anti-CD19 CAR T-cell exposure for subjects with baseline tumour burden in the highest quartile.

Pharmacokinetics by MCL Morphologic Characteristics

Seventeen subjects in Cohort 1 and 6 subjects in Cohort 2 (28% overall) had blastoid variant of MCL, which is an aggressive subtype of MCL that may predict poorer prognosis than classical morphology MCL. Subjects with blastoid variant MCL showed reduced anti-CD19 CAR T-cell expansion and overall exposure compared with subjects with classical MCL morphology (2- to 3-fold differences between median values)

Exploratory Analyses

Correlative analyses of potential association of pharmacokinetics and pharmacodynamics parameters with key safety and efficacy endpoints were performed for Cohort 1. For the correlative analyses described below, possible associations were identified by p values of 0.05 or lower obtained from either Wilcoxon rank-sum (pairwise comparisons) or Kruskal- Wallis tests (across 3 groups). Multiplicity adjustment was not performed, and p values do not indicate statistical significance, but rather a possible trend in association between individual serum analytes or CAR T-cell levels and CAR-related toxicity.

Association of pharmacokinetics parameters with disease response

Anti-CD19 CAR T-cell peak levels or AUC0-28 in blood in subjects with complete responses (CR), partial response (PR) and non-responders (CR = stable disease + progressive disease) is shown below

Figure 2: Peak number of anti-CD19 CAR T cells in blood (cells/µL) by responder group (Cohort 1; mITT))

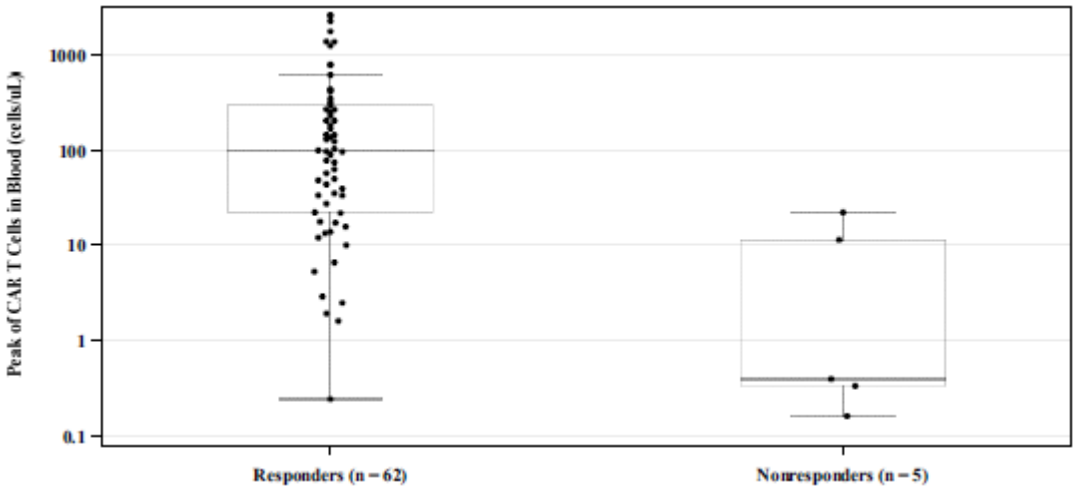


Figure 3: $AUC_{0\text{-}28}$ for number of anti-CD19 CAR T cells in blood (cells/µL•days) by responder group (Cohort 1; mITT))

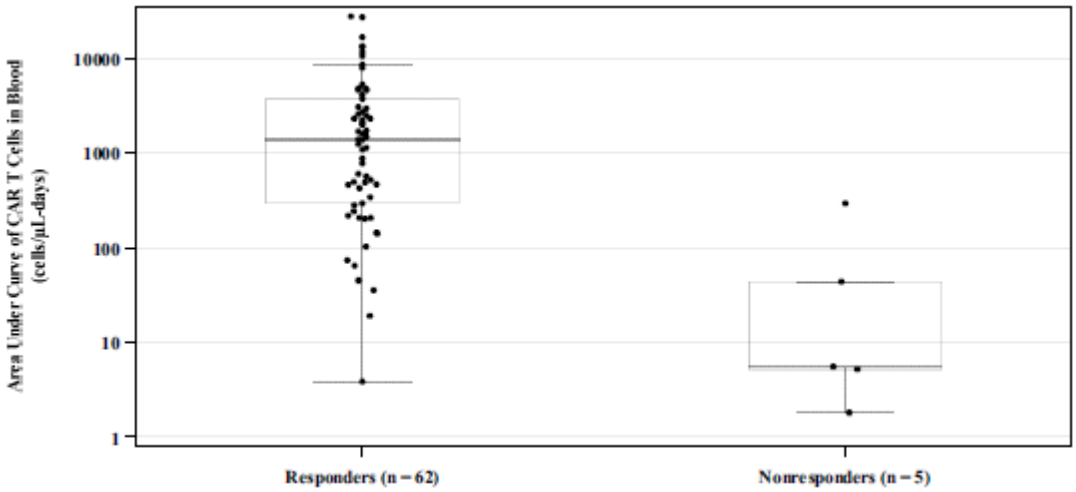


Table 4 Kinetic parameters of autologous anti-CD19-transduced CD3+ cells in ZUMA-2

Number of anti-CD19 CAR T cell	**Responding patients (CR or PR) (N=63)**	**Non-responding patients (N=5)**	**P-Value**
Peak (cells/µL) Median [min; max], n	97.52 [0.24, 2589.47], 62	0.39 [0.16, 22.02], 5	0.0020

Number of anti-CD19 CAR T cell	**Responding patients (CR or PR) (N=63)**	**Non-responding patients (N=5)**	**P-Value**
AUC_{0-28} (cells/µL·days) Median [min; max], n	1386.28 [3.83 to 2.77×10^4], 62	5.51 [1.81, 293.86], 5	0.0013

P-value is calculated by Wilcoxon test

Figure 4: Peak number of anti-CD19 CAR T cells in blood (cells/µL) by best response (Cohort 1; mITT)

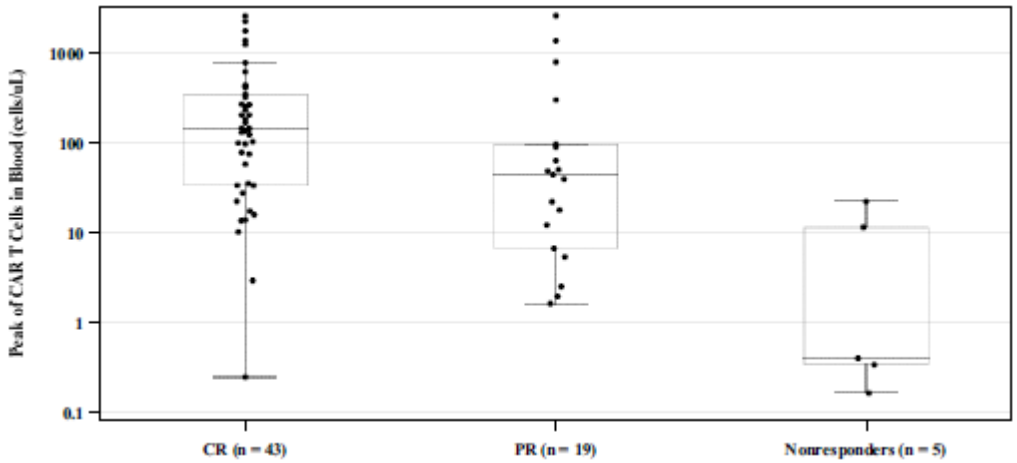
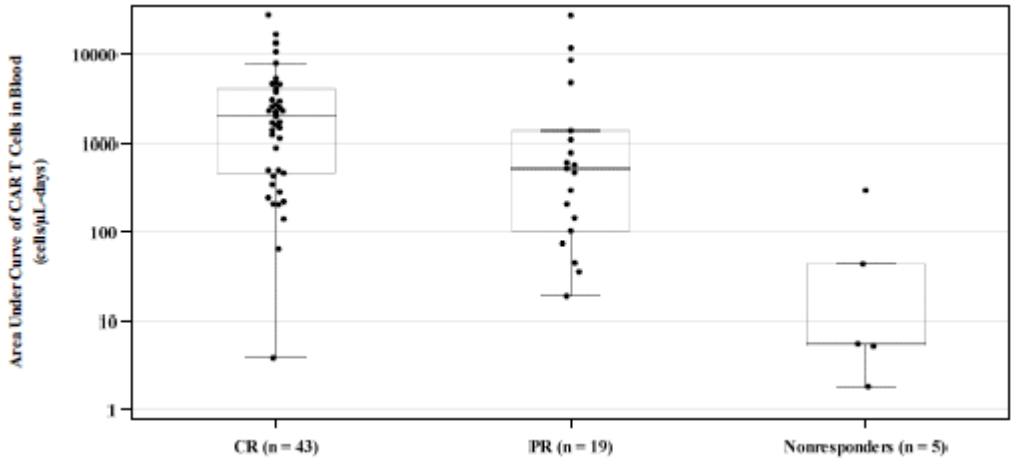


Figure 5: AUC_{0-28} for number of anti-CD19 CAR T cells in blood (cells/µL•days) by best response (Cohort 1; mITT))



Association of pharmacokinetics parameters with CRS or neurologic events

Anti-CD19 CAR T-cell levels in blood (peak and AUC0-28) were examined according to the severity of key safety outcomes (incidence of Grade 3 or higher versus Grade 2, Grade 1, or no CRS or neurologic events) Data collected on Day 7 and Day 14 were used to determine association of pharmacokinetic parameters with AEs. Peak blood levels of anti-CD19 CAR T cells were higher for subjects with higher grades of CRS. The median peak level of anti-CD19 CAR T cells was 4.8-fold higher for subjects with Grade 3 or higher CRS compared with subjects with Grade 2, Grade 1, or no CRS (273.72 versus 57.07 cells/µL). Median AUC_{0-28} was 7.77-fold higher in subjects with Grade 3 or higher CRS than in subjects with Grade 2, Grade 1, or no CRS (4664.32 versus 600.59 cells/µL•days).

The median peak anti-CD19 CAR T-cell level in blood was 8.27-fold higher in subjects with Grade 3 or higher neurologic events relative to the median peak level in subjects with Grade 2, Grade 1, or no neurologic events (361.50 versus 43.71 cells/µL). Similarly, the median AUC_{0-28} was 9.46-fold higher in subjects with Grade 3 or higher neurologic events than in subjects with Grade 2, Grade 1, or no neurologic events (4664.32 versus 493.16 cells/µL•days). Summarizing, higher anti-CD19 CAR T-cell levels (peak and AUC_{0-28}) were associated with Grade 3 or higher CRS and Grade 3 or higher neurologic events.

2.4.3. Pharmacodynamics

For evaluation of pharmacodynamics, subjects' serum samples were collected according to the ZUMA-2 clinical protocol schedule of assessments and per institutional guidelines at baseline (prior to conditioning chemotherapy), on Day 0 (after conditioning chemotherapy and prior to KTE-X19 infusion), and on Days 3, 7, 14, and 28 after the KTE-X19 infusion. Additional unscheduled samples were collected if a subject had prolonged treatment-related toxicity or was re-admitted to the hospital with any KTE-X19-related adverse event and at the time of disease progression (optional). In addition, Cerebrospinal Fluid (CSF) was obtained from subjects who experienced Grade 2 or higher neurologic events after KTE-X19 infusion and from subjects who consented to optional lumbar punctures at baseline (prior to KTE-X19 infusion) and Day 5 (± 3 days) after KTE-X19 infusion. However, Cerebrospinal Fluid analyses were exploratory and descriptive in nature and the methods used were not qualified for CSF.

A total of 40 analytes has been evaluated on blood and tumour samples with 17 key analytes, which comprised pro-inflammatory and immune-modulating cytokines, chemokines, and effector molecules. The analysis of primary biomarkers is performed on blood and tumour samples to evaluate predictive and pharmacodynamic markers for anti-CD19 CAR T cells. Prognostic markers specific for MCL and related to the tumour immune environment are evaluated in archived and fresh tumour biopsies (at baseline, on Day 7, and at Month 6 for subjects who sign the optional consent form).

The following 17 analytes were considered key analytes:

- Homeostatic/proliferative: interleukin (IL)-2, IL-7, and IL-15
- Inflammatory/immune modulating: C-reactive protein (CRP), interferon-gamma (IFN-γ), IL-1 receptor antagonist (IL-1RA), IL-2 receptor alpha (IL-2Rα), IL-6, IL-10, and tumour necrosis factor-alpha (TNF-α)
- Chemokine: C-X-C motif chemokine (CXCL)10, and IL-8
- Immune effector: granzyme B and perforin
- Other analytes: ferritin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1)

Key observations

After infusion of KTE-X19, the serum levels of the key analytes remained steady at baseline levels (TNF-α and VCAM-1) or were elevated relative to baseline (CXCL10, ferritin, granzyme B, ICAM-1, IFN-γ, IL-1RA, IL-2, IL-2Rα, IL-6, IL-8, IL-10, and perforin). CRP levels generally decreased to baseline or below baseline at Week 4. Three of 65 subjects (4.6%) still demonstrated a 2-fold or higher change in the level of CRP over baseline at that time. The median time to peak for all key analytes was within 8 days after infusion of KTE-X19 (range of medians: 4 to 8 days), preceding the peak anti-CD19 CAR T-cell expansion at 14 days; the median time to peak for perforin was 22 days. The majority of analytes increased by 2-fold or more at peak in ≥ 50% of subjects (exceptions: ICAM-1, perforin, TNF-α, and VCAM-1).

Association of Pharmacodynamic Parameters with CRS or Neurologic Events

Of the 17 key analytes, the median peak serum levels for the following were nominally higher (nominal Wilcoxon rank-sum p value $\leqslant 0.05$) among subjects who experienced Grade 3 or higher CRS versus Grade 2, Grade 1, or no CRS after infusion of KTE-X19: ferritin, granzyme B, IL-2Rα, IL-6, IL-8, IL-10, IL-15, perforin, and TNF-α. The 3 analytes with the lowest p values (highest statistical signal) for peak serum levels with Grade 3 or higher CRS compared with Grade 2, Grade 1, or no CRS were IL-10, granzyme B and IL-2RA.The 3 analytes with the greatest fold change by grade of CRS were IL-6 (12.7-fold), IL-10 (6.3-fold), and TNF-α (5.7-fold).

With the exception of perforin (median estimated time to peak of 22 days) , the median estimated time to peak for all key analytes was within 8 days after infusion of KTE-X19 (range of medians: 4 to 8 days), preceding the peak anti-CD19 CAR T-cell expansion at 14 days. The majority of the analytes increased by 2-fold or more at peak in ≥ 50% of subjects (exceptions: ICAM-1, perforin, TNF-α, and VCAM-1). By Week 4 after KTE-X19 infusion, the majority of the 17 key serum analytes had returned to near-baseline levels; ie, 6 analytes remained elevated by 2-fold or more in ≥ 20% of subjects (CXCL10, ferritin, IFN-γ, IL 6, IL-8, and IL-15). The monocyte chemokine protein 1 (MCP-1) as an important chemokine for cerebral immune response and cerebral inflammation has been evaluated in the course of the trial. However, the observation of MCP-1 peak levels at upper limit of quantification at both high and low grade neurologic events suggest the use of a not quite adequate assay. Therefore, unfortunately, the results cannot be regarded representative.

Additionally, of the 40 analytes measured, 3 cytokines with the highest increases in peak and total exposure in subjects with Grade 3 or higher CRS were granzyme A, GM-CSF and macrophage inflammatory protein-1alpha.

The results on upregulation of pro-inflammatory cytokines in the ZUMA 2 trial with higher grades of CRS can be regarded in line with literature data on other anti-CD19 CAR T cells. This also applies to the observation that by Week 4 after KTE-X19 infusion, the majority of the 17 key serum analytes had returned to near-baseline levels; i.e., six analytes remained elevated by 2-fold or more in ≥ 20% of subjects (CXCL10, ferritin, IFN-γ, IL-6, IL-8, and IL-15).

Association of B-cell levels with Pharmacokinetic parameters and disease response.

B-cell levels were calculated as a percentage of viable leukocytes, representing the number of CD19+, CD20+, or CD19+CD20+ B cells relative to total viable CD45+ immune cells in a flow cytometry assay. It should be noted that the flow cytometry assay used did not discriminate between circulating normal and cancerous CD19+CD20+ B cells. At baseline, after conditioning therapy but prior CAR T-cell infusion, median CD19+/CD20+ B-cell levels were 8.7% of viable CD45+ leukocytes (range: 0.024% to 95.237%). After KTE-X19 infusion, the first measurement of B-cells was at Month 3, the second by Month 18. By Month 3, the median B-cell levels declined to 0.1% (range: 0.017% to 96.147%), and by Month 18, median B-cell levels demonstrated recovery (median: 10.6%). Subjects in ongoing response and subjects whose MCL had relapsed had numerically lower levels of B cells compared with non-responders (10.6% and 7.1% versus 35.7%, respectively). In subjects with ongoing response, B cells seem to have recovered.

Association of Product Characteristics with KTE-X19 Pharmacokinetics

Associations between a number of key product-related characteristics and peak post-infusion levels of anti-CD19 CAR T cells were explored. These analyses are only exploratory in nature. They included: transduction rate (%), IFN-γ (pg/mL), CD4:CD8 ratio, T cell phenotype, total number of T cells infused (x 10^6), $CCR7^+$ ($T_{naïve}$ + T_{cm}), %, total number of $CCR7^+$ T cells infused (x 10^6), $CCR7^-$ (T_{em} + T_{eff}), %, and vector copy number (copies per cell).

IFN-γ in co-culture, and CD4:CD8 ratio showed potential associations ($p \leq 0.05$) with post-infusion levels of anti-CD19 CAR T cells. Although a potential association was seen with IFN-γ in co-culture and CD4:CD8 ratio with KTE-X19 pharmacokinetics, these associations were not monotonic; ie, no apparent trend existed in a quartile analyses of product characteristic with Grade 3 or higher neurologic events, Grade 3 or higher CRS, or objective response.

No association was identified (based on nominal p values > 0.05) between other observed characteristics and post-infusion levels of anti-CD19 CAR T cells.

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.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics and response rate

For subjects treated with the KTE-X19 in Cohort 1 at the target dose of 2 x 10^6 CAR T cells/kg, robust CAR T expansion was observed with a median time to peak levels of anti-CD19 CAR T cells in blood of 15 days after KTE-X19 infusion. Anti-CD19 CAR T-cell levels decreased to near background levels by Month 3 although still detectable by qPCR at Month 24 in 6 of 10 subjects (60%) with evaluable samples.

Median exposure level for subjects in Cohort 2 was approximately 60% of the median exposure in subjects in Cohort 1. The range of individual times to peak for subjects in Cohort 2 compared with subjects in Cohort 1 was slower, the overall expansion less robust, and the relative percentage of subjects with detectable anti-CD19 CAR T cells at 12 and 15 months was lower. The results suggest that the higher dose in Cohort 1 leads to greater anti-CD19 CAR T-cell persistence.

Given the known MoA of CAR-T cells, as well as the correlative analyses indicating that anti-CD19 CAR T-cell peak and AUC0-28 were associated with objective response (CR or PR), the rationale for not selecting the lower 0.5 x 10^6 anti-CD19 CAR T cells/kg as the dose carried forward might be supported. With respect to ORR, DOR and PFS, however, there were no differences observed between the two dose cohorts, although the limited number of subjects in cohort 2 hampers a meaningful comparison.

ZUMA-2 pharmacokinetics parameters demonstrated a positive association with disease response as well as toxicity, including higher grades of neurologic events and CRS. The median peak anti-CD19 CAR T-cell level in responders was more than 100-fold higher than the corresponding level in non-responders, 97.52 versus 0.39

cells/µL (p = 0.0020), respectively. This is consistent with earlier observations from other CD19 directed CAR T cell therapies.

With regards to pharmacokinetics in specific populations and subgroups of interest the following observation were made. Answers on arising concerns have been provided, which are considered acceptable in view of a granted conditional approval and obligations on post-authorisation measurements:

- Median anti-CD19 CAR T-cell levels (peak and AUC0-28) were markedly higher in subjects younger than 65 years of age in comparison with subjects aged 65 years or older. It is not clear to which degree the observed difference may be influenced by CAR-T quality attributes, by differences related to in clinical presentation or other unknown factors. Considerations on an age-dependent quality of the CAR T cells are contrasted by the results of the subgroup analyses on ORR, which revealed no clear differences between both age cohorts. In order to achieve a better understanding for age specific interactions of pharmacology and clinical outcome additional subgroup analyses are considered to be provided in the studies adopted as specific obligation for the conditional Marketing authorisation.
- No differences with regard to race were observed for Anti-CD19 CAR T-cell expansion.
- Higher values of Cmax and AUC-values for anti-CD19 CAR T cells were associated with tocilicumab and/or steroids administered for the management of CRS or ICANS, an observation that is not surprising. CAR T cells are the presumed cause for higher levels of CRS and neurologic events subsequently treated with immunosuppressive drugs.
- While no simple monotonic association with anti-CD19 CAR T-cell expansion and base line tumour burden was observed, there still seems to be a trend towards less anti-CD19 CAR T-cell expansion in subjects with the highest baseline tumour burden. Median anti-CD19 CAR T-cell peak values reported were 133 cells/µL for subjects in the third quartile, but dropped down to 48 cells/µL for subjects in the fourth quartile, with corresponding AUC0-28, median values being 2168 cells/µL•days in the third quartile, vs 566 cells/µL•days in the fourth quartile. While subgroup analysis revealed no difference in ORR rates in subject ≥ median base line tumour burden vs subject < median base line tumour burden, it is noted that for the subgroup analysis of ongoing response rates (Cohort 1, Inferential analysis set), a trend towards lower response rates for subject ≥ median base line tumour burden was observed. Data on the ongoing response rates according to tumour burden broken down into quartiles have been provided and clearly show that while subjects with high tumour burden had similar ORR as compared to subjects with lower tumour burden, CR rates where lower and fewer subjects experienced durable long-term responses. Discussion on the underlying mechanisms for inferior T-cell expansion in subjects with the highest tumour burden, citing relevant literature, has been provided indicating that recent data from subjects with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel also demonstrate that subjects with high tumour volume have worse outcomes (Dean 2020, Locke 2018). The mechanisms underlying these observations are not fully elucidated but may include insufficient CAR T-cell expansion relative to the tumour burden, owing to possible detrimental impact of the tumour microenvironment in large tumour lesions (Rossi 2019). Whether limitation with regards to efficacy could be overcome by adjusting CAR-T dose in subjects with higher tumour burden has not been discussed.
- Pharmacokinetics analysis by MCL morphologic characteristics showed that subjects with blastoid variant MCL had reduced anti-CD19 CAR T-cell expansion and overall exposure compared with subjects with classical MCL morphology (2- to 3-fold differences between median values).

Interestingly, no correlation with lower ORR or DOR were observed for subjects with blastoid variant MCL. However, subjects with diffuse MCL morphology had even more reduced anti anti-CD19 CAR T-cell expansion and overall exposure. For these subjects, subgroup analysis indicated a trend towards lower ORR and DOR.

Bioanalysis of 17 key serum biomarkers measured prior to and after KTE-X19 treatment showed trends consistent with the known mechanism of action of anti-CD19 CAR T-cell therapy (including lymphodepletion) and associations with neurologic events and CRS. Homeostatic cytokines CRP, ferritin, IL-7, and IL-15 increased after conditioning chemotherapy treatment, and were elevated at Day 0. At peak, the majority of analytes increased by 2-fold or more in ≥ 50% of subjects. Most analytes returned to near baseline by Week 4. Overall, these results were consistent with previously reported results observed with anti-CD19 CAR T-cell treatment of NHL. Exploratory analysis of the same biomarkers in CSF found pro-inflammatory cytokines CRP, CXCL-10, and IL-6 to be elevated at peak by 5-fold or more in comparison with baseline median.

In an exploratory analysis conducted to evaluate the association of pre-infusion product characteristics with anti-CD19 CAR T-cell expansion only 2 pre-infusion product characteristics were shown to have a positive association with post-infusion levels of anti-CD19 CAR T-cell levels: IFN-γ in co-culture and CD4:CD8 ratio. The association, however, was not monotonic and the relevance of these findings is unknown, since association between these product attributes and clinical outcomes was not observed. Moreover, a relevance of biomarkers such as IFN-gamma or IL-15 or macrophage inflammatory protein 1 alpha for prognostic purpose on treatment outcome was not established.

Analysis of association of B-cell levels with pharmacokinetic parameters and disease response showed that at month 3, median B-cell levels declined to 0.1% (range: 0.017% to 96.147%). Subjects in ongoing response who had B-cell aplasia had numerically higher median CAR T-cell levels than subjects in ongoing response who had detectable B-cells. However, ongoing B-cell depletion was not required for maintaining disease response to month 24, since B cells had recovered by Month 24 in subjects in ongoing response. There is still substantial uncertainty with regards to B-cell aplasia as a marker for durable responses in subjects treated with CD19 directed CAR T cells. Results for KTE-X19 are in line with results obtained with other CAR T products, for which a number of patients are in long-term remission with B-Cell recovery.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics data for KTE-X19 are based on 1 clinical study and comparison and analyses of results across studies is not applicable. ZUMA-2 was not designed to test for differences between subgroups and formal comparisons were not pre-specified. The results of the subgroup analyses are descriptive only. The influence of intrinsic and extrinsic factors has been assessed in an explorative manner. No population analysis has been performed due to the sparse PK data base available.

Assessments for clinical pharmacology in the ZUMA 2 trial were based on the known mechanism of action of anti-CD19 CAR T cell and the current knowledge of the safety profile of the conditioning chemotherapy and anti-CD19 CAR T-cell infusion. Conventional studies on pharmacokinetics including absorption, distribution, metabolism and excretion of KTE-X19 are not applicable. The clinical benefit of KTE-X19, i.e. a complete or partial response after treatment with KTE-X19 is supported by the results of pharmacology data. However, a conclusion on a possible correlation of cell persistence and long-term efficacy outcomes is not possible due to the limited data available. With respect to pharmacodynamics, there is currently no evidence of a positive correlation between certain biomarkers and a positive treatment outcome.

Although extrapolation of data on pharmacology of KTE-C19 to KTE-X19 is somehow acceptable, there are remaining uncertainties concerning differences in gender and age in the ZUMA-2 population particularly due to the lack of results on population PK and PD. Given the general low number of treated patients in the ZUMA-2 trial, the unequal distribution gender and the very rough age classification (<65 years old and ≥65 years old), the following incomprehensibilities require detailed analyses:

- Medium peak of anti-CD19 CAR T cell value: 112.45 cells/γL (<65 years old) and 74.08 cells/γL (≥65 years old
- Median anti-CD19 CAR T-cell AUC0-28 value: 876.48 cells/µL•days in subjects ≥ 65 years of age and 1640.21 cells/µL•days in subjects < 65 years of age

This is particularly noteworthy since both median peak of anti-CD19 CAR T levels and AUC_{0-28} were associated with better results on objective response.

The issue was partially addressed by the applicant and it will be further followed post marketing in the studies proposed as specific obligation in the frame of the adopted Conditional marketing authorisation.

The CHMP endorse the CAT assessment regarding the conclusions on the Clinical pharmacology as described above.

2.5. Clinical efficacy

The primary data for this marketing application are from one ongoing, uncontrolled, open label multi-centre Phase 2 clinical study, KTE-C19-102 (ZUMA-2), (Table 5), evaluating safety and efficacy of KTE-X19 at 33 sites in the United States, France, Germany and the Netherlands. The remaining ongoing studies listed in Table 5 provide clinical experience of KTE-X19 in the context of other indications.

Table 5. Clinical trials of KTE-X19

Study Identifier	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Uncontrolled Efficacy and Safety Studies							
KTE-C19-102 (ZUMA-2)	Evaluate the efficacy and safety of KTE-X19 in adult subjects with r/r MCL	Phase 2, open-label; efficacy and safety; multicenter	Conditioning chemotherapy[a] KTE-X19 anti-CD19 CAR T cell infusion[b]: • Cohort 1: 2 x 10^6 cells/kg • Cohort 2: 0.5 x 10^6 cells/kg Axicabtagene ciloleucel anti-CD19 CAR T cells[b] • 2 x 10^6 cells/kg	Planned: up to approximately 130 Enrolled: 105[b] Treated with KTE-X19: 82 Treated with axicabtagene ciloleucel: 10[c]	Adults with r/r MCL after ≤ 5 lines of prior therapy that included anthracycline or bendamustine containing therapy, anti-CD20 monoclonal antibody, ibrutinib or acalabrutinib	Single infusion of KTE-X19[d]	Study ongoing; Primary Analysis CSR (m5.3.5.2)
KTE-C19-103 (ZUMA-3)	Evaluate the safety and efficacy of KTE-X19 in adult subjects with r/r B-precursor ALL	Phase 1/2, open-label; safety and efficacy; multicenter	Conditioning chemotherapy[a] KTE-X19 anti-CD19 CAR T cell infusion: • 2 x 10^6 cells/kg • 1 x 10^6 cells/kg • 0.5 x 10^6 cells/kg in 68 mL • 0.5 x 10^6 cells/kg in 40 mL	Planned: 100 Enrolled: 107[b] Treated with KTE-X19: 82	Adults with r/r B-precursor ALL (r/r defined as: primary refractory, first relapse following a remission of ≤ 12 months, r/r after second line or higher therapy or r/r after allogenic SCT)	Single infusion of KTE-X19[d]	Phase 1: completed, Phase 2: ongoing; Clinical Summary of Safety (CSS, m2.7.4)
KTE-C19-104 (ZUMA-4)	Evaluate the safety and efficacy of KTE-X19 in pediatric and adolescent subjects with r/r B-precursor ALL and r/r B-cell NHL	Phase 1/2, open-label; safety and efficacy; multicenter	Conditioning chemotherapy[a] KTE-X19 anti-CD19 CAR T cell infusion: • 2 x 10^6 cells/kg • 1 x 10^6 cells/kg in 68 mL • 1 x 10^6 cells/kg in 40 mL	Planned: 116 Enrolled: 40[b] Treated: 29	Pediatric and adolescent subjects with r/r B-precursor ALL or r/r B-cell NHL (r/r defined as: primary refractory, r/r after second-line or higher therapy or r/r after allogenic SCT)	Single infusion of KTE-X19	Phase 1: completed, Phase 2: ongoing; CSS (m2.7.4)
KTE-C19-108 (ZUMA-8)	Evaluate the safety and efficacy of KTE-X19 in adult subjects with r/r CLL	Phase 1/2, open-label; safety and efficacy; multicenter	Conditioning chemotherapy[a] KTE-X19 anti-CD19 CAR T cell infusion: • 0.5 x 10^6 cells/kg • 1 x 10^6 cells/kg • 2 x 10^6 cells/kg	Planned: Up to approximately 108 Enrolled: 7[b] Treated: 5	Adults with r/r CLL whose disease had progressed following treatment with ≥ 2 lines of prior therapy, 1 of which was a BTK inhibitor	Single infusion of KTE-X19	Phase 1 enrolling, CSS (m2.7.4)

a In ZUMA-2 and ZUMA-8, subjects received conditioning chemotherapy consisting of both cyclophosphamide 500 mg/m2/day and fludarabine 30 mg/m2/day for 3 days. In ZUMA-3 and ZUMA-4, subjects received conditioning chemotherapy consisting of cyclophosphamide 900 mg/m2/day for 1 day and fludarabine 25 mg/m2/day for 3 days.
b ZUMA-2 had completed enrolment as of the data cut-off date for results reported in this application, 24 July 2019. For studies ZUMA-3, ZUMA-4 and ZUMA-8, the number of subjects enrolled represent enrolment as of the data cut-off date for results reported in this application, 26 June 2019.
c In ZUMA-2, 10 subjects were treated with axicabtagene ciloleucel. Results from these 10 subjects were reported separately and are not included in this application.
d 3 subjects in ZUMA-2 and 4 subjects in ZUMA-3 were enrolled for retreatment with KTE-X19.

2.5.1. Dose response studies

Dose-response studies have not been performed. The proposed dose (2 x 10^6 anti-CD19 CAR T cells/kg, Cohort 1), is based on results obtained with axicabtagene ciloleucel (Yescarta) in subjects with refractory aggressive large B-cell lymphoma (ZUMA-1), a different CAR T cell product, and by peak expansion and cumulative exposure data for KTE-X19 in the Zuma 2 trial.

Cohort 2 explored the safety and efficacy of a 4-fold lower dose (0.5 x 10^6 anti-CD19 CAR T cells/kg). This cohort was opened following an interim analysis of 28 patients in Cohort 1, demonstrating 3- to 5-fold higher peak expansion and cumulative exposure values of anti-CD19 CAR T cells relative to that observed in ZUMA-1. The cohort was subsequently closed following a preliminary analysis revealing that anti-CD19 CAR T-cell expansion in these subjects was less robust than anticipated.

Based on this, the KTE-X19 dose of 2 x 10^6 anti-CD19 CAR T cells/kg used in Cohort 1 was deemed the optimal dose for treatment of MCL. Cohort 1 was re-opened, and additional subjects were enrolled and treated at the dose of 2 x 10^6 anti-CD19 CAR T cells/kg

2.5.2. Main study(ies)

The applicant submitted data on the key trial ZUMA-2 trial and on the historical control, which is regarded as supportive. ZUMA-2 is an ongoing (but not recruiting), uncontrolled, Phase 2, multicentre, open-label clinical study evaluating the safety and efficacy of KTE-X19 in subjects with r/r MCL whose disease had relapsed or progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTK inhibitor (ibrutinib and/or acalabrutinib). The study involved two dose cohorts (see dose response section). Only data from Cohort 1 is considered pivotal for the MAA.

Data from Cohort 2 are descriptive only, and do not contribute to the primary efficacy analysis.

Title of Study

A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)

Methods and Study Participants

ZUMA-2 is evaluating the safety and efficacy of KTE-X19 in subjects with r/r MCL whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, anti-CD20 antibody, and a Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib and/or acalabrutinib). Data cut-off date of the primary analysis was the 24 July 2019. ZUMA-2 was carried out at 33 sites in the United States, France, Germany and the Netherlands.

Up to approximately 130 subjects are to be enrolled into two dose cohorts. Cohort 1, the pivotal cohort, is to treat approximately 80 subjects with a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. The first 60 subjects in Cohort 1 who were treated with KTE-X19 were to form the basis for statistical hypothesis testing of the primary endpoint. Cohort 2 is to treat up to 40 subjects with KTE-X19 at a target dose of 0.5 x 10^6 anti-CD19 CAR T cells/kg. Data from Cohort 2 are descriptive only.

Each subject in both cohorts was to proceed through the following study periods: Screening, enrollment/leukapheresis, bridging therapy (if applicable), conditioning chemotherapy, investigational product treatment and post-treatment assessment.

Long-term follow-up Study Participants

Not applicable.

Key inclusion Criteria

1) Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or presence of t(11;14)

2) Up to 5 prior regimens for MCL. Prior therapy must have included all of the following:

- Anthracycline or bendamustine-containing chemotherapy
- Anti-CD20 monoclonal antibody therapy
- Ibrutinib or acalabrutinib

3) Relapsed or refractory disease, defined by one of the following:

- Disease progression after last regimen
- Refractory disease is defined as failure to achieve a partial response (PR) or CR to the last regimen

4) Magnetic resonance imaging of the brain showed no evidence of central nervous system (CNS) lymphoma

5) Toxicities due to prior therapy must have been stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia)

6) Age 18 years or older

7) ECOG performance status of 0 or 1

8) Adequate renal, hepatic, pulmonary, and cardiac function

Key Exclusion Criteria

1) History of malignancy other than non-melanomatous skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) unless disease-free for at least 3 years

2) Autologous stem cell transplant (auto-SCT) within 6 weeks of planned KTE-X19 infusion

3) History of allo-SCT

4) Prior CD19-targeted therapy with the exception of subjects who received KTE-X19 in this study and were eligible for retreatment

5) Prior CAR therapy or other genetically modified T-cell therapy

6) Presence of fungal, bacterial, viral, or other infection that was uncontrolled or required intravenous (IV) antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis were permitted if responding to active treatment and after consultation with the Kite medical monitor

7) History of human immunodeficiency virus (HIV) infection or acute or chronic active hepatitis B or C infection. Subjects with a history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing.

8) History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/haemorrhage, dementia, cerebellar disease, cerebral oedema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement

9) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, active arrhythmias, or other clinically significant cardiac disease within 12 months before enrolment

10) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

11) History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months before enrolment

12) Live vaccine ≤ 6 weeks prior to the planned start of conditioning regimen

Treatments

The treatments received during the study are shown in figure 6. Subjects were considered to be enrolled when they commenced leukapheresis to obtain leukocytes for the manufacturing of KTE-X19. Screening PET-CT scans were to be completed as close to enrolment as possible.

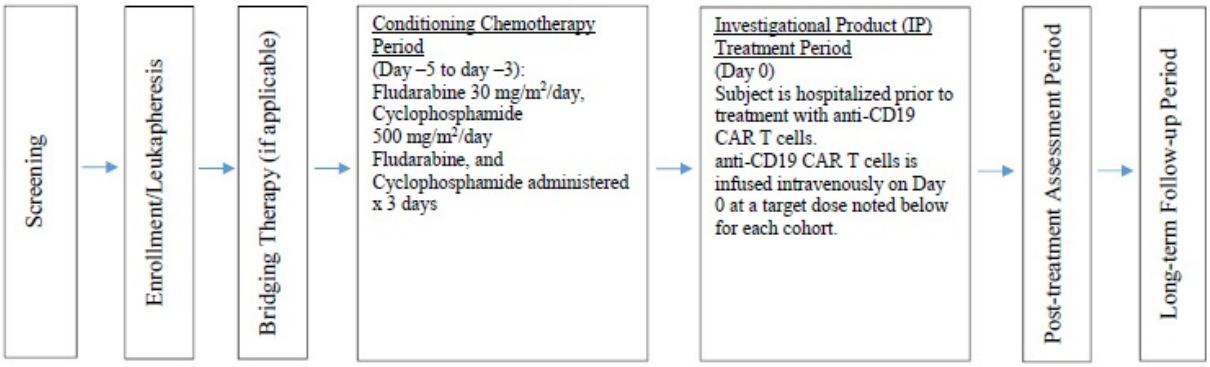


Figure 6. Study Scheme for ZUMA-2 (KTE-C19-102)

Leukapheresis:

Subjects were to avoid corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs for 7 days prior to leukapheresis. If leukapheresis was delayed beyond 5 days, baseline complete blood count with differential and chemistry panel was to be repeated to reconfirm the subject's eligibility.

Bridging Therapy

Bridging therapy could be administered at the discretion of the investigator after leukapheresis at any subject with high disease burden at screening and had to be completed at least 5 days prior to initiation of conditioning therapy. According to the trial protocol, allowed drugs were dexamethasone PO or IV, ibrutinib or acalabrutinib. If bridging therapy was administered, PET-CT scans and bone marrow aspirate/biopsy, if applicable, had to be repeated prior to the start of conditioning therapy in order to establish a new baseline.

Conditioning Chemotherapy (Day –5 to day –3):

• Cyclophosphamide 500 mg/m2 IV over approximately 60 minutes, followed by

• Fludarabine 30 mg/m2 IV over approximately 30 minutes, followed by

• 1 L of 0.9% NaCl at the completion of the cyclophosphamide infusion, addition of

• Mesna per institutional guidelines (administered according institutional guidelines and package insert to inhibit cyclophosphamide induced haemorrhagic cystitis)

69 subjects (of 68 treated with KTE-X19) in Cohort 1 and 15 subjects (of 14 treated with KTE-X19) in Cohort 2 received conditioning therapy.

KTE-X19 administration (Day 0):

Subjects in the pivotal Cohort 1 received a single IV infusion of CAR transduced autologous T cells administered at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg, and 68 patients have been treated with KTE-X19 in this dosage.

Subjects in Cohort 2 received a single IV infusion of CAR-transduced autologous T cells administered intravenously at a target dose of 0.5 x 10^6 anti-CD19 CAR T cells/kg, and 14 subjects received KTE-X19 in this dosage.

Objectives

Primary Objective: Evaluation of efficacy of KTE-X19, as measured by ORR

Secondary Objective: Evaluation of safety and tolerability of KTE-X19 and assessment of additional efficacy endpoints (listed below as 'other key endpoints')

Hypothesis

The hypothesis is that ORR to KTE-X19 using central assessment would be significantly higher than the pre-specified historical control rate of 25%. This hypothesis was tested in the inferential analysis set of Cohort 1 at the 1-sided significance level of 0.025 using an exact binominal test.

Outcomes/endpoints

Primary efficacy endpoint

- ORR, defined as CR or PR using central assessment per Lugano Classification (Cheson 2014).

Secondary efficacy endpoints

- BOR, defined as CR, PR, SD, PD, and not available using central assessment per Lugano Classification (Cheson 2014)
- ORR and BOR using investigator assessment per IWG 2007 criteria (Cheson 2007)
- DOR, defined only for subjects who achieved CR or PR
- PFS, defined as time from KTE-X19 infusion to the date of disease progression or death from any cause
- OS, defined as the time from KTE-X19 infusion to the date of death from any cause

Secondary safety endpoints

- Incidence of AEs and clinically significant laboratory values
- Incidence of antibodies to KTE-X19

Other key endpoints

- Changes in the EQ-5D and Visual Analogue Scale from baseline to Month 6
- PK/PD-levels

Sample size

Up to approximately 130 subjects with r/r MCL were to be enrolled and treated in 2 cohorts. Cohort 1 was to include at least 60, and up to approximately 80, subjects who received KTE-X19 at a dose of 2 x 10^6 anti-CD19 CAR T cells/kg (an additional 10 subjects were treated with axicabtagene ciloleucel). Cohort 2 was to include up to approximately 40 subjects who received KTE-X19 at a dose of 0.5 x 10^6 anti-CD19 CAR T cells/kg.

The primary analysis was to be conducted after 60 subjects in Cohort 1 were treated with KTE-X19 and had the opportunity to be assessed for response 6 months after the Week 4 disease assessment. A sample size of 60 subjects in Cohort 1 had at least 96% power to distinguish between an active therapy with a true response rate of 50% or higher from a therapy with an ORR of 25% or less, with a 1-sided alpha level of 0.025.

Analysis population sets

For statistical evaluations, the trial population has been assorted as follows:

- Inferential analysis set: The first 60 subjects in Cohort 1 who were treated with KTE-X19 and who had had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment. This analysis set was used for efficacy analyses in Cohort 1 and the hypothesis testing of the primary endpoint ORR at the time of the primary analysis.
- Full analysis set: All subjects who were enrolled in Cohort 1. This analysis set was used for the summary of subject disposition, as well as for analyses of ORR and other key efficacy endpoints (best objective response, DOR, PFS, and OS).
- Safety analysis set (=modified intent-to-treat analysis set): All subjects who received any dose of KTE-X19
- Subgroup analysis sets: subgroup analyses of selected efficacy and safety endpoints were performed in subgroups defined by baseline covariates, use of concomitant tocilizumab and corticosteroids, and use of bridging therapy.

In the end, 74 subjects were part of Cohort 1 (Full Analysis Set) and 17 in Cohort 2 (Full Analysis Set).

Randomisation and Blinding (masking)

Not applicable

Statistical methods

Cohort 1: Efficacy analyses were conducted using the inferential analysis set (=first 60 subjects who were treated with KTE-X19 at a dose of 2x10Exp6 anti-CD19 CAR T cells/kg) and the full analysis set (=all subjects enrolled and leukapheresed). A sample size of 60 KTE-X19 subjects in Cohort 1 provided at least 96% power to distinguish between an active therapy with a 50% true response rate from a therapy with a response rate of 25% or less, with a 1-sided alpha level of 0.025.

Cohort 2 (descriptive only): Efficacy analyses were conducted using the modified-intent-to-treat analysis set.

Confidence intervals for the primary efficacy endpoint ORR were calculated using the following methods:

- Clopper-Pearson

- Wilson's method
- Agresti-Coull method
- Modfied Jeffrey's method

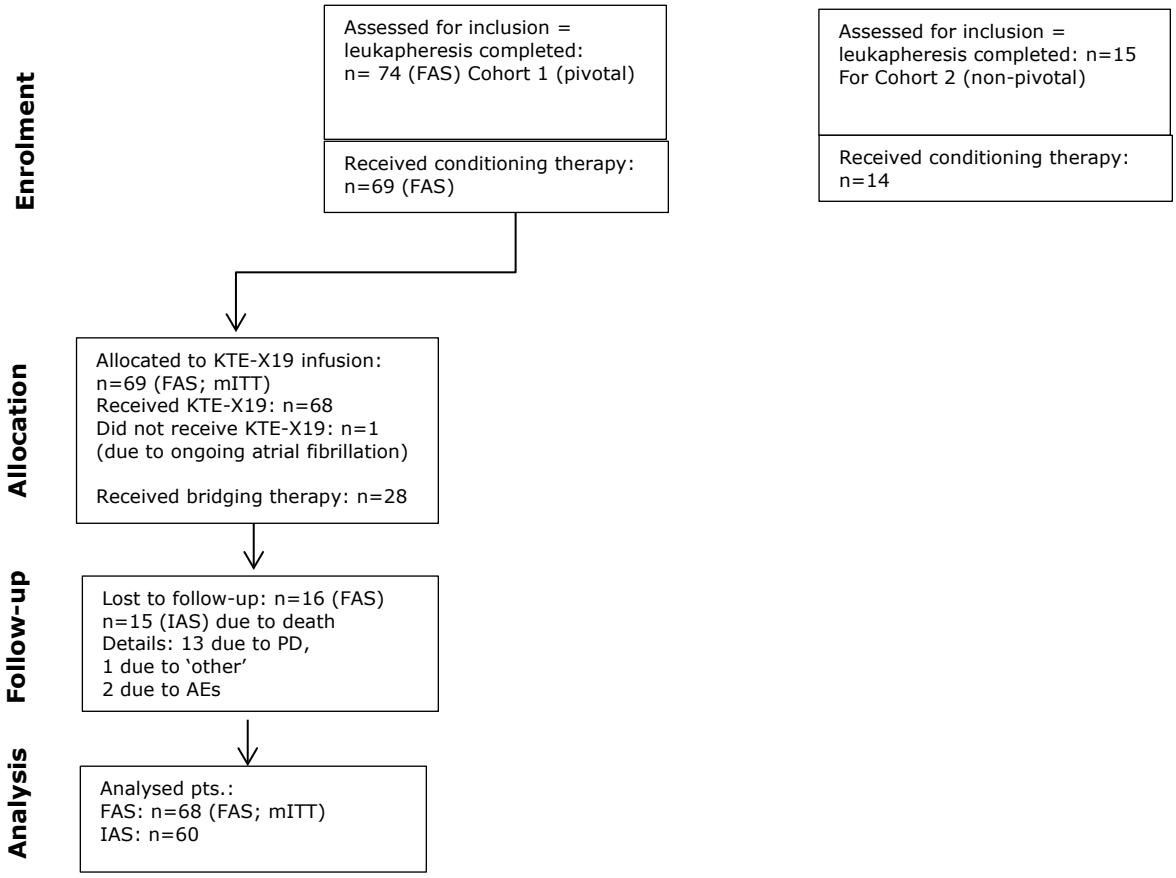
DOR estimates and FU- time for DOR were determined using the KM-approach (for FU-time for DOR the reverse KM approach) and derived using disease assessments obtained prior to initiation of a new anticancer therapy including SCT.

Analyses were based on data accrued up until the cut-off date of 24th July 2019. According to the trial protocol, the outcomes of the study were to be based on the inferential analysis set (i.e. the first 60 subjects in Cohort 1 who were treated with KTE-X19 and had had the opportunity to be followed for response for at least 6 months after the Week 4 disease assessment). For the purpose of this report, the focus has been put on the full analysis set.

Results

Participant flow

Screened 97 patients; screen failure 23 patients



Recruitment

Conduct of the study

Protocol amendments

The original protocol, dated 12 March 2015, was amended 6 times during the course of the trial. The first patient has been enrolled on 16 May 2016 in accordance to Trial Protocol Version 2, dated, 21 April 2016. The change of the manufacturing process from axicabtagene ciloleucel (Yescarta) to KTE-X19 has been implemented with Amendment 3, dated 23 August 2016. Amendment 4, dated 13 November 2017, has been introduced in preparation of the intended marketing Authorisation: A) Identification of two separate treatment cohorts (Cohort 1 and Cohort 2), and B) Addition of BTK inhibitors to permissible prior regimens. The Amendment 5, dated 22 June 2018, designed Cohort 1 as the pivotal cohort. The last subject has been enrolled on 16 April 2019 in accordance to trial protocol version 6, dated 29 October 2018.

Protocol deviations

According to the table below, 28 subjects (41% of the safety analysis set) experienced 31 protocol deviations. These were not considered to impact on the efficacy of the study, because patients with major deviations with regard to in- and exclusion criteria have not been considered in the efficacy analyses sets. The most common protocol deviation was for baseline (screening) PET-CT scans not being performed within 35 days of conditioning chemotherapy (10 subjects, 15%); two subjects had baseline PET-CT scans at screening but did not undergo new baseline scans after completing bridging therapy and before initiating conditioning chemotherapy. One subject in Cohort 1 was not previously treated with anthracycline or bendamustine but was enrolled, and another subject received chemotherapy (ibrutinib) after KTE-X19 infusion and before documented disease progression.

Table 6: Important Protocol deviation

Category	(N = 68) n (%)
Number of subjects with any IPD	28 (41)
Eligibility criteria not satisfied	
113 - Adequate renal, hepatic, pulmonary and cardiac function	2 (3)
102 - Adequate (up to 5) prior therapy	1 (1)
Excluded medication received	
502 - Received other investigational therapy	1 (1)

Missing data	
803 - Missed lab assessments at 3 (or ALC, PBMC or Cytokines at 2) consecutive time points between enrollment and discharge of initial hospitalization	7 (10)
813 - On study scan not performed	3 (4)
806 - Failure to submit archived tumour tissue	2 (3)
808 - Missed baseline PET-CT after bridging therapy and before conditioning therapy	2 (3)
811 - CRP results not available prior to conditioning chemotherapy	2 (3)
809 - Missed ALC, platelets, ANC, or PBMC assessments at 2 consecutive time points after initial hospitalisation	1 (1)
Off schedule procedure	
701 - Baseline PET-CT not performed within 35 days of conditioning chemo	10 (15)

Baseline data

Table 7: Summary of baseline characteristics for ZUMA-2

Category	All leukapheresed (ITT) (N=74)	Inferential Analysis Set[a] (N=60)
Age (years)		
Median (min, max)	65 (38, 79)	65 (38, 79)
≥ 65	58%	53%
Male gender	84%	85%
Median number of prior therapies (min, max)	3 (1; 5)	3 (2; 5)
Relapsed/refractory subgroup		
Relapsed after auto-SCT	42%	43%
Refractory to last MCL therapy	39%	40%
Relapsed after last MCL therapy	19%	17%
Patients with disease stage IV	86%	83%
Patients with bone marrow involvement	51%	58%
Morphological characteristic		
Classical MCL	54%	58%
Blastoid MCL	26%	23%
Other	1%	2%
Unknown	19%	17%
Received bridging therapy		
Yes	38%	35%
No	62%	65%
Ki-67 IHC by central laboratory		
N	49	46
Median	65%	65%

Auto-SCT, autologous stem cell transplant; IHC, immunohistochemistry; Max, maximum; MCL, mantle cell lymphoma; Min, minimum;
a. Inferential analysis set consists of the first 60 patients treated with Tecartus who were evaluated for response 6 months after the Week 4 disease assessment after Tecartus infusion.

Numbers analysed

The analysis sets are shown in Table 8 below.

Table 8. Analysis sets

	Cohort 1 (N = 74) n (%)	Cohort 2 (N = 17) n (%)	Overall (N = 91) n (%)
Full analysis set[a], n (%)	74 (100)	17 (100)	91 (100)
Inferential analysis set[b], n (%)	60 (81)	n/a	n/a
Safety analysis set[c], n (%)	68 (92)	14 (82)	82 (90)
Modified intent-to-treat analysis set[d], n (%)	68 (92)	14 (82)	82 (90)
Safety retreatment analysis set, n (%)	2 (3)	1 (6)	3 (3)
Modified intent-to-treat retreatment analysis set, n (%)	2 (3)	1 (6)	3 (3)

Data cut-off date = 24JUL2019
Abbreviation: n/a, not applicable.
Note: Percentages are based on the number of subjects enrolled.
a Full analysis set is defined as all enrolled (leukapheresed) subjects.
b Inferential analysis set consists of the first 60 subjects treated with KTE-X19 in Cohort 1 and have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment after KTE-X19 infusion.
c Safety analysis set is defined as all subjects treated with any dose of KTE-X19.
d Modified intent-to-treat analysis set is defined as all subjects treated with KTE-X19.

The following 5 patients in Cohort 1 underwent leukapheresis but did not receive conditioning therapy or KTE-X19 (please also refer to list below, *Disposition of full analysis set subjects)*:

- 1 subject due to rapidly progression of MCL 10 days after leukapheresis (listed as not treated due to death)
- 1 subject due to withdrawal for therapy with high-dose cytarabine and lenalidomide (listed as not treated due to death)
- 2 subjects due to unsuccessful manufacturing of the KTE-X19 product from the initial leukapheresis material. 1 patient died due to PD before a second leukapheresis could take place (listed as not treated due to death), and 1 patient developed AE of symptomatic deep vein thrombosis (listed as not treated due to AE)
- 1 subject due to unsuccessful manufacturing of 2 leukapheresis sets. The patient ultimately withdrew IC (listed as not having been treated)

Response data are not available for these subjects, and they are included in the analysis as non-responders and with a response of "not done".

For Cohort 1, as of the data cutoff date, 16 of the 68 patients (24) who received KTE-X19 had died.

For Cohort 2, as of data cutoff date, 4 of the 14 patients (29%) who received KTE-X19 had died.

Outcomes and estimation

Primary endpoint

The ORR was defined as CR and PR per central assessment with the following results:

Response Rate	IAS (N = 60)	FAS (N = 74)
RR (95% CI)	56/60 (93%:83.8%, 98.2%)	63/74 (85%:75.0%, 92.3%)
CR (95% CI)	40/60 (67%:53.3%, 78.3%)	44/74 (59%:47.4%, 70.7%)
PR (95% CI)	16/60 (27%:16.1%, 39.7%)	19/74 (26%: 16.2%, 37.2%)

No subgroup analysis of ORR (central assessment) in the full analysis set were carried out.

The primary endpoint was met, since ORR was significantly higher than the pre-specified control rate of 25% at 1-sided significance level of 0.025 ($p < 0.0001$). Of 42 subjects who initially had a PR or SD, 24 subjects (57%) went on to achieve a CR after a median of 2.2 months (range: 1.8 to 8.3 months). Of the 24 subjects whose responses improved over time, 21 subjects (88%) converted from PR to CR, and 3 subjects (13%) converted from SD to CR.

Objective response and CR using the investigators' assessment had a concordance rate of 95% ($\kappa = 0.70$; 95% CI: 0.39, 1.00) and 90% ($\kappa = 0.77$, 95% CI: 0.60, 0.94), respectively, with the ORR and CR rate using central assessment.

Table 9: Summary of best objective response using central assessment per Lugano classification (Cohort 1 Full Analysis set)

	Cohort 1 (N = 74)
Number of objective responders (CR + PR), n (%)	63 (85)
95% CI (Clopper-Pearson method)	75.0, 92.3
95% CI (Wilson's method)	75.3, 91.5
95% CI (Agresti-Coull method)	75.1, 91.7
95% CI (Modified Jeffrey's method)	75.8, 91.8
p-value of exact test for objective response rate <= 25%	<.0001
CR, n (%)	44 (59)
95% CI (Clopper-Pearson method)	47.4, 70.7
PR, n (%)	19 (26)
95% CI (Clopper-Pearson method)	16.2, 37.2
Stable disease, n (%)	3 (4)
95% CI (Clopper-Pearson method)	0.8, 11.4
Progressive disease, n (%)	2 (3)
95% CI (Clopper-Pearson method)	0.3, 9.4
Not done[a], n (%)	6 (8)
95% CI (Clopper-Pearson method)	3.0, 16.8

Data cut-off date = 24JUL2019
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response.
Notes: Percentages are based on the number of subjects enrolled.

a Not done = no assessment at time of analysis

For comparison purpose: Results on ORR (ORR, defined as CR and PR) per investigator assessment (calculated only for IAS):

Response Rate	IAS (N = 60)
ORR (95% CI)	53/60 (88%:77.4%, 95.2%)
CR (95% CI)	42/60 (70%:56.8%, 81.2%)
PR (95% CI)	11/60 (18%)

During the assessment a re-analysis at a later Cutoff date (31 December 2019) has been provided by the applicant with the following results:

Table. 10. Summary of Best Overall Response using Central Read per Cheson 2014 (Cohort 1, KTE-X19) (Inferential Analysis Set)

	Cohort 1 (N = 60)
Number of objective responders (CR + PR), n (%)	55 (92)
95% CI (Clopper-Pearson method)	81.6, 97.2
95% CI (Wilson's method)	81.9, 96.4
95% CI (Agresti-Coull method)	81.5, 96.8
95% CI (Modified Jeffrey's method)	82.7, 96.7
p-value of exact test for objective response rate <= 25%	<.0001
CR, n (%)	40 (67)
95% CI (Clopper-Pearson method)	53.3, 78.3
PR, n (%)	15 (25)
95% CI (Clopper-Pearson method)	14.7, 37.9
Stable disease, n (%)	2 (3)
95% CI (Clopper-Pearson method)	0.4, 11.5
Progressive disease, n (%)	2 (3)
95% CI (Clopper-Pearson method)	0.4, 11.5
Not evaluable, n (%)	1 (2)
95% CI (Clopper-Pearson method)	0.0, 8.9
Not done[a], n (%)	0 (0)
95% CI (Clopper-Pearson method)	0.0, 6.0

Data cutoff date = 31DEC2019, snapshot date = 10JUN2020
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response.
Note: Percentages are based on the inferential analysis set, ie, the first 60 subjects treated with KTE-X19 in Cohort 1 who have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment.
a. Not done = no assessment at time of analysis.

Data Source: ADSL, ADEFF Program Name: t_bor Output Generated: 20200715T13:22

Table 11. Summary of Best Overall Response using Central Read per Cheson 2014 (Cohort 1, KTE-X19) (Full Analysis Set)

	Cohort 1 (N = 74)
Number of objective responders (CR + PR), n (%)	62 (84)
95% CI (Clopper-Pearson method)	73.4, 91.3
95% CI (Wilson's method)	73.8, 90.5
95% CI (Agresti-Coull method)	73.6, 90.6
95% CI (Modified Jeffrey's method)	74.2, 90.8
p-value of exact test for objective response rate <= 25%	<.0001
CR, n (%)	44 (59)
95% CI (Clopper-Pearson method)	47.4, 70.7
PR, n (%)	18 (24)
95% CI (Clopper-Pearson method)	15.1, 35.7
Stable disease, n (%)	3 (4)
95% CI (Clopper-Pearson method)	0.8, 11.4
Progressive disease, n (%)	2 (3)
95% CI (Clopper-Pearson method)	0.3, 9.4
Not evaluable, n (%)	1 (1)
95% CI (Clopper-Pearson method)	0.0, 7.3
Not done[a], n (%)	6 (8)
95% CI (Clopper-Pearson method)	3.0, 16.8

Data cutoff date = 31DEC2019, snapshot date = 10JUN2020
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response.
Note: Percentages are based on the number of subjects enrolled.
a. Not done = no assessment at time of analysis.

Data Source: ADSL, ADEFF Program Name: t_bor Output Generated: 20200715T13:22

Secondary endpoints

The primary endpoint was supported by key secondary endpoints of DOR, PFS and OS.

Duration of Response (FAS)

As determined per central assessment, subjects responded a median of 1.0 month (range: 0.8 to 3.1 months) after the KTE-X19 infusion. After a median DOR follow-up of 8.6 months, the median KM DOR was not reached. 34 of 60 subjects (57%) presented with an ongoing response as of the data cutoff date. The longest response duration was 29.2 months as of the data cutoff date.

A summary of DOR estimates using central assessment per the Lugano Classification {Cheson 2014} in the full analysis set is provided in Table 12.

Table 12: DOR Using Central Assessment per Lugano Classification (Cohort 1 Full Analysis Set: Subjects With an Objective Response)

	Cohort 1 (N = 63)
DOR[a]	
Subjects with an objective response	63
Event, n (%)	18 (29)
Censored, n (%)	45 (71)
KM median (95% CI) DOR time (months)	NR (8.6, NE)
Min, max DOR (months)	0.0^{+}, 29.2^{+}
Type of event	
Disease progression, n (%)	15 (24)
Death, n (%)	3 (5)
Censoring reason	
Response ongoing, n (%)	39 (62)
SCT, n (%)	2 (3)
Started non-SCT new anticancer therapy, n (%)	3 (5)
Withdrawal of consent or lost to follow-up, n (%)	1 (2)
Event-free rate (% [95% CI]) by KM estimation at	
3 months	84.4 (72.0, 91.6)
6 months	76.0 (62.0, 85.4)
9 months	63.5 (46.6, 76.3)
12 months	63.5 (46.6, 76.3)
15 months	59.3 (41.5, 73.2)
18 months	59.3 (41.5, 73.2)
Median (95% CI) follow-up time (months)	
for DOR (reverse KM approach)	8.1 (7.6, 14.1)

Data cutoff date = 17APR2019
Abbreviations: CI, confidence interval; DOR, duration of response; KM, Kaplan-Meier; Max, maximum; Min, minimum; NE, not estimable; NR, not reached; SCT, stem cell transplant.
Note: Percentages are based on the number of subjects in the full analysis set who had an objective response. "+" indicates censored record.
a DOR is defined as the time from the first objective response to disease progression or to death prior to new anticancer therapy (including SCT). Subjects not meeting the criteria by the analysis data cutoff date were censored at their last evaluable disease assessment date prior to the data cutoff date or new anticancer therapy (including SCT) start date, whichever was earlier.

For the 40 subjects who achieved a CR, the median DOR was not reached (95% CI: 13.6 months, not evaluable). For the 16 subjects who achieved a PR, the median DOR was 2.2 months (95% CI: 1.4 months, not evaluable). KM plots of the DOR in subjects who achieved a CR or PR are provided in figure 7.

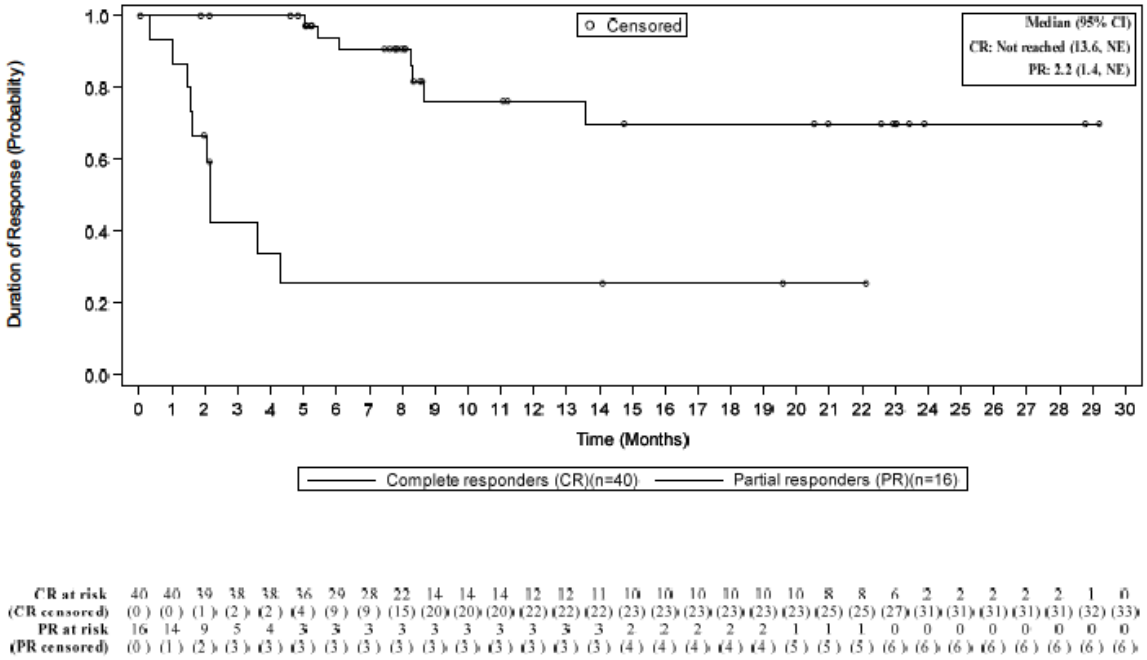


Figure 7. DOR by Best Overall Response Using Central Assessment Per Lugano Classification (Cohort 1 Inferential Analysis Set: CR vs PR)

Data cutoff = 24JUL2019
Abbreviations: CI, confidence interval; CR, complete responders, DOR, duration of response, NE, not estimable, PR, partial responders.

The updated analysis with data cutoff date 31 December 2019 provided the following data:

Table 13. Duration of Response (DOR) using Central Read per Cheson 2014 (Cohort 1: KTE-X19) (Inferential Analysis Set: Subjects with Objective Response)

	Cohort 1 (N = 55)
DOR[a]	
Subjects with an objective response	55
Event, n (%)	21 (38)
Censored, n (%)	34 (62)
KM median (95% CI) DOR time (months)	NR (13.6, NE)
Min, max DOR (months)	0.0+, 35.0+
Type of event	
Disease progression, n (%)	18 (33)
Death, n (%)	3 (5)
Censoring reason	
Response ongoing, n (%)	29 (53)
SCT, n (%)	1 (2)
Started non-SCT new anticancer therapy, n (%)	3 (5)
Withdrawal of consent or lost to follow-up, n (%)	1 (2)
Event-free rate (% [95% CI]) by KM estimation at	
3 months	84.9 (72.1, 92.2)
6 months	77.2 (63.4, 86.4)
9 months	67.6 (53.1, 78.4)
12 months	65.6 (51.1, 76.8)
15 months	58.6 (42.5, 71.7)
18 months	58.6 (42.5, 71.7)
21 months	58.6 (42.5, 71.7)
24 months	58.6 (42.5, 71.7)
27 months	58.6 (42.5, 71.7)
30 months	52.7 (34.5, 68.1)
33 months	52.7 (34.5, 68.1)
Median (95% CI) follow-up time (months) for DOR (reverse KM approach)	14.1 (11.4, 26.5)

Data cutoff date = 31DEC2019, snapshot date = 10JUN2020
Abbreviations: CI, confidence interval; DOR, duration of response; KM, Kaplan-Meier; NE, not estimable; NR, not reached; SCT, stem cell transplant; "+" indicates censored record.
Note: Percentages are based on the inferential analysis set with subjects who had an objective response.
a. DOR is defined as the time from the first objective response to disease progression or death prior to new anti-cancer therapy (including SCT). Subjects not meeting the criteria by the analysis data cutoff date were censored at their last evaluable disease assessment date prior to the data cutoff date or new anticancer therapy (including SCT) start date, whichever was earlier.

Data Source: ADSL, ADTTE, ADEFF Program Name: t_dor.sas Output Generated: 20200715T13:22

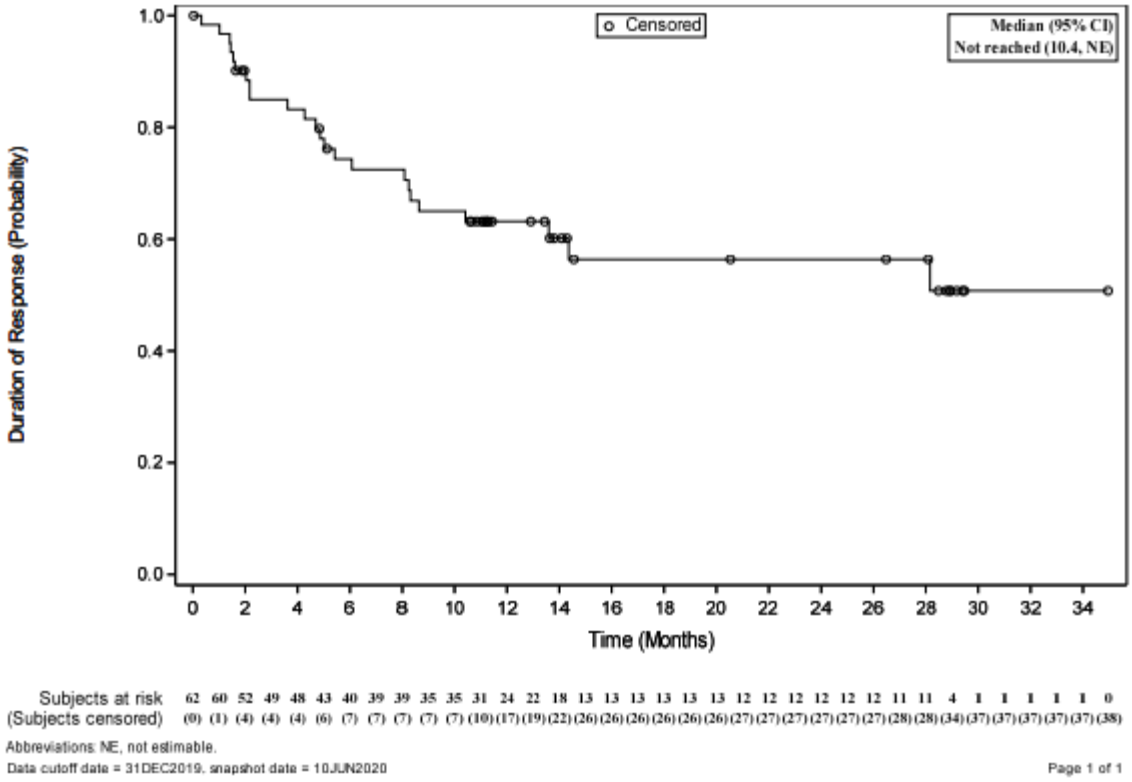
Table 14. Duration of Response (DOR) using Central Read per Cheson 2014 (Cohort 1: KTE-X19) (Full Analysis Set: Subjects with Objective Response)

	Cohort 1 (N = 62)
DOR[a]	
Subjects with an objective response	62
Event, n (%)	24 (39)
Censored, n (%)	38 (61)
KM median (95% CI) DOR time (months)	NR (10.4, NE)
Min, max DOR (months)	0.0+, 35.0+
Type of event	
Disease progression, n (%)	21 (34)
Death, n (%)	3 (5)
Censoring reason	
Response ongoing, n (%)	32 (52)
SCT, n (%)	2 (3)
Started non-SCT new anticancer therapy, n (%)	3 (5)
Withdrawal of consent or lost to follow-up, n (%)	1 (2)
Event-free rate (% [95% CI]) by KM estimation at	
3 months	85.0 (73.1, 91.9)
6 months	74.3 (61.0, 83.7)
9 months	65.0 (51.1, 75.9)
12 months	63.2 (49.2, 74.3)
15 months	56.4 (40.9, 69.3)
18 months	56.4 (40.9, 69.3)
21 months	56.4 (40.9, 69.3)
24 months	56.4 (40.9, 69.3)
27 months	56.4 (40.9, 69.3)
30 months	50.8 (33.3, 65.8)
33 months	50.8 (33.3, 65.8)
Median (95% CI) follow-up time (months) for DOR (reverse KM approach)	13.8 (11.3, 20.5)

Data cutoff date = 31DEC2019, snapshot date = 10JUN2020
Abbreviations: CI, confidence interval; DOR, duration of response; KM, Kaplan-Meier; NE, not estimable; NR, not reached; SCT, stem cell transplant; "+" indicates censored record.
Note: Percentages are based on the number of subjects in the full analysis set with objective response.
a. DOR is defined as the time from the first objective response to disease progression or death prior to new anti-cancer therapy (including SCT). Subjects not meeting the criteria by the analysis data cutoff date were censored at their last evaluable disease assessment date prior to the data cutoff date or new anticancer therapy (including SCT) start date, whichever was earlier.
Median Follow-up Time for DOR is estimated using reverse KM approach.

Data Source: ADSL, ADTTE, ADEFF Program Name: t_dor_o Output Generated: 20200715T13:22

Figure 8. Kaplan-Meier Plot of Duration of Response Using Central Read per Cheson 2014 (Cohort 1: KTE-X19) (Full Analysis Set: Subjects with Objective Response, N = 62)



Progression Free Survival (FAS)

A summary of PFS estimates using central assessment per the Lugano Classification {Cheson 2014} in the full analysis set is provided in Table 15. The median PFS was not reached.

Table 15: PFS Using Central Assessment per Lugano Classification (Cohort 1 Full Analysis Set)

	Cohort 1 (N = 74)
PFS[a]	
Number of subjects, n	74
Event, n (%)	27 (36)
Censored, n (%)	47 (64)
KM median (95% CI) PFS time (months)	NR (9.9, NE)
Min, max PFS time (months)	0.0+, 30.9+
Type of event	
Disease progression, n (%)	18 (24)
Death, n (%)	9 (12)
Censoring reason	
Response/SD ongoing, n (%)	39 (53)
Started non-SCT new anticancer therapy, n (%)	4 (5)
SCT, n (%)	2 (3)
Withdrawal of consent or lost to follow-up, n (%)	1 (1)
No disease assessment, n (%)	1 (1)
PFS rate (% [95% CI]) by KM estimation	
3 months	87.6 (77.5, 93.3)
6 months	75.2 (63.0, 83.8)
9 months	64.1 (50.7, 74.7)
12 months	55.6 (40.8, 68.1)
15 months	55.6 (40.8, 68.1)
18 months	51.9 (36.4, 65.3)
21 months	51.9 (36.4, 65.3)
24 months	51.9 (36.4, 65.3)

Data cutoff date = 24JUL2019
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; Max, maximum; Min, minimum; NE, not estimable; PFS, progression-free survival; SCT, stem cell transplant; SD, stable disease.
Note: Percentages are based on the number of subjects enrolled. PFS is defined as the time from enrollment date to the date of disease progression or death from any cause. "+" indicates censored record.

PFS rate estimates in the inferential analysis set were also derived using investigator assessment of progression per IWG 2007 Criteria {Cheson 2007}. KM estimates of PFS rates at 6 months and 12 months were 77.4% and 63.7%, respectively, and the median PFS was not reached with a median potential follow-up of 12.3 months (range: 7.0 to 32.3 months).

The updated analysis with data cutoff date 31 December 2019 provided the following data:

Table 16. Progression-free Survival using Central Read per Cheson 2014 (Cohort 1: KTE-X19) (Inferential Analysis Set)

	Cohort 1 (N = 60)
PFS[a]	
Number of subjects, n	60
Event, n (%)	24 (40)
Censored, n (%)	36 (60)
KM median (95% CI) PFS time (months)	NR (9.6, NE)
Min, max PFS time (months)	0.0+, 35.9+
Type of event	
Disease progression, n (%)	21 (35)
Death, n (%)	3 (5)
Censoring reason	
Response/SD ongoing, n (%)	29 (48)
Started non-SCT new anticancer therapy, n (%)	4 (7)
SCT, n (%)	1 (2)
Withdrawal of consent or lost to follow-up, n (%)	1 (2)
No disease assessment, n (%)	1 (2)
PFS rate (% [95% CI]) by KM estimation	
3 months	85.9 (73.8, 92.7)
6 months	76.8 (63.4, 85.8)
9 months	71.3 (57.5, 81.4)
12 months	62.2 (48.1, 73.5)
15 months	59.2 (44.6, 71.2)
18 months	55.5 (40.0, 68.5)
21 months	55.5 (40.0, 68.5)
24 months	55.5 (40.0, 68.5)
27 months	55.5 (40.0, 68.5)
30 months	50.5 (33.6, 65.2)
33 months	50.5 (33.6, 65.2)

Data cutoff date = 31DEC2019, snapshot date = 10JUN2020
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; NR, not reached; PFS, progression-free survival; SCT, stem cell transplant; SD, stable disease; "+" indicates censored record.
Note: Percentages are based on the inferential analysis set, ie, the first 60 subjects treated with KTE-X19 in Cohort 1 who have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment.
a. PFS is defined as the time from the KTE-X19 infusion date to the date of disease progression or death from any cause. Subjects not meeting the criteria by the analysis data cutoff date were censored at their last evaluable disease assessment date prior to the data cutoff date or new anticancer therapy (including SCT) start date, whichever was earlier.

Data Source: ADSL, ADTTE Program Name: t_pfs Output Generated: 20200715T13:23

Table 17. Progression-free Survival (PFS) using Central Read per Cheson 2014 (Cohort 1: KTE-X19) (Full Analysis Set)

	Cohort 1 (N = 74)
PFS[a]	
Number of subjects, n	74
Event, n (%)	33 (45)
Censored, n (%)	41 (55)
KM median (95% CI) PFS time (months)	16.2 (9.9, NE)
Min, max PFS time (months)	0.0+, 36.6+
Type of event	
Disease progression, n (%)	24 (32)
Death, n (%)	9 (12)
Censoring reason	
Response/SD ongoing, n (%)	32 (43)
Started non-SCT new anticancer therapy, n (%)	4 (5)
SCT, n (%)	2 (3)
Withdrawal of consent or lost to follow-up, n (%)	1 (1)
No disease assessment, n (%)	2 (3)
PFS rate (% [95% CI]) by KM estimation	
3 months	87.4 (77.2, 93.2)
6 months	75.7 (63.8, 84.1)
9 months	63.3 (50.6, 73.5)
12 months	56.8 (44.0, 67.7)
15 months	55.2 (42.4, 66.2)
18 months	49.1 (35.3, 61.6)
21 months	49.1 (35.3, 61.6)
24 months	49.1 (35.3, 61.6)
27 months	49.1 (35.3, 61.6)
30 months	49.1 (35.3, 61.6)
33 months	43.0 (26.7, 58.3)
36 months	43.0 (26.7, 58.3)

Data cutoff date = 31DEC2019, snapshot date = 10JUN2020
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; PFS, progression-free survival; SCT, stem cell transplant; SD, stable disease; "+" indicates censored record.
Note: Percentages are based on the number of subjects enrolled.
PFS is defined as the time from enrollment date to the date of disease progression or death from any cause.

Data Source: ADSL, ADTTE Program Name: t_pfs_o Output Generated: 20200715T13:23

Overall Survival (FAS)

In the full analysis set, OS was defined as the time from the date of enrolment (i.e. date of leukapheresis) to the date of death from any cause. A summary of OS estimates in the full analysis set is provided in Table 18. A graphical display of the KM OS curve is provided in figure 9.

Table 18: OS (Cohort 1 Full Analysis Set)

	Cohort 1 (N = 74)
OS[a]	
Number of subjects, n	74
Died, n (%)	21 (28)
Alive, n (%)	53 (72)
KM median (95% CI) OS time (months)	NR (21.1, NE)
Min, max OS time (months)	0.4, 33.0+
Survival rate (% [95% CI]) by KM estimate	
3 months	91.8 (82.7, 96.2)
6 months	83.2 (72.3, 90.1)
9 months	77.1 (65.3, 85.3)
12 months	77.1 (65.3, 85.3)
15 months	67.5 (52.1, 78.9)
18 months	67.5 (52.1, 78.9)
21 months	67.5 (52.1, 78.9)
24 months	64.3 (48.3, 76.4)

Data cutoff date = 24JUL2019
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; Max, maximum; Min, minimum; NE, not estimable; NR, not reached; OS, overall survival; "+" indicates censored record.
Note: Percentages are based on the number of subjects enrolled.
a OS is defined as the time from the enrollment date to the date of death from any cause. Subjects who were alive at the analysis data cutoff date were censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date were censored at the data cutoff date.

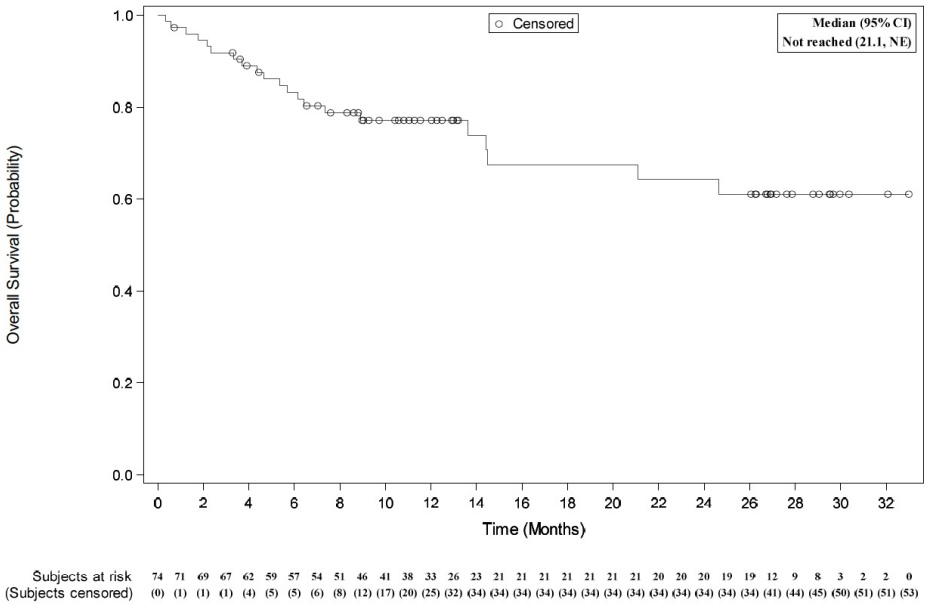


Figure 9. Kaplan-Meier of OS (Cohort 1 Full Analysis Set)

Data cutoff date = 24JUL2019
Abbreviations: CI, confidence interval; NE, not estimable; OS, overall survival.

The updated analysis with data cutoff date 31 December 2019 provided the following data:

Table 19. Overall Survival (Cohort 1: KTE-X19) (Inferential Analysis Set)

	Cohort 1 (N = 60)
OS[a]	
Number of subjects, n	60
Died, n (%)	16 (27)
Alive, n (%)	44 (73)
KM median (95% CI) OS time (months)	NR (NE, NE)
Min, max OS time (months)	1.2, 37.6+
Survival rate (% [95% CI]) by KM estimate	
3 months	95.0 (85.3, 98.4)
6 months	86.7 (75.1, 93.1)
9 months	83.3 (71.2, 90.7)
12 months	83.3 (71.2, 90.7)
15 months	76.0 (62.8, 85.1)
18 months	76.0 (62.8, 85.1)
21 months	72.4 (57.5, 82.8)
24 months	68.8 (52.7, 80.3)
27 months	68.8 (52.7, 80.3)
30 months	68.8 (52.7, 80.3)
33 months	68.8 (52.7, 80.3)
36 months	68.8 (52.7, 80.3)

Data cutoff date = 31DEC2019, snapshot date = 10JUN2020
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; NR, not reached; OS, overall survival; "+" indicates censored record.
Note: Percentages are based on the inferential analysis set, ie, the first 60 subjects treated with KTE-X19 in Cohort 1 who have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment.
a. OS is defined as the time from the KTE-X19 infusion date to the date of death from any cause. Subjects who were alive by the analysis data cutoff date were censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date were censored at the data cutoff date.

Data Source: ADSL, ADTTE Program Name: t_os Output Generated: 20200715T13:22

Table 20. Overall Survival (Cohort 1: KTE-X19) (Full Analysis Set)

	Cohort 1 (N = 74)
OS[a]	
Number of subjects, n	74
Died, n (%)	23 (31)
Alive, n (%)	51 (69)
KM median (95% CI) OS time (months)	NR (24.6, NE)
Min, max OS time (months)	0.4, 38.2+
Survival rate (% [95% CI]) by KM estimate	
3 months	91.8 (82.7, 96.2)
6 months	83.6 (72.9, 90.3)
9 months	78.1 (66.7, 86.0)
12 months	76.6 (65.1, 84.8)
15 months	69.9 (57.5, 79.3)
18 months	69.9 (57.5, 79.3)
21 months	69.9 (57.5, 79.3)
24 months	66.5 (52.8, 77.1)
27 months	63.2 (48.5, 74.8)
30 months	63.2 (48.5, 74.8)
33 months	63.2 (48.5, 74.8)
36 months	63.2 (48.5, 74.8)

Data cutoff date = 31DEC2019, snapshot date = 10JUN2020
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; NR, not reached; OS, overall survival; "+" indicates censored record.
Note: Percentages are based on the full analysis set.
a. OS is defined as the time from the enrollment date to the date of death from any cause. Subjects who were alive by the analysis data cutoff date were censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date were censored at the data cutoff date.

Data Source: ADSL, ADTTE Program Name: t_os_o Output Generated: 20200715T13:23

Other secondary endpoints

Across all 5 domains of the EQ-5D, the proportion of subjects who reported no health problems at screening ranged from 66% to 95%, with the highest percentages observed for mobility (85%), self-care (95%), and usual activity (82%). HRQoL improvements over time are indicated by increases of ≥ 16 percentage points being observed by Month 3. In addition, the proportion of subjects reporting more severe problems for mobility, self-care, and usual activities relative to screening, improved significantly by Month 6.

For the visual analogue scale (VAS), the median score was 85.0 (range: 45 to 100) at screening and 78.0 (range: 38 to 100) at Week 4, with higher median scores of 83.0 (range: 40 to 100) at Month 3 and 90.0 (range: 20 to 100) at Month 6. The proportion of patients with a decrease of ≥ 10 points in VAS scores relative to screening was 50% at Week 4, 29% by Month 3, and 12% by Month 6.

The study was not designed to evaluate associations between efficacy outcomes or AEs and pre-infusion product characteristics.

Secondary endpoints in the Inferential Analysis Set

In the inferential analysis set, the ORR using the investigators' assessment of response was 88% (53 of 60 subjects, 95% CI per the Clopper-Pearson method: 77.4%, 95.2%), and the CR rate was 70% (42 of 60 subjects, 95% CI per the Clopper-Pearson method: 56.8%, 81.2%). Objective response and CR using the investigators' assessment had a concordance rate of 95% (κ = 0.70; 95% CI: 0.39, 1.00) and 90% (κ = 0.77, 95% CI: 0.60, 0.94), respectively, with the ORR and CR rate using central assessment.

Subjects responded a median of 1.0 month (range: 0.8 to 3.1 months) after the KTE-X19 infusion as determined by central assessment. After a median DOR follow-up of 8.6 months, the median KM DOR was not reached, with 34 of 60 subjects in the inferential analysis set (57%) in an ongoing response as of the data cutoff date. The longest response duration was 29.2 months as of the data cutoff date.

PFS rate estimates at 6 months and 12 months using central assessment in the inferential analysis set were 77.0% and 60.9%, respectively, and the KM median PFS was not reached with a median potential follow-up of 12.3 months (range: 7.0 to 32.3 months). As of the data cutoff date, the longest PFS was 30.2 months. Among subjects who achieved a CR, PFS rate estimates at 6 months and 12 months were 100% and 76.6%, and the KM median PFS was not reached.

OS rate estimates for subjects in the inferential analysis set at 6 months and 12 months were 86.7% and 83.2%, respectively, and the KM median OS was not reached after a median potential follow-up of 12.3 months (range: 7.0 to 32.3 months). Among subjects in the inferential analysis set who achieved a CR, OS rate estimates at 6 months and 12 months were 100.0% and 97.2%, respectively, and the median OS was not reached.

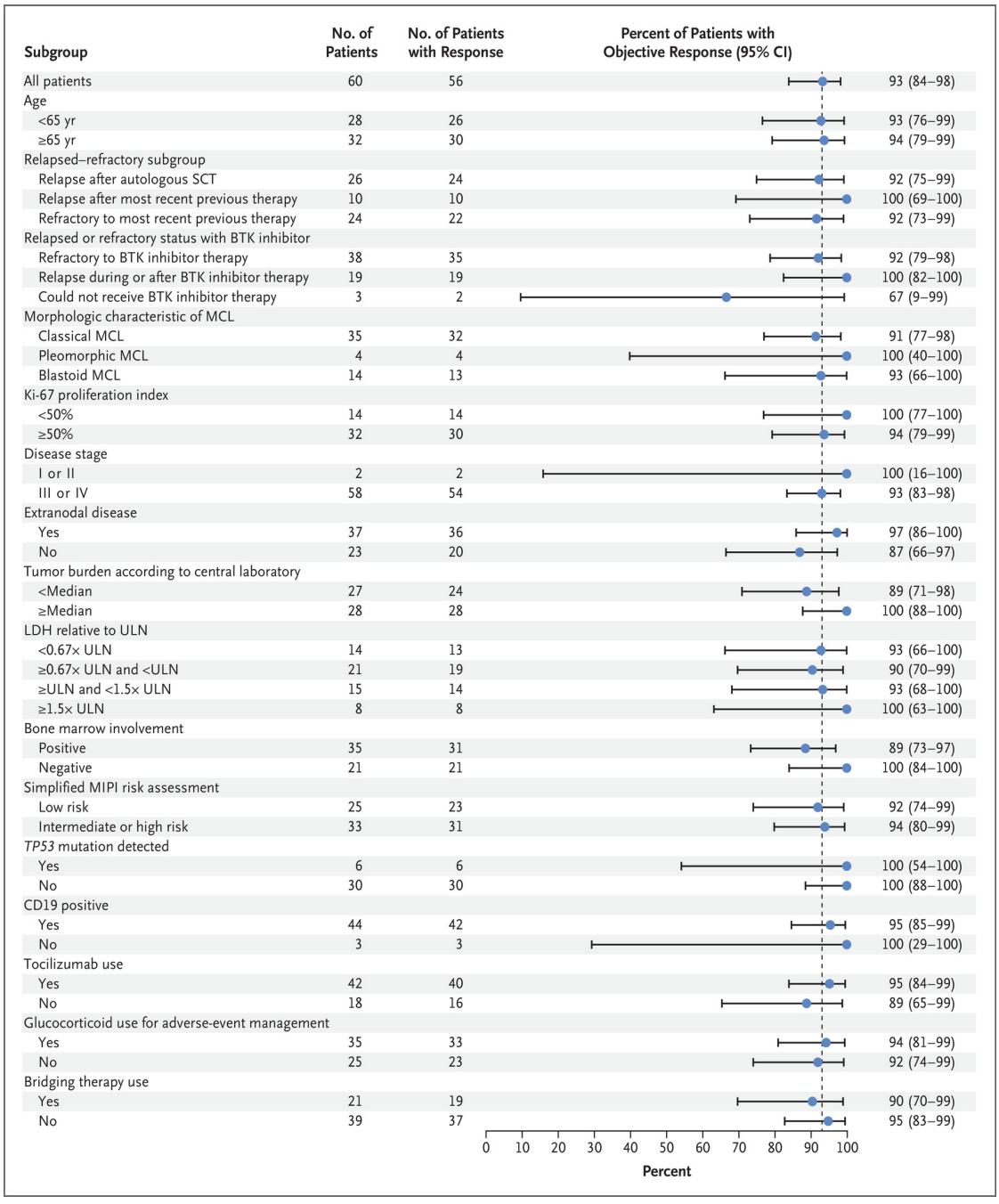
Efficacy Results in Cohort 2 for information purposes; Cohort 2 descriptive only

ORR per central assessment was 93% (13 of 14 subjects, 95% CI per the Clopper-Pearson method: 66.1%, 99.8%), and the CR rate was 64% (9 of 14 subjects, 95% CI per the Clopper-Pearson method: 35.1%, 87.2%) in the MITT set.

After a median follow-up of 11.3 months for DOR, the median KM DOR using the central assessment of response was not reached, with 8 of 14 subjects in the modified intent-to-treat analysis set (57%) in an ongoing response as of the data cutoff date. PFS rate estimates using central assessment at 6 months and 12 months were each 77.9%, and the KM median PFS was not reached with a median potential follow-up of 16.0 months (range: 13.9 to 18.0 months). OS rate estimates at 6 months and 12 months for subjects in Cohort 2 who received KTE-X19 were 92.9% and 78.6%, respectively, and the KM median OS was not reached with a median potential follow-up of 16.0 months (range: 13.9 to 18.0 months).

Ancillary analyses

The following table (**table 21**) provides an overview of ancillary analysis:



Subgroup	No. of Patients	No. of Patients with Response	Percent of Patients with Objective Response (95% CI)
All patients	60	56	93 (84–98)
Age			
<65 yr	28	26	93 (76–99)
≥65 yr	32	30	94 (79–99)
Relapsed–refractory subgroup			
Relapse after autologous SCT	26	24	92 (75–99)
Relapse after most recent previous therapy	10	10	100 (69–100)
Refractory to most recent previous therapy	24	22	92 (73–99)
Relapsed or refractory status with BTK inhibitor			
Refractory to BTK inhibitor therapy	38	35	92 (79–98)
Relapse during or after BTK inhibitor therapy	19	19	100 (82–100)
Could not receive BTK inhibitor therapy	3	2	67 (9–99)
Morphologic characteristic of MCL			
Classical MCL	35	32	91 (77–98)
Pleomorphic MCL	4	4	100 (40–100)
Blastoid MCL	14	13	93 (66–100)
Ki-67 proliferation index			
<50%	14	14	100 (77–100)
≥50%	32	30	94 (79–99)
Disease stage			
I or II	2	2	100 (16–100)
III or IV	58	54	93 (83–98)
Extranodal disease			
Yes	37	36	97 (86–100)
No	23	20	87 (66–97)
Tumor burden according to central laboratory			
<Median	27	24	89 (71–98)
≥Median	28	28	100 (88–100)
LDH relative to ULN			
<0.67× ULN	14	13	93 (66–100)
≥0.67× ULN and <ULN	21	19	90 (70–99)
≥ULN and <1.5× ULN	15	14	93 (68–100)
≥1.5× ULN	8	8	100 (63–100)
Bone marrow involvement			
Positive	35	31	89 (73–97)
Negative	21	21	100 (84–100)
Simplified MIPI risk assessment			
Low risk	25	23	92 (74–99)
Intermediate or high risk	33	31	94 (80–99)
TP53 mutation detected			
Yes	6	6	100 (54–100)
No	30	30	100 (88–100)
CD19 positive			
Yes	44	42	95 (85–99)
No	3	3	100 (29–100)
Tocilizumab use			
Yes	42	40	95 (84–99)
No	18	16	89 (65–99)
Glucocorticoid use for adverse-event management			
Yes	35	33	94 (81–99)
No	25	23	92 (74–99)
Bridging therapy use			
Yes	21	19	90 (70–99)
No	39	37	95 (83–99)

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application.

These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of efficacy for trial KTE-C19-102 (ZUMA-2)

Title: A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)			
Study identifier	KTE-C19-102		
Design	A Phase 2, multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in subjects with relapsed or refractory (r/r) Mantle Cell Lymphoma (MCL) whose disease had progressed on anthracycline or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib and/or acalabrutinib).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		After completing anti-CD19 chimeric antigen receptor (CAR) T cell infusion, all subjects will be followed in the post-treatment assessment period counting from Day 0 to Month 3 visit. Not applicable After Month 3 visit, all treated subjects will be followed in a long-term follow-up period for survival and disease status. The duration of the study is planned to be up to 15 years
Hypothesis	The hypothesis is that the objective response rate (ORR) to KTE-X19 in Cohort 1 KTE-X19 subjects is significantly greater than 25% at the 1-sided significance level of 0.025.		
Treatments groups	KTE-X19, Cohort 1		Single infusion of KTE-X19 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg.
Endpoints and definitions	Primary endpoint	Objective response rate (ORR)	ORR is defined as the incidence of complete response (CR) or partial response (PR) using central assessment per the Lugano Classification {Cheson 2014}.
	Secondary endpoint	Duration of response (DOR)	DOR was defined only for subjects who had an objective response (CR or PR) and was the time from the first objective response to disease progression or death.
		Progression-free survival (PSF)	PFS was defined as the time from the KTE-X19 infusion date to the date of disease progression or death from any cause. For PFS in intention to treat (ITT) set, enrollment (leukapheresis) date was used as starting time.
		Overall survival (OS)	OS was defined as the time from the KTE-X19 infusion to the date of death from any cause. For OS in ITT set, enrollment (leukapheresis) date was used as starting time.
Database lock	24 July 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Inferential analysis set consists of the first 60 patients treated with KTE-X19 who were evaluated for response 6 months after the Week 4 disease assessment after KTE-X19 infusion.		
Descriptive statistics and estimate variability	Treatment group	**KTE-X19, Cohort 1 Inferential analysis set**	
	Number of subjects	60	
	ORR (CR+PR) n(%), [95% CI per the Clopper-Pearson Method]	56 (93%), [83.8, 98.2]	
	CR n(%), [95% CI per the Clopper-Pearson Method]	40 (67%), [53.3, 78.3]	
	DOR median in months, [95% CI]	NR, [8.6, NE]	
	PFS median in months, [95% CI;]	NR, [9.2, NE]	
	OS Median in months, [95% CI]	NR, [24.0, NE]	
Effect estimate per comparison	Primary endpoint	Comparison groups	ORR vs. 25% historic ORR
		P-value	p < 0.0001
Notes	Results presented above are from analyses in the inferential analysis set using the central assessment of disease based on the Lugano Classification {Cheson 2014}. The historical control ORR of 25% was informed by 2 retrospective studies of patients with r/r MCL who had progressed following treatment with a BTK inhibitor (a required prior therapy for ZUMA-2 eligibility) {Cheah 2015, Martin 2016}.		
Analysis description	**Minimum follow-up of 12-months post-infusion update (data cutoff 31 December 2019)**		
Analysis population and time point description	Inferential analysis set consists of the first 60 patients treated with KTE-X19 who were evaluated for response 6 months after the Week 4 disease assessment after KTE-X19 infusion.		
Descriptive statistics and estimate variability	Treatment group	**KTE-X19, Cohort 1 Inferential analysis set**	
	Number of subjects	60	
	ORR (CR+PR) n(%), [95% CI per the Clopper-Pearson Method]	55 (92%), [81.6, 97.2]	
	CR n(%), [95% CI per the Clopper-Pearson Method]	40 (67%), [53.3, 78.3]	

	DOR median in months, [95% CI]	NR, [13.6, NE]
	PFS median in months, [95% CI;]	NR, [9.6, NE]
	OS Median in months, [95% CI]	NR, [NE, NE]
Analysis description	Intention to treat (ITT) set consists of all subjects who were leukapheresed (data cutoff: 31 December 2019).	
Descriptive statistics and estimate variability	Treatment group	**KTE-X19, Cohort 1 ITT set**
	Number of subjects	74
	ORR (CR+PR) n(%), [95% CI per the Clopper-Pearson method]	62 (84%), [73.4, 91.3]
	CR n(%), [95% CI per the Clopper-Pearson Method]	44 (59%), [47.4, 70.7]
	DOR median in months, [95% CI]	NR, [10.4, NE]
	PFS median in months, [95% CI;]	16.2, [9.9, NE]
	OS Median in months, [95% CI]	NR, [24.6, NE]
Notes	In the ITT set, PFS was defined as the time from the date of enrollment (ie, date of leukapheresis) to the date of disease progression or death from any cause. OS was defined as the time from enrollment (ie, date of leukapheresis) to the date of death from any cause.	

NE, not estimable; NR, not reached

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

The average age of the disease condition is 60 years with a gender distribution male : female = 4:1. The median age of the study population in ZUMA 2 was 65 years (range: 38 to 79) and the gender distribution was approximately corresponding.

With regard to the gender, there have been differences observed: For female patients, higher levels of anti-CD 19 T cell levels are reached, and there is a discrepancy in complete response rates at males and females

(61% for males and 50% for females). However, there is no conclusion possible due to the limited number of patients.The limited knowledge regarding gender for the use of KTE.X19 in this clinical setting is one of the reason for adopting a conditiona Marketing authorisation for tecartus, post authorisation studies have been imposed to provide further information on this subgroup of patients.

Similar lack of data and confirmatory efficacy in elderly and more severe patients is not clear based on the set of data provided in the pivotal study so far. The specific obligation adopted together with the Conditional Marketing authorisation are set up to further complement this missing data and to reach completeness of the dossier.

Supportive study(ies)

Historical Control

The historical control comprises 6 clinical trials. The meta-analysis was to be used to calculate a pooled ORR reflective of clinical outcomes with therapies that are currently available and to support the preselected control ORR of 25%.

The following criteria were required for a study's inclusion in the meta-analysis:

- Subjects must have had r/r MCL.
- Subjects' disease must have progressed while receiving, or relapsed after, a BTK inhibitor.
- Subjects must have received salvage therapy after disease progression or relapse following the BTK inhibitor.
- Response outcomes must have been included in the publication.

Through the literature search, 255 subjects across 6 published studies were identified for inclusion in the meta-analysis. In addition to the 2 studies (N = 92) originally used to determine the historical control rate in ZUMA-2, 4 studies were identified that met the criteria for inclusion in the meta-analysis. All 6 of these studies described outcomes for patients who had discontinued ibrutinib. Average ORR on salvage therapy in these studies was as follows:

Table 23:

Study (sorted by response)	**ORR (on salvage therapy after BTKi)**	**N (on salvage therapy after BTKi)**
Dreyling 2016	20%	40
Martin 2016*	26%	73 (61 evaluable)
Jain 2018a	27%	36
Wang 2017	29%	58
Cheah 2015*	32%	31
Epperla 2017	42%	29

* Included in original derivation of historic ORR rate

Two additional studies were identified but not incorporated in the meta-analysis. These studies had much higher ORR on salvage therapy after BTKi of ~50% (Jain 2018b), 53% (Eyre 2019), 67% (Regny 2019), and 82% (McCulloch 2019). The applicant did not include these studies due to one study allowing compassionate use of venetoclax, which is not approved for the treatment of r/r MCL in USA or Europe, and the other due to availability of only preliminary data.

The pooled ORR from the meta-analysis of 6 studies was 28% (95% CI: 23%, 34%), which is clinically consistent with the historical control ORR of 25%. In addition, response rates published in these studies were based on investigator assessment, and the majority were single-institution studies. Considering that 1) response rates determined by central assessment are often lower than those determined by investigator review (Zhang 2017), and 2) the primary efficacy endpoint of ZUMA-2 is the ORR per central assessment, the results of the meta-analysis support the pre-specified 25% historical control ORR in ZUMA-2.

Primarily, the use of the historical control rate for ORR was based on two retrospective studies (Cheah 2015 and Martin 2016). In these two studies, outcomes after salvage therapy were evaluated in patients with r/r MCL who had progressed during or following treatment with a BTK inhibitor (a required prior therapy for ZUMA-2 eligibility). Both studies demonstrated that patients with r/r MCL who had ≥ 3 prior lines before receiving the BTK inhibitor had ORRs to salvage therapy of approximately 25%.

In February 2019, an updated literature search was undertaken to further understand the outcomes of patients with r/r MCL whose disease had progressed during or following treatment with a BTK inhibitor. Studies identified through this search were to be included in a meta-analysis of ORRs to salvage therapy after discontinuing treatment with a BTK inhibitor. The meta-analysis was to be used to calculate a pooled ORR reflective of clinical outcomes with therapies that are currently available and to support the preselected control ORR of 25%. The following criteria were required for a study's inclusion in the meta-analysis:

☐ Subjects must have had r/r MCL.

☐ Subjects must have progressed while receiving, or relapsed after receiving, a BTK inhibitor.

☐ Subjects must have received salvage therapy after progression or relapse following the BTK inhibitor.

☐ Response outcomes must have been included in the publication.

Through this literature search, 255 subjects across 6 published studies were identified for inclusion in the meta-analysis. In addition to the 2 studies originally used to determine the historical control rate in ZUMA-2, 4 studies were identified that met the criteria for inclusion in the meta-analysis (Dreyling 2016, Epperla 2017, Jain 2018a, Wang 2017). All 6 of these studies described outcomes for patients who had discontinued ibrutinib. Two additional studies that were identified from the literature search of outcomes following BTK inhibitor treatment, were not included in the meta-analysis: 1 due to the preliminary single institution report of the results (Jain 2018b) and the subsequent inclusion of some of the same subjects in ZUMA-2, and 1 study of venetoclax, which is not approved for the treatment of r/r MCL in the US or Europe and was administered off-label via a compassionate use programme (Eyre 2019).

After the meta-analysis was conducted in February 2019, 2 additional studies of outcomes following BTK inhibitor treatment were identified (both conference presentations) (McCulloch 2019, Regny 2019). However, the meta-analysis was not updated because the studies included preliminary data that had not yet been peer reviewed.

The applicant provided satisfactory responses on the concerns with regard to the representativeness of the historical control data. Based on them, it appears the historical controls may have been somewhat less "fit"

than the study population (i.e. there were more patients with ECOG ≥2, fewer patients with prior STC, and (for the 293 patients where data were available) only approximately half of patients received combination salvage therapies). Furthermore, for several studies the baseline data (including the data on number of prior therapies) seem to be recorded at the start of BTKi treatment, thus indicating that the historical cohort were more heavily pre-treated at the time of post-BTKi salvage therapy.

Therefore, there is heterogeneity amongst the several trials serving as historical control and the representativeness of the historical data for the study population cannot be verified. This remaining uncertainty supports the decision of a conditional approval and the necessity to amend the clinical data in order to be comprehensive.

2.5.3. Discussion on clinical efficacy

The applicant submitted a marketing authorisation application (MAA) for KTE-X19 at a dose of 2x10Exp6 cells/kg, indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

Design and conduct of clinical studies

The primary efficacy endpoint of ORR (CR and PR) assessed by central assessment as well as the key secondary endpoints of DOR and PFS have been accepted in prior protocol assistance.

As currently, there is only little information on general efficacy results in some of the subgroups (female, elderly and more severe patients). This will be further addressed by the specific obligations imposed in the frame of the conditional marketing authorisation.

The pivotal data comes from one single, uncontrolled open-label ongoing, Phase 2 study, KTE-C19-102 (ZUMA-2), and is based on a two data cut-off points, 24th July 2019 and 31 December 2019.

Dose: No formal dose-finding studies were conducted. The proposed dose (Cohort 1: 2 x 10^6 anti-CD19 CAR T cells/kg), was informed by results obtained with Yescarta (axicabtagene ciloleucel) administered to subjects with refractory aggressive large B-cell lymphoma (DLBCL) in the ZUMA-1 trial, and further substantiated by PK cell expansion data. The data on the lower dose are too limited to draw any conclusion therefore, considering the shown efficacy and the balanced and manageable safety, the dose used in the pivotal study cohort 1 is considered acceptable.

Pivotal study design: The Zuma-2 study is an uncontrolled, open label, multicentre, Phase 2 study evaluating the safety and efficacy of KTE-X19 in two dose cohorts of subjects with r/r MCL. The uncontrolled study design, has been considered acceptable in prior scientific advice. The pivotal cohort (Cohort 1) was to enrol and treat up to 80 subjects with KTE-X19 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. An additional ten subjects enrolled in Cohort 1 received Yescarta (axicabtagene ciloleucel). Seventeen subjects were enrolled in Cohort 2 and received 0.5 x 10^6 anti-CD19 CAR T cells/kg. Only patients enrolled to receive KTE-X19 in Cohort 1 contributed to the primary efficacy analyses.

The applicant defined the first 60 subjects treated with KTE-X19 (inferential analysis set) as the primary efficacy population that would form the basis for statistical hypothesis testing. This was not endorsed by the CHMP (EMEA/H/SA/3117/7/2019/PA/ADT/PR/III), as it contradicts the ITT principle and makes the primary analysis population not clearly representative of any definable external population. The assessment therefore focused on data for the full analysis set and the required presentation of the data for the FAS has been provided, indicating that there were no noticeable differences.

Subjects were considered enrolled at the time of leukapheresis. Bridging therapy was allowed at the discretion of the investigator and included single agent drugs from the same classes as those used in the previous treatment lines (dexamethasone or a BTKi). The CHMP expressed concern over the potential carry over effect from bridging therapy (EMEA/H/SA/3117/7/2019/PA/ADT/PR/III). In accordance to the clinical trial protocol, subjects receiving bridging therapy were to have a repeat diagnostic PET-CT scan prior to conditioning chemotherapy.

The non-myeloablative conditioning regimen was identical to that used for Yescarta (axicabtagene ciloleucel) in large B-cell lymphoma, and could be repeated if the KTE-X19 infusion was delayed by > 2 weeks. This is considered acceptable.

Subjects who achieved a PR or CR had the option to receive a second course of conditioning chemotherapy and KTE-X19 if experiencing CD-19 positive disease progression > 3 months after the initial infusion. Two subjects were retreated with KTE-X19, where 1 subject achieved a best overall response of CR and the other subject had a best overall response of PD, respectively.

Patient population: The study included patients with pathologically confirmed r/r MCL (documented by either overexpression of cyclin D1 or presence of t(11;14)). Patients were to have received up to 5 prior regimens for MCL, including an anthracycline or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody as well as a BTKi. The initial discrepancy between the study population which did not specify a lower limit to prior therapies and the proposed indication (r/r MCL, i.e. from 2nd line) was corrected by the applicant.

Further key eligibility criteria included PS 0-1, no toxicities from previous therapies and adequate renal, hepatic, pulmonary, and cardiac function. Patients with a history of allo-SCT were excluded, as were patients with a history of HBV and HIV infection. These criteria define a rather selected patient population, with implications for the external validity of the trial and the comparisons to external data on which the ORR cut-off has been established.

Endpoints: The primary endpoint, ORR by IRRC, is acceptable in the context of an uncontrolled trial. Responses were assessed according to the Lugano Classification, which is endorsed. However, the requirement for bone marrow confirmation of CR in patients with baseline bone marrow involvement was only introduced in protocol Amendment 5 (i.e. after inclusion of the first 28 patients in Cohort 1). However the majority of patients with baseline bone marrow involvement has been evaluated with a bone-marrow confirmed CR.

The secondary endpoints include endpoints conventional for oncology trials such as DOR, PFS and OS and are considered acceptable.

ORR control rate: The historical control rate for ORR (25%) was pre-specified based on 2 retrospective published studies evaluating post-BTKi salvage therapy outcomes in patients with r/r MCL. Subsequently, a meta-analysis of 6 studies (including the original 2 studies) was undertaken (February 2019), to further inform the historical response rates. The pooled ORR from this meta-analysis was 28% (95% CI: 23%, 34%). Concerns were expressed by the CHMP (EMEA/H/SA/3117/7/2019/PA/ADT/PR/III) that the ORR cut-off was not an a priori decision and that an ORR above 25% would not be considered sufficiently compelling in the context of a single pivotal, single arm trial. These issues, however, are considered overcome by the high response rates reported for KTE-X19 (ORR 85%, 95% CI 75.0%, 92.3%), indicating significant results would be achieved also with a substantially higher ORR success criterion.

Nevertheless, there are several uncertainties related to the way the historical control rate was defined and its representativeness for the study population. Specifically, it remains unclear how heterogeneity between studies in the meta-analysis affected the estimation of the pooled ORR. Furthermore, limited details were provided

concerning the search protocol and the publications excluded from the meta-analysis. In conclusion the study population may include a larger proportion of patients which would have been eligible for allo-SCT in a standard of care setting, for which the outcomes of the historical cohort may not be representative.

Statistical methods, interim analysis and study conduct: The statistical design, sample sizes, sensitivity analyses and alpha correction for the pre-specified interim analyses are considered acceptable. Four interim analyses to be reviewed by DSMB were conducted (3 in Cohort 1 and 1 in Cohort 2). An additional interim analysis (Cohort 1 interim analysis 3) was performed for a Kite internal review. The implication of this analysis for the trial integrity requires further clarification. Furthermore, there is a discrepancy between the description of the interim analyses and data monitoring in the study protocol and the series of events as described in CRS. Whereas the study protocol describes a Cohort 1, interim 2 analysis to be conducted after 20 subjects had the opportunity to be followed for 3 months post infusion, the CRS reports that the opening of dosing Cohort 2 was based on an interim analysis of 28 subjects, followed for 3 months after the CAR T-cell infusion. In addition, a late protocol amendment (Amendment 5) describes the "identification" of two interim analyses (Cohort 1, analysis 2 and 3) and the addition of one interim analysis (Cohort 1, analysis 4). Thus, there is uncertainty concerning the number of interim analyses conducted and the degree to which these analyses were pre-specified, including the time-point at which they were introduced into the study protocol.

The original protocol, dated 12 March 2015, was amended 6 times, with subjects receiving KTE-X19 in Cohort 1 enrolling from Amendment 3 and onwards. Several key design elements were introduced in protocol Amendment 5, including the definition of the primary efficacy population and the statistical testing strategy for the primary endpoint. The applicant is requested to clarify the conduct of the study both with respect to the timing of the interim analyses, and the protocol amendments (Section 3.3), and to justify that these interim analyses and protocol amendments did not compromise the integrity of the study.

Efficacy data and additional analyses

The provided results are based on one main clinical trial, ZUMA 2, an ongoing, uncontrolled open-label, multicentre trial with two treatment cohorts (Cohort 1: 2.0x10Exp6 cells/kg; Cohort 2: 0.5x10Exp6 cells/kg) with a primary data cut-off 24 July 2019. Additional efficacy results for a secondary data cut-off 31 December 2019 have been provided on request. The study was conducted in 40 clinical centres in USA, Netherlands, France and Germany. Dose selection for Cohort 1 is based upon pharmacology results due to an interim analysis in ZUMA-2 indicating the dose of 2.0x10Exp6 cells/kg to be safe and effective, and on results of the ZUMA-1 trial where the administered CAR T-Cell product was axicabtagene ciloleucel. Cohort 1 of ZUMA 2 is regarded the pivotal data set. Of the 74 patients that were included in the trial 68 subjects received treatment with KTE-X19 at the target dose of 2x10Exp6 cells/kg. In Cohort 2, which is descriptive only, 14 subjects received treatment with KTE-X19 at the target dose of 0.5x10Exp6 cells/kg.

The primary efficacy endpoint of ORR (CR and PR) assessed by central assessment as well as the key secondary endpoints of DOR and PFS have been accepted in prior scientific advice. The study population has been analyzed by FAS (n=74), IAS (n=60), mITT (n=68) including subgroup sets.

As requested, the applicant provided an update on efficacy data, presented for FAS only for cut-off date 24 July 2019 and 31 December 2019.

Cut-off-24 July 2019:

The FAS is not significantly different in terms of durability of responses observed in patients achieving a best ORR of CR, PR. The FAS confirms the previous assessment of PFS or OS, and is consistent with the results from

the IAS. The subgroup analyses for ORR, DOR and ongoing response are overall consistent with the results based on the inferential analyses set. ORRs ranging from 50% to 100% are reported in the FAS across the subgroups analysed, where ORRs ranged from 75% to 100% in the inferential analysis set. In all subgroups with >5 subjects the lower limit of the 95% confidence intervals were above the pre-specified historic control ORR of 25% and also above the upper CI reported for the meta-analysis (34%).

Cut-off 31 December 2019:

The results are consistent with the analyses based on the 24 July 2019 cut-off, with ORRs from 50% to 100% across the subgroups analysed. In all subgroups with >5 subjects the lower limit of the 95% confidence intervals were above the pre-specified historic control ORR of 25% and also above the upper CI reported for the meta-analysis (34%).The median DOR was not reached (95% CI:10.4 months, NE) with a median follow-up time for DOR of 13.8 months (95% CI: 11.3, 20.5 months), and no subgroup analysis of DOR is therefore presented.

In subgroups with ≥ 5 subjects, the ongoing response rates at data cutoff ranged from 17% to 70% and were generally consistent with the analysis at the 24 July 2019 cut-off. A durable response is observed in patients achieving a best ORR of CR (median DOR (95% CI: 14.4, NE). For the 18 subjects who achieved a PR, the median DOR remains short (2.2 months, 95% CI: 1.4, 4.9 months). Estimates of the ongoing response rate at 6 months and 12 months were each 25.9%. Sensitivity analyses remains consistent between the analysis sets.

In the updated analysis set, median PFS was still not reached in patients achieving a best ORR of CR, with PFS rate estimates at 6 and 12 months of 100% and 80.2%, respectively. Median PFS among subjects who achieved a PR was 5.4 months (95% CI: 3.3, 6.7 months), with PFS rate estimates of at 6 months and 12 months of 46.3% and 26.5%, respectively. Consistency across most subgroups was observed, although lower point estimates were reported in some subgroups with small patient numbers. CIs were wide and overlapping.

The quality of life data has been collected with the EQ-5D questionnaire throughout the trial. While very welcome on a principle level, interpretation is hampered by lack of control and an open label design.

The definition of patients to be treated with KTE-X19, is now addressed satisfactorily in the agreed indication, which now reflects adequately the patient population in the clinical trial.

Additional efficacy data needed in the context of a conditional MA

The current clinical data set is not regarded to be comprehensive as the number of evaluated patients in the ZUMA-2 trial, an open label study, is regarded rather low; long-term data are not available yet. Furthermore, data on some subgroups such as female, elderly and more severely diseased patients are non exhaustive at this point in time. Moreover, as to the historical control, there is heterogeneity in the populations, and the representativeness of the historical data cannot be verified.

Additional efficacy data will be generated post-authorisation, within a registry study and a long-term follow-up data collection from ZUMA-2. Data to be collected will provide further long term efficacy data together with reassurance of efficacy in subgroups of patients (female, elderly and more severe patients) which are now underrepresented in the data set provided in the pivotal study.

2.5.4. Conclusions on the clinical efficacy

The definition of patients to be treated with KTE-X19, is now addressed satisfactorily as the applicant updated the indication, which now reflects adequately the patient population in the clinical trial.

The unmet medical need for effective treatments for patients suffering from r/r MCL after failure of BTK inhibitors is acknowledged. The results on primary and secondary endpoints in the ZUMA-2 trial indicate efficacy of KTE-X19 for the treatment of r/r MCL in the target population.

The provided update on efficacy-analyses with the cut-off date of 31 December 2019 indicates consistency of results on subgroup analysis for ORR and DOR compared with results of the cut-off date 24 July 2019. Moreover, the results in the FAS with regard to ORR, CR, PFS and OS confirm the efficacy of KTE-X19 as evaluated on basis of the results in the IAS.

The remaining uncertainties result from the limited dataset in the ZUMA-2 pivotal Cohort 1. The applicant agreed to amend the data post-marketing by a registry for the evaluation of efficacy of KTE-X19 in terms of objective response rate as primary objective including the required population (female, elderly and more severe patients) and to include further specific assessments for efficacy as secondary objectives. Moreover, the safety of KTE-X19 will be assessed as secondary objective in this post-approval study.

As regards the required long-term follow up of patients in the pivotal cohort of the ZUMA-2 trial, the applicant is required to provide long-term results for efficacy and safety for those patients and to submit the anticipated study report in 2022 to the EMA.

Therefore, the CAT considers the following measures necessary to ensure the follow-up of efficacy:

- A long term follow up: In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory Mantle cell Lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.

The CAT furthermore considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.
- In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2.

The CHMP endorse the CAT conclusion on clinical efficacy as described above.

2.6. Clinical safety

Patient exposure

The safety data were obtained from 82 r/r MCL patients treated with KTE-X19 in the pivotal study ZUMA-2 with a data cutoff date of 31 December 2019. Additional safety data was presented for 116 patients treated with KTE-X19 in supportive studies (ZUMA-3, ZUMA-4, and ZUMA-8).

In the ZUMA-2 trial a total of 91 r/r MCL subjects were enrolled in the study and 82 (90%) subjects were treated with KTE-X19. Importantly, only the 68 patients in Cohort 1 received KTE-X19 at the target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. In Cohort 2 the 14 subjects received the dose of 0.5 x 10^6 anti-CD19 CAR T cells/kg.

In Cohort 1, 74 subjects were enrolled. 69 subjects (93%) received conditioning chemotherapy, and 68 subjects (92%) received KTE-X19. The median potential follow-up time from the KTE-X19 infusion for all subjects dosed in Cohort 1 was 16.8 months (range: 7.2 to 37.6 months)

In Cohort 2, 17 subjects were enrolled, 15 subjects (88%) received conditioning chemotherapy, and 14 subjects (82%) received KTE-X19. The median potential follow-up time from the KTE-X19 infusion for subjects in Cohort 2 was 21.3 months (range: 19.1 to 23.2 months).

All subjects in the study received conditioning chemotherapy consisting of fludarabine 30 mg/m2/day and cyclophosphamide 500 mg/m2/day administered for 3 days. Bridging therapy was permitted and administered to a total of 32 subjects at the discretion of the treating investigator. In Cohort 1, 25 subjects (37%) received bridging therapy consisting mostly of ibrutinib (14 subjects, 21%) and dexamethasone (12 subjects, 18%). In cohort 2, a total of 7 subjects (50%) received bridging therapy.

There were 76 subjects treated with KTE-X19 in the US, 3 in France, 2 in the Netherlands and 1 in Germany. Sixty-eight (83%) patients were males and 14 (17%) were females, whereas 49% of the patients were < 65 years, 51% were ≥ 65 years.

Supporting data are provided from 3 Phase 1/2 studies of KTE-X19: KTE-C19-103 (ZUMA-3), KTE-C19-104 (ZUMA-4), and KTE-C19-108 (ZUMA-8) with a data cutoff date of 31 December 2019. In these studies, a total of 143 subjects were treated with various doses of KTE-X19 in different indications. Of note, there were only 13 patients in the supportive studies with various other indications who were treated with 2 x 10^6 anti-CD19 CAR T cells/kg.

Adverse events

Safety assessments included monitoring of AEs and use of concomitant medications to manage AEs, clinical laboratory analyses, vital sign measurements, physical examinations, important identified and potential risks seen for other CAR-T products. Subjects in ZUMA-2 were also administered the Mini Mental State Exam (MMSE), a 5 to 10-minute, 11-questions assessment that examines cognitive functions.

All 82 patients treated with KTE-X19 experienced at least one AE, 7% had worst grade 5, most of these in cohort 1. CRS was seen in 91%, neurologic AEs in 68%, cytopenia – thrombocytopenia in 70%, neutropenia in 85% and anaemia in 66%, infections in 56% and hypogammaglobulinaemia in 16%.

These AEs could be directly linked to the conditioning chemotherapy or to the administration of KTE-X19. The AEs described here are in line with the AEs of CAR T cell products and are a direct consequence of the mode of

action of these products. These AEs are expected to occur based on the previous experience with this product class.

The applicant has identified the following categories of risks associated with the clinical use of this drug product: CRS, neurologic events (including cerebral oedema), cytopenias, infections, hypogammaglobulinemia. There are some potential risks linked to the use of this product: secondary malignancy, immunogenicity, RCR, tumour lysis syndrome, and aggravation of GvHD. These risks are include din the RMP of the product and will be lowed post-marketing. Events of cardiac arrhythmias, cardiac failure, and autoimmune disorders were also examined. The important identified risks and the potential risks identified for KTE-X19 are similar to the AEs identified for this product class.

Table 24: Overall Summary of AEs (Cohorts 1 and 2 Safety Analysis Set)

	Cohort 1 (N = 68)	Cohort 2 (N = 14)	Overall (N = 82)
Any TEAE	68 (100)	14 (100)	82 (100)
Worst Grade 5	5 (7)	1 (7)	6 (7)
due to disease progression	3 (4)	0 (0)	3 (4)
Worst Grade ≥ 3	67 (99)	13 (93)	80 (98)
Any serious TEAE	48 (71)	8 (57)	56 (68)
Worst Grade 5	4 (6)	1 (7)	5 (6)
due to disease progression	2 (3)	0 (0)	2 (2)
Worst Grade ≥ 3	38 (56)	7 (50)	45 (55)
Any KTE-X19 related TEAE	66 (97)	14 (100)	80 (98)
Worst Grade 5	1 (1)	0 (0)	1 (1)
Worst Grade ≥ 3	54 (79)	10 (71)	64 (78)
Any serious KTE-X19 related TEAE	37 (54)	7 (50)	44 (54)
Worst Grade 5	1 (1)	0 (0)	1 (1)
Worst Grade ≥ 3	29 (43)	6 (43)	35 (43)
Any CRS or neurologic event[a]	63 (93)	14 (100)	77 (94)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	23 (34)	7 (50)	30 (37)
Any CRS[a]	62 (91)	13 (93)	75 (91)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	10 (15)	2 (14)	12 (15)
Any neurologic event	43 (63)	13 (93)	56 (68)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	21 (31)	6 (43)	27 (33)
Any serious neurologic event	22 (32)	4 (29)	26 (32)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	18 (26)	3 (21)	21 (26)
Any thrombocytopenia	50 (74)	7 (50)	57 (70)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	36 (53)	6 (43)	42 (51)
Any neutropenia	59 (87)	11 (79)	70 (85)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	58 (85)	11 (79)	69 (84)

Any anaemia	47 (69)	7 (50)	54 (66)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	36 (53)	6 (43)	42 (51)
Any infection	38 (56)	8 (57)	46 (56)
Worst Grade 5	1 (1)	0 (0)	1 (1)
Worst Grade ≥ 3	23 (34)	3 (21)	26 (32)
Any serious infection	20 (29)	3 (21)	23 (28)
Worst Grade 5	1 (1)	0 (0)	1 (1)
Worst Grade ≥ 3	18 (26)	3 (21)	21 (26)
Any hypogammaglobulinemia	13 (19)	0 (0)	13 (16)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	1 (1)	0 (0)	1 (1)
Any tumor lysis syndrome	1 (1)	0 (0)	1 (1)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	1 (1)	0 (0)	1 (1)

Data cutoff date = 31DEC2019
Abbreviations: AE, adverse event; CRS, cytokine release syndrome; TEAE, treatment-emergent adverse event.
Notes: A TEAE is defined as any AE with onset on or after the KTE-X19 infusion. AEs that occurred on/after retreatment are not included.
a CRS events are graded per the revised grading system of Lee and colleagues {Lee 2014}. All other events are graded per Common Terminology Criteria for Adverse Events version 4.03.
Source: modified from m5.3.5.3, Table 14.3.1.1.1a, Table 14.3.1.1.1b, Table 14.3.1.1.1c
Data Source: ADSL, ADAE Program Name: t_ae_sumry Output Generated: 20200224T15:44

Table 25: Subject Incidence of Treatment-emergent Adverse Events by Preferred Term and Worst Grade > 10% of Subjects

MedDRA Preferred Term n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any TEAE	82 (100)	0 (0)	2 (2)	12 (15)	62 (76)	6 (7)
Pyrexia	77 (94)	18 (22)	46 (56)	13 (16)	0 (0)	0 (0)
Anaemia	53 (65)	0 (0)	12 (15)	41 (50)	0 (0)	0 (0)
Hypotension	46 (56)	5 (6)	18 (22)	21 (26)	2 (2)	0 (0)
Neutrophil count decreased	43 (52)	0 (0)	1 (1)	5 (6)	37 (45)	0 (0)
Platelet count decreased	40 (49)	6 (7)	3 (4)	10 (12)	21 (26)	0 (0)
White blood cell count decreased	35 (43)	0 (0)	0 (0)	6 (7)	29 (35)	0 (0)
Chills	34 (41)	23 (28)	11 (13)	0 (0)	0 (0)	0 (0)
Fatigue	33 (40)	13 (16)	19 (23)	1 (1)	0 (0)	0 (0)
Hypoxia	33 (40)	2 (2)	15 (18)	10 (12)	6 (7)	0 (0)
Cough	31 (38)	19 (23)	12 (15)	0 (0)	0 (0)	0 (0)
Tremor	31 (38)	20 (24)	9 (11)	2 (2)	0 (0)	0 (0)
Neutropenia	30 (37)	0 (0)	2 (2)	6 (7)	22 (27)	0 (0)
Headache	29 (35)	18 (22)	10 (12)	1 (1)	0 (0)	0 (0)
Hypophosphataemia	29 (35)	3 (4)	9 (11)	16 (20)	1 (1)	0 (0)
Nausea	29 (35)	16 (20)	12 (15)	1 (1)	0 (0)	0 (0)
Hypoalbuminaemia	27 (33)	7 (9)	18 (22)	2 (2)	0 (0)	0 (0)
Hypokalaemia	26 (32)	16 (20)	5 (6)	3 (4)	2 (2)	0 (0)
Hyponatraemia	26 (32)	16 (20)	0 (0)	10 (12)	0 (0)	0 (0)
Tachycardia	26 (32)	19 (23)	7 (9)	0 (0)	0 (0)	0 (0)
Constipation	24 (29)	22 (27)	2 (2)	0 (0)	0 (0)	0 (0)
Alanine aminotransferase increased	23 (28)	14 (17)	2 (2)	6 (7)	1 (1)	0 (0)
Diarrhoea	23 (28)	13 (16)	6 (7)	4 (5)	0 (0)	0 (0)
Hypocalcaemia	23 (28)	9 (11)	9 (11)	4 (5)	1 (1)	0 (0)
Decreased appetite	21 (26)	11 (13)	10 (12)	0 (0)	0 (0)	0 (0)
Encephalopathy	21 (26)	4 (5)	4 (5)	7 (9)	6 (7)	0 (0)
Confusional state	20 (24)	5 (6)	6 (7)	9 (11)	0 (0)	0 (0)
Dyspnoea	20 (24)	8 (10)	7 (9)	4 (5)	1 (1)	0 (0)
Oedema peripheral	20 (24)	11 (13)	9 (11)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	19 (23)	2 (2)	4 (5)	4 (5)	9 (11)	0 (0)
Hyperglycaemia	17 (21)	7 (9)	5 (6)	5 (6)	0 (0)	0 (0)
Insomnia	17 (21)	12 (15)	5 (6)	0 (0)	0 (0)	0 (0)
Pleural effusion	17 (21)	6 (7)	7 (9)	3 (4)	1 (1)	0 (0)
Aspartate aminotransferase increased	16 (20)	7 (9)	1 (1)	8 (10)	0 (0)	0 (0)
Hypertension	16 (20)	1 (1)	6 (7)	9 (11)	0 (0)	0 (0)
Aphasia	15 (18)	5 (6)	6 (7)	4 (5)	0 (0)	0 (0)
Asthenia	15 (18)	10 (12)	4 (5)	1 (1)	0 (0)	0 (0)
Anxiety	14 (17)	9 (11)	5 (6)	0 (0)	0 (0)	0 (0)
Dizziness	14 (17)	9 (11)	2 (2)	3 (4)	0 (0)	0 (0)
Hypomagnesaemia	14 (17)	14 (17)	0 (0)	0 (0)	0 (0)	0 (0)
Leukopenia	14 (17)	0 (0)	1 (1)	4 (5)	9 (11)	0 (0)
Pneumonia	14 (17)	0 (0)	4 (5)	9 (11)	1 (1)	0 (0)
Blood creatinine increased	11 (13)	6 (7)	3 (4)	2 (2)	0 (0)	0 (0)
Hypogammaglobulinaemia	11 (13)	1 (1)	9 (11)	1 (1)	0 (0)	0 (0)
Sinus tachycardia	11 (13)	8 (10)	3 (4)	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection	11 (13)	0 (0)	9 (11)	2 (2)	0 (0)	0 (0)

Data cutoff date = 31DEC2019
Abbeviations: AE, adverse event; TEAE, treatment-emergent adverse event.
Note: Preferred terms are sorted in descending order of total frequency in the "Any" column.
TEAE is defined as any adverse event with onset on or after the anti-CD19 CAR T cells infusion. AEs occurred on/after retreatment are not included.
AEs are coded using MedDRA Version 22.1 and graded per CTCAE 4.03.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for that subject.
Percentages are calculated using the total number of subjects in the treatment group as the denominator.
For the AE with a missing CTCAE grade, it is counted in the 'Any' column only.

Data Source: ADSL, ADAE Program Name: t_teae Output Generated: 20200224T15:47

Table 26: Incidence of KTE-X19-related Adverse Events by Preferred Term and Worst Grade in > 10% of Subjects

MedDRA Preferred Term n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any KTE-X19-related AE	80 (98)	3 (4)	13 (16)	22 (27)	41 (50)	1 (1)
Pyrexia	76 (93)	18 (22)	47 (57)	11 (13)	0 (0)	0 (0)
Hypotension	46 (56)	6 (7)	18 (22)	21 (26)	1 (1)	0 (0)
Chills	32 (39)	21 (26)	11 (13)	0 (0)	0 (0)	0 (0)
Tremor	31 (38)	21 (26)	9 (11)	1 (1)	0 (0)	0 (0)
Hypoxia	30 (37)	1 (1)	14 (17)	11 (13)	4 (5)	0 (0)
Anaemia	28 (34)	0 (0)	7 (9)	21 (26)	0 (0)	0 (0)
White blood cell count decreased	27 (33)	0 (0)	2 (2)	4 (5)	21 (26)	0 (0)
Neutrophil count decreased	25 (30)	0 (0)	2 (2)	4 (5)	19 (23)	0 (0)
Tachycardia	25 (30)	19 (23)	6 (7)	0 (0)	0 (0)	0 (0)
Fatigue	24 (29)	9 (11)	14 (17)	1 (1)	0 (0)	0 (0)
Headache	22 (27)	12 (15)	9 (11)	1 (1)	0 (0)	0 (0)
Platelet count decreased	22 (27)	4 (5)	4 (5)	5 (6)	9 (11)	0 (0)
Encephalopathy	21 (26)	4 (5)	4 (5)	7 (9)	6 (7)	0 (0)
Hypoalbuminaemia	21 (26)	3 (4)	17 (21)	1 (1)	0 (0)	0 (0)
Confusional state	20 (24)	5 (6)	6 (7)	9 (11)	0 (0)	0 (0)
Hyponatraemia	20 (24)	13 (16)	0 (0)	7 (9)	0 (0)	0 (0)
Alanine aminotransferase increased	19 (23)	11 (13)	1 (1)	6 (7)	1 (1)	0 (0)
Hypophosphataemia	18 (22)	0 (0)	5 (6)	12 (15)	1 (1)	0 (0)
Nausea	18 (22)	9 (11)	9 (11)	0 (0)	0 (0)	0 (0)
Dyspnoea	17 (21)	6 (7)	8 (10)	3 (4)	0 (0)	0 (0)
Cough	15 (18)	8 (10)	7 (9)	0 (0)	0 (0)	0 (0)
Aphasia	14 (17)	5 (6)	5 (6)	4 (5)	0 (0)	0 (0)
Aspartate aminotransferase increased	14 (17)	5 (6)	1 (1)	8 (10)	0 (0)	0 (0)
Diarrhoea	14 (17)	9 (11)	2 (2)	3 (4)	0 (0)	0 (0)
Neutropenia	14 (17)	0 (0)	1 (1)	3 (4)	10 (12)	0 (0)
Hypocalcaemia	13 (16)	6 (7)	5 (6)	1 (1)	1 (1)	0 (0)
Asthenia	12 (15)	8 (10)	3 (4)	1 (1)	0 (0)	0 (0)
Decreased appetite	11 (13)	5 (6)	6 (7)	0 (0)	0 (0)	0 (0)
Dizziness	11 (13)	7 (9)	2 (2)	2 (2)	0 (0)	0 (0)
Hypogammaglobulinaemia	10 (12)	1 (1)	8 (10)	1 (1)	0 (0)	0 (0)
Hypokalaemia	10 (12)	10 (12)	0 (0)	0 (0)	0 (0)	0 (0)
Oedema peripheral	10 (12)	7 (9)	3 (4)	0 (0)	0 (0)	0 (0)
Pleural effusion	10 (12)	3 (4)	5 (6)	1 (1)	1 (1)	0 (0)
Sinus tachycardia	10 (12)	7 (9)	3 (4)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	10 (12)	1 (1)	3 (4)	3 (4)	3 (4)	0 (0)
Constipation	9 (11)	8 (10)	1 (1)	0 (0)	0 (0)	0 (0)
Pneumonia	9 (11)	0 (0)	3 (4)	6 (7)	0 (0)	0 (0)
Somnolence	9 (11)	6 (7)	1 (1)	2 (2)	0 (0)	0 (0)
Upper respiratory tract infection	9 (11)	0 (0)	7 (9)	2 (2)	0 (0)	0 (0)

Data cutoff date = 31DEC2019
Abbreviations: AE, adverse event.
Note: Preferred terms are sorted in descending order of total frequency in the "Any" column.
AEs occurred on/after retreatment are not included.
AEs are coded using MedDRA Version 22.1 and graded per CTCAE 4.03.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for that subject.
Percentages are calculated using the total number of subjects in the treatment group as the denominator.
For the AE with a missing CTCAE grade, it is counted in the 'Any' column only.

Data Source: ADSL, ADAE Program Name: t_kae Output Generated: 20200224T15:45

Severity of AEs

In Cohort 1, all 68 subjects had at least 1 AE. 67 subjects (99%) had worst Grade 3 or higher AEs, and 48 subjects (71%) had serious AEs (SAEs). 62 subjects (91%) had CRS; 8 subjects (12%) had worst Grade 3 CRS, and 2 subjects (3%) had worst Grade 4 CRS. 43 subjects (63%) had at least 1 neurologic event; 15 subjects (22%) had a worst Grade 3 neurologic event, and 6 subjects (9%) had a worst Grade 4 neurologic event. 22 subjects (32%) had serious neurologic events. No subject had Grade 5 CRS or a Grade 5 neurologic event. Two subjects (3%) died due to AEs other than disease progression: 1 subject had a Grade 5 AE of staphylococcal bacteraemia that was deemed related to conditioning chemotherapy and KTE-X19, and 1 subject had a Grade 5 AE of organizing pneumonia deemed related to conditioning chemotherapy.

In Cohort 2, all 14 subjects had at least 1 AE. 13 subjects (93%) had worst Grade 3 or higher AEs, and 8 subjects (57%) had SAEs. Thirteen subjects (93%) had CRS, and 2 subjects (14%) had worst Grade 3 CRS. No subject had Grade 4 or Grade 5 CRS. Thirteen subjects (93%) had at least 1 neurologic event; 6 subjects (43%) had worst Grade 3 neurologic events, and 4 subjects (29%) had serious neurologic events. No subject had a neurologic event of Grade 4 or Grade 5. One subject (7%) had a fatal AE of cardiac arrest.

AEs related to KTE-X19

AEs related to KTE-X19 in ZUMA-2 (cohort 1 and cohort 2 combined, 82 subjects): In total 98% of subjects had KTE-x19 related AEs. Most common were pyrexia (93% of subjects), hypotension (56% of subjects), chills (39% of subjects), tremor (38% of subjects), hypoxia (37% of subjects), anaemia and white blood cell count decreased (34% and 33%, respectively), tachycardia (30%) and encephalopathy (26%).

Most of the common AEs are symptoms of AEs of special interest, based on experience from other CAR T cell products.

Adverse events of special interest

Cytokine Release Syndome (CRS)

Frequencies of CRS in ZUMA-2 (both cohorts combined): In total 91% of subjects had CRS of any grade, most common symptoms were pyrexia (99% of subjects), hypotension (60% of subjects), hypoxia (37% of subjects) and chills (33% of subjects).

In cohort 1 in total 91% had CRS. The most common CRS symptoms by PT of any grade were pyrexia (100%), hypotension (56%), and hypoxia (37%). The majority of subjects (76%) had worst Grade 1 or worst Grade 2, 12% had worst Grade 3 and 3% had worst Grade 4 CRS. No subject had Grade 5 CRS. The median time to onset was 2 days (range: 1 to 13 days) after the KTE-X19 infusion. As of the data cut-off date, CRS had resolved in all subjects. The median duration of CRS was 11 days (range: 1 to 50 days). Almost the same was seen in cohort 2: The median time to onset of CRS in cohort 2 was 6 days (range: 1 to 11 days) after the KTE-X19 infusion. As

of the data cutoff date, CRS had resolved in all subjects in both cohorts. The median duration of CRS was 10 days (range: 3 to 31 days).

Neurologic AEs, including cerebral oedema

Frequency in neurologic events in ZUMA-2 (combined cohorts): Neurologic event of any grade in 68% of subjects, most frequent was tremor (38% of subjects), encephalopathy (30% of subjects), confusional state (24% of subjects and aphasia (18% of subjects).

In cohort 1 in total 63% had at least 1 neurologic event of any grad, 32% had serious neurologic events. The most common neurologic events of any grade were tremor (35%), encephalopathy (26%), and confusional state (21%). The most common Grade 3 or higher neurological events were encephalopathy (18%), confusional state (12%) and aphasia (4%).

The median time to onset of a neurologic event was 7 days (range: 1 to 32 days) after the KTE-X19 infusion. Neurologic events had resolved in all but 6 subjects as of the data cutoff date. Neurologic events for 2 subjects had not resolved at the time of death: 1 subject had Grade 2 nonserious agitation (deemed related to KTE-X19) and Grade 3 serious confusional state (deemed related to conditioning chemotherapy and KTE-X19), and 1 subject had Grade 2 nonserious hyperesthesia. Ongoing neurologic events for the remaining 4 subjects were Grade 1 or Grade 2.

The duration of neurologic events for each subject was calculated as the last date of resolution for all qualifying neurologic events - the date of first onset of all qualifying neurologic events + 1. For the 37 subjects whose neurologic events had resolved, the median duration of neurologic events was 12 days (range: 1 to 567 days). Three subjects had neurologic events beyond Day 200 that were attributed to conditioning chemotherapy and KTE-X19. Two subjects had events of Grade 1 tremor (from Day 12 to Day 236 and Day 60 to Day 280, respectively) and 1 subject had Grade 2 memory impairment that started on Day 533 and resolved on Day 571 (this subject had other neurologic events that occurred between Day 5 and Day 72).

In cohort 2, in total 93% had at least 1 neurologic event of any grade. The most common neurologic events of any grade were tremor (50%), confusional state (43%), and aphasia (36%). The median time to onset of a neurologic event was 12 days (range: 3 to 262 days) after the KTE-X19 infusion. Three subjects had neurologic events that were ongoing as of the data cutoff date: 1 subject had non-serious Grade 1 memory impairment and 2 subjects had non-serious Grade 1 tremor. In addition, 1 subject had ongoing neurologic events at the time of death (serious Grade 3 encephalopathy, non-serious Grade 2 confusional state, and non-serious Grade 2 dysarthria). For the 9 subjects whose neurologic events had resolved, the median event duration was 17 days (range: 4 to 178 days).

All CRS and most neurologic AEs were reversible following adequate management, including treatment with tocilizumab and/or corticosteroids, according to guidelines.

Cytopenias (thrombocytopenia, neutropenia, or anaemia)

Frequency of cytopenia in ZUMA-2 (cohorts combined): In total 93% of subjects had cytopenia of any grade; thrombocytopenia (70% of subjects), neutropenia (85% of subjects) and anaemia 65% of subjects).

In Cohort 1, in total 74% had thrombocytopenia AEs, and 51% had worst Grade 3 or higher. In total 87% had neutropenia AEs, and 85% had worst Grade 3 or higher. There were 68% with anaemia AEs of any grade, 50% had worst Grade 3, and no subject had worst Grade 4.

Duration was measured as present on or after Day 30. Grade 3 and Grade 4 thrombocytopenia AEs were present on or after Day 30 in 12% and 28%, respectively and in 16% and 25% of those with neutropenia. Thirteen

subjects (19%) had Grade 3 anaemia AEs on or after Day 30, and no subject had Grade 4 anaemia on or after Day 30.

In Cohort 2, 50% had thrombocytopenia AEs, 79% had neutropenia AEs and 50% had anaemia AEs. Grade 3 and Grade 4 thrombocytopenia were present on or after Day 30 in 14% and 14% had Grade 4 neutropenia AEs that were present on or after Day 30. One subject (7%) had a Grade 3 anaemia AE, and no subject had a Grade 4 anaemia AE on or after Day 30.

Infections

Frequency of infections in ZUMA-2 (cohorts combined): In total 56% of subjects had infections. Most common were upper respiratory tract infection (13% of subjects) and pneumonia (11% of subjects).

Within the SOC of infections and infestations, in Cohort 1, 56% had AEs of any grade, and 32% had worst Grade 3 or higher AEs. One subject had a Grade 5 infection (fatal staphylococcal bacteraemia). There were 15% of subjects that had bacterial infections, including the one that had Grade 5 staphylococcal bacteraemia. The most common bacterial infections were cellulitis and staphylococcal bacteraemia (each 3%). Viral infections where seen in 16% of patients, the most common were herpes zoster and influenza (each 4%). Opportunistic infections were seen in 9% of patients. Two types of opportunistic infections were reported: oral candidiasis (6%) and fungal skin infections (3%). As many as 44% of subjects had other types of infections with pathogens unspecified, the most common were upper respiratory tract infections (13%), pneumonia (10%), and sinusitis (7%).

In Cohort 2, 57% had AEs related to SOC Infections and infestations of any grade. No subject had a Grade 5 AE within the SOC. The most common were pneumonia and upper respiratory tract infection (each 14%). There were 7% bacterial infection, 29% with viral infections, 7% with an opportunistic infection and 36% with infections with pathogens unspecified.

Hypogammaglobulinemia

In Cohort 1, 13 subjects (19%) had hypogammaglobulinemia. No subject in Cohort 2 had an AE of hypogammaglobulinemia.

Other AE of special interest

No cases of secondary malignancies related to KTE-X19 treatment, no cases of immunologic events, replication-competent retrovirus or Graft-versus Host Disease were reported. One KTE-X19 related case, Grade 3 Tumour lysis syndrome, was reported in cohort 1. The subject was treated with rasburicase, and the event resolved the following day.

Other AEs of interest

The incidence and severity of other AEs of interest were identified as following: cardiac arrhythmias (SMQ narrow with selected broad SMQ PTs), cardiac failure (SMQ narrow), and autoimmune disorders (HLGT).

Cardiac Arrhythmias

The subject incidence of cardiac arrhythmias in Cohort 1 is summarised in Table 27.

Table27. Subject Incidence of Cardiac Arrhythmias: ZUMA-2 (Cohort 1 Safety Analysis Set) (N = 68)

Event n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects who had cardiac arrhythmias	40 (59)	26 (38)	12 (18)	1 (1)	1 (1)	0 (0)
Tachycardia	21 (31)	14 (21)	7 (10)	0 (0)	0 (0)	0 (0)
Sinus tachycardia	9 (13)	7 (10)	2 (3)	0 (0)	0 (0)	0 (0)
Bradycardia	6 (9)	4 (6)	2 (3)	0 (0)	0 (0)	0 (0)
Atrial fibrillation	5 (7)	3 (4)	1 (1)	0 (0)	1 (1)	0 (0)
Ventricular arrhythmia	2 (3)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Atrial flutter	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Sinus bradycardia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)

Data cutoff date = 31DEC2019
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardised MedDRA Query.
Notes: Preferred terms are sorted in descending order of total frequency in the "Any" column.
Adverse events are coded using MedDRA version 22.1 and graded per Common Terminology Criteria for Adverse Events version 4.03.
Percentages are calculated using the total number of subjects in the treatment group as the denominator.
Cardiac arrhythmias are identified using the SMQ (narrow) of cardiac arrhythmias with selected broad SMQ preferred terms.
Source: m5.3.5.3, Table 14.3.32.1a
Data Source: ADSL, ADAE Program Name: t_prisk Output Generated: 20200224T15:46

Cardiac failures

Three subjects (4%) had cardiac failure (two subjects with pulmonary oedema, one subject with ejection fraction decreased) in cohort 1. No subject had Grade 4 or Grade 5 cardiac failure.

One subject (7%) in Cohort 2 had cardiac failure (worst Grade 3 pulmonary oedema), which occurred in the setting of CRS.

In ZUMA-2 (both cohorts) 5% of subjects had any grade cardiac failure, none had severe grade ≥ 4.

Concomitant medication to manage AEs

Medications of interest were considered concomitant if they were administered on or after the date of KTE-X19 infusion but before the hospital discharge date (except for immunoglobulins, which were included regardless of whether they were administered before or after the hospital discharge date). In particular, steroids and tocilizumab are important medications to manage serious cases of CRS and neurologic AEs and both are part of the treatment guidance included in SmPC section 4.4. As can be seen from the Table 28 below, as many as 59% subjects in cohort 1 were treated with corticosteroids (with or without tocilizumab), 71% were treated with tocilizumab (with or without corticosteroids) and 56% were treated with corticosteroids and tocilizumab. Fewer needed vasopressors (22%), and 32% needed immunoglobulins. About the same was seen in cohort 2 even with the lower dose: 71% received corticosteroids (with or without tocilizumab), 79% were treated with tocilizumab (with or without corticosteroids), and 64% were treated with corticosteroids and tocilizumab, 50% were treated with vasopressors, and 14% were treated with immunoglobulins.

Table 28 Concomitant Medications of Interest (Safety Analysis Set)

	Cohort 1 (N = 68)	Cohort 2 (N = 14)	Overall (N = 82)
Subjects with any concomitant medications of interest, n (%)	55 (81)	12 (86)	67 (82)
Steroids			
Any	40 (59)	10 (71)	50 (61)
Used for treatment of CRS	15 (22)	5 (36)	20 (24)
Used for treatment of neurologic events	26 (38)	7 (50)	33 (40)
Other AEs	11 (16)	4 (29)	15 (18)
Other use	14 (21)	4 (29)	18 (22)
Tocilizumab			
Any	48 (71)	11 (79)	59 (72)
Used for treatment of CRS	40 (59)	10 (71)	50 (61)
Used for treatment of neurologic events	18 (26)	1 (7)	19 (23)
Other AEs	8 (12)	3 (21)	11 (13)
Other use	1 (1)	1 (7)	2 (2)
Steroids or Tocilizumab			
Any	50 (74)	12 (86)	62 (76)
Steroids and Tocilizumab			
Any	38 (56)	9 (64)	47 (57)
Vasopressors			
Any	15 (22)	7 (50)	22 (27)
Used for treatment of CRS	11 (16)	6 (43)	17 (21)
Other AEs	3 (4)	2 (14)	5 (6)
Other use	2 (3)	1 (7)	3 (4)
Nonsteroidal immunsuppresive agents other than tocilizumab			
Any	5 (7)	2 (14)	7 (9)
Used for treatment of CRS	0 (0)	2 (14)	2 (2)
Used for treatment of neurologic events	4 (6)	0 (0)	4 (5)
Other AEs	0 (0)	0 (0)	0 (0)
Other use	1 (1)	0 (0)	1 (1)
Immunoglobulins			
Any	24 (35)	2 (14)	26 (32)

Data cutoff date = 31DEC2019
Abbreviations: CRS, cytokine release syndrome.
Note: Concomitant medications of interest included in this table are those started on or after the start date of the first KTE-X19 dose but prior to hospital discharge date, except for immunoglobulin, for which all immunoglobulin uses administered on or after the first KTE-X19 dose are included. Medications with an onset during the retreatment period are excluded.
Concomitant medications of systemic steroids, vasopressors, nonsteroidal immunosuppressants other than Tocilizumab, immunoglobulins are based on WHO Drug Dictionary Version March 2019 search terms defined by Kite.

Data Source: ADSL, ADCM Program Name: t_cm_mae3 Output Generated: 20200224T15:44

Serious adverse event/deaths/other significant events

Table 29: **Subject Incidence of Serious Treatment-emergent Adverse Events by Preferred Term and Worst Grade in ≥ 2 Subjects**

MedDRA Preferred Term n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any serious TEAE	56 (68)	2 (2)	9 (11)	25 (30)	15 (18)	5 (6)
Pyrexia	16 (20)	8 (10)	3 (4)	5 (6)	0 (0)	0 (0)
Hypotension	14 (17)	0 (0)	3 (4)	9 (11)	2 (2)	0 (0)
Encephalopathy	13 (16)	1 (1)	0 (0)	6 (7)	6 (7)	0 (0)
Pneumonia	11 (13)	0 (0)	1 (1)	9 (11)	1 (1)	0 (0)
Hypoxia	7 (9)	0 (0)	0 (0)	3 (4)	4 (5)	0 (0)
Acute kidney injury	5 (6)	0 (0)	0 (0)	1 (1)	4 (5)	0 (0)
Confusional state	5 (6)	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)
Anaemia	4 (5)	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)
Aphasia	4 (5)	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)
Pleural effusion	4 (5)	0 (0)	1 (1)	2 (2)	1 (1)	0 (0)
Respiratory failure	4 (5)	0 (0)	0 (0)	0 (0)	4 (5)	0 (0)
Sepsis	4 (5)	0 (0)	0 (0)	1 (1)	3 (4)	0 (0)
CAR T-cell-related encephalopathy syndrome	3 (4)	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)
Dyspnoea	3 (4)	0 (0)	0 (0)	2 (2)	1 (1)	0 (0)
Atrial fibrillation	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
B-cell lymphoma	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
Blood creatinine increased	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Diarrhoea	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Hypertension	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Lethargy	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Mental status changes	2 (2)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Platelet count decreased	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Seizure	2 (2)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)
Staphylococcal bacteraemia	2 (2)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Tachycardia	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)

Data cutoff date = 31DEC2019
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.
Note: Preferred terms are sorted in descending order of total frequency in the "Any" column.
TEAE is defined as any adverse event with onset on or after the anti-CD19 CAR T cells infusion. AEs occurred on/after retreatment are not included.
AEs are coded using MedDRA Version 22.1 and graded per CTCAE 4.03.
Percentages are calculated using the total number of subjects in the treatment group as the denominator.

Data Source: ADSL, ADAE Program Name: t_stene Output Generated: 20200224T15:47

Table 30: Subject Incidence of KTE-X19-related Serious Adverse Events by Preferred Term and Worst Grade in ≥ 2 Subjects

MedDRA Preferred Term n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any KTE-X19-related serious AE	44 (54)	2 (2)	7 (9)	22 (27)	12 (15)	1 (1)
Pyrexia	14 (17)	7 (9)	4 (5)	3 (4)	0 (0)	0 (0)
Encephalopathy	13 (16)	1 (1)	0 (0)	6 (7)	6 (7)	0 (0)
Hypotension	12 (15)	0 (0)	2 (2)	9 (11)	1 (1)	0 (0)
Pneumonia	7 (9)	0 (0)	1 (1)	6 (7)	0 (0)	0 (0)
Confusional state	5 (6)	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)
Hypoxia	5 (6)	0 (0)	0 (0)	2 (2)	3 (4)	0 (0)
Anaemia	4 (5)	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)
Aphasia	4 (5)	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)
Acute kidney injury	3 (4)	0 (0)	0 (0)	1 (1)	2 (2)	0 (0)
CAR T-cell-related encephalopathy syndrome	3 (4)	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)
Pleural effusion	3 (4)	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)
Sepsis	3 (4)	0 (0)	0 (0)	1 (1)	2 (2)	0 (0)
Atrial fibrillation	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Lethargy	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Mental status changes	2 (2)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Seizure	2 (2)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)

Data cutoff date = 31DEC2019
Abbreviations: AE, adverse event.
Note: Preferred terms are sorted in descending order of total frequency in the "Any" column.
AEs occurred on/after retreatment are not included.
AEs are coded using MedDRA Version 22.1 and graded per CTCAE 4.03.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for that subject.
Percentages are calculated using the total number of subjects in the treatment group as the denominator.

Data Source: ADSL, ADAE Program Name: t_skae Output Generated: 20200224T15:47

In Cohorts 1 and 2 combined, 22 subjects (27%) had died as of the data cutoff date: 18 subjects (26%) in Cohort 1 and 4 subjects (29%) in Cohort 2. Eighteen subjects died due to PD (16 subjects in Cohort 1 and 2 subjects in Cohort 2). One subject in Cohort 2 died on Day 286 due to a toxicity associated with an allo-SCT regimen (reported as "other").

Five subjects died within 3 months of the KTE-X19 infusion, and 17 subjects died > 3 months after the KTE X19 infusion. Three subjects died due to AEs:

☐ A patient in Cohort 1 died due to organizing pneumonia on Day 37 following SAEs of Grade 4 respiratory failure and Grade 4 acute respiratory distress syndrome; both Grade 4 events started on Day 21 and were ongoing as of the date of death. Preceding events included Grade 3 increased blood creatinine (Day 32 to Day 34) followed by Grade 3 decreased urine output (starting on Day 34 and ongoing as of the date of death). The subject had also experienced 2 earlier events of CRS, both of maximum Grade 3 (from Day 3 to Day 10 and from Day 16 to Day 20, respectively) as well as an SAE of confusional state, maximum Grade 3 (starting on Day 10 and ongoing as of the date of death). The death was deemed related to conditioning chemotherapy but unrelated to KTE-X19.

☐ A patient in Cohort 1 died due to staphylococcal bacteraemia (methicillin-resistant Staphylococcus aureus) on Day 134 after the KTE-X19 infusion; the fatal event was listed as streptococcal bacteraemia as of the data cutoff date. Per the subject's request, he was discharged on Day 132 and discontinued treatments. On Day 134, he died due to sepsis (staphylococcal bacteraemia). No autopsy was performed. Per the investigator, treatment with high-dose steroids likely contributed to susceptibility to the infection. The death was deemed related to conditioning chemotherapy and KTE-X19.

☐ A patient in Cohort 2 died on Day 18 from an event of cardiac arrest. This subject was noted to have an elevated anion gap before receiving KTE-X19, suggesting that pre-existing underlying disease contributed to the metabolic acidosis that was linked to the cardiac arrest. The metabolic acidosis and elevated anion gap worsened on Day 6, followed by CRS on Day 10 (which resolved on Day 13) and encephalopathy on Day 12 (which was ongoing as of the date of death). This death was considered to be unrelated to study treatment (i.e. due to leukapheresis, conditional chemotherapy, or KTE-X19).

Table 31: Deaths, Including Cause of Deaths (Safety Analysis Set)

	Cohort 1 (N = 68)	Cohort 2 (N = 14)	Overall (N = 82)
Subjects who died, n (%)	18 (26)	4 (29)	22 (27)
Deaths that occurred ≤ 30 days after KTE-X19 infusion, n (%)	0 (0)	1 (7)	1 (1)
Deaths that occurred > 30 days through 3 months (92 days) after KTE-X19 infusion, n (%)	4 (6)	0 (0)	4 (5)
Deaths that occurred > 3 months (92 days) after KTE-X19 infusion, n (%)	14 (21)	3 (21)	17 (21)
Primary cause of death, n (%)			
Adverse event	2 (3)	1 (7)	3 (4)
Progressive disease	16 (24)	2 (14)	18 (22)
Other[a]	0 (0)	1 (7)	1 (1)

Data cutoff date = 31DEC2019
a One subject died on Day 286 due to a toxicity associated with an allo-SCT regimen.
Source: modified from m5.3.5.3, Table 14.3.40a, Table 14.3.40b, and Table 14.3.40a
Data Source: ADSL Program Name: t_dth Output Generated: 20200224T15:45

Laboratory findings

Table 32: Summary of Incidence of Post-KTE-X19 Infusion Laboratory Value Increases by Worst Toxicity Grade

	Overall (N = 82)					
	Post-KTE-X19 Infusion Worst Grade Laboratory Toxicity (Increased Value)					
	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥ 3
Hematology						
Hemoglobin (mmol/L)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leukocytes (10^9/L)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Lymphocytes (10^9/L)	15 (18)	0 (0)	14 (17)	1 (1)	0 (0)	1 (1)
Chemistry						
Potassium (mmol/L)	14 (17)	8 (10)	6 (7)	0 (0)	0 (0)	0 (0)
Calcium (mmol/L)	3 (4)	3 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Magnesium (mmol/L)	3 (4)	0 (0)	0 (0)	3 (4)	0 (0)	3 (4)
Sodium (mmol/L)	17 (21)	11 (13)	3 (4)	2 (2)	1 (1)	3 (4)
Alanine aminotransferase (U/L)	67 (82)	34 (41)	21 (26)	10 (12)	2 (2)	12 (15)
Aspartate aminotransferase (U/L)	65 (79)	44 (54)	9 (11)	12 (15)	0 (0)	12 (15)
Bilirubin (umol/L)	42 (51)	21 (26)	20 (24)	1 (1)	0 (0)	1 (1)
Creatinine (umol/L)	64 (78)	50 (61)	9 (11)	4 (5)	1 (1)	5 (6)
Urate (mmol/L)	14 (17)	0 (0)	0 (0)	13 (16)	1 (1)	14 (17)
Direct bilirubin (umol/L)	38 (46)	13 (16)	21 (26)	3 (4)	1 (1)	4 (5)
Glucose (mmol/L)	74 (90)	38 (46)	29 (35)	7 (9)	0 (0)	7 (9)
Alkaline phosphatase (U/L)	39 (48)	37 (45)	2 (2)	0 (0)	0 (0)	0 (0)

Data cutoff date = 31DEC2019
Note: Percentages are calculated using the total number of subjects treated as the denominator.
Post-KTE-X19 infusion laboratory toxicity includes laboratory toxicities observed on or after the KTE-X19 infusion date.
Grading categories are determined by CTCAE version 4.03.

Data Source: ADSL, ADLB Program Name: t_lbtx Output Generated: 20200224T15:46

Table 33: Summary of Incidence of Post-KTE-X19 Infusion Laboratory Value Decreases by Worst Toxicity Grade

	Overall (N = 82)					
	Post-KTE-X19 Infusion Worst Grade Laboratory Toxicity (Decreased Value)					
	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥ 3
Hematology						
Hemoglobin (mmol/L)	82 (100)	2 (2)	34 (41)	46 (56)	0 (0)	46 (56)
Neutrophils (10^9/L)	82 (100)	0 (0)	1 (1)	9 (11)	72 (88)	81 (99)
Platelets (10^9/L)	81 (99)	14 (17)	14 (17)	18 (22)	35 (43)	53 (65)
Leukocytes (10^9/L)	82 (100)	0 (0)	2 (2)	8 (10)	72 (88)	80 (98)
Lymphocytes (10^9/L)	82 (100)	1 (1)	2 (2)	5 (6)	74 (90)	79 (96)
Chemistry						
Potassium (mmol/L)	42 (51)	0 (0)	34 (41)	5 (6)	3 (4)	8 (10)
Calcium (mmol/L)	80 (98)	23 (28)	40 (49)	10 (12)	7 (9)	17 (21)
Magnesium (mmol/L)	43 (52)	42 (51)	1 (1)	0 (0)	0 (0)	0 (0)
Sodium (mmol/L)	68 (83)	55 (67)	0 (0)	13 (16)	0 (0)	13 (16)
Albumin (g/L)	73 (89)	13 (16)	54 (66)	6 (7)	0 (0)	6 (7)
Glucose (mmol/L)	12 (15)	9 (11)	1 (1)	2 (2)	0 (0)	2 (2)
Phosphate (mmol/L)	78 (95)	21 (26)	32 (39)	24 (29)	1 (1)	25 (30)

Data cutoff date = 31DEC2019
Note: Percentages are calculated using the total number of subjects treated as the denominator.
Post-KTE-X19 infusion laboratory toxicity includes laboratory toxicities observed on or after the KTE-X19 infusion date.
Grading categories are determined by CTCAE version 4.03.

Data Source: ADSL, ADLB Program Name: t_lbtx Output Generated: 20200224T15:46

The most common increased laboratory values observed in Cohort 1 were for glucose levels, AST and ALT. The other most common decreased laboratory values observed were calcium, phosphate, and albumin.

In Cohort 2, the most common increases observed in laboratory values were for glucose levels, ALT, bilirubin and creatinine. All had decreases in haematological values, as well as calcium, albumin, and phosphate.

Five subjects in ZUMA-2 met initial laboratory criteria for Hy's law (4 subjects in Cohort 1 and 1 subject in Cohort 2). Upon clinical review, an alternate explanation for liver dysfunction was noted in all 5 subjects. Thus, no subject in ZUMA-2 was considered to have met criteria for Hy's law.

As many as 17% of subjects had increase in urate of Grade≥3. This may be associated with the risk of TLS. In SmPC section 4.4 there is a recommendation to administer allopurinol in patients with elevated uric acid and high tumour burden prior to infusion.

Safety in special populations

Age

The applicant presented two age groups, subjects who were ≥ 65 years and < 65 years old. In Cohort 1 by comparison to the younger subgroup subjects who were ≥ 65 years old showed a trend toward a higher incidence of SAEs (72% versus 62%), KTE-X19-related SAEs (59% versus 45%), Grade 3 or higher CRS (21% versus 7%), Grade 3 or higher neurologic events (36% versus 24%), Grade 3 or higher thrombocytopenia (56% versus 45%), and Grade 3 or higher infections (38% versus 24%). Compared with subjects who were ≥ 65 years old, subjects who were < 65 years old showed a trend toward a higher incidence of CRS of any grade (97% versus 87%).

Results in Cohorts 1 and 2 combined were generally consistent with results observed in Cohort 1.

There is a relatively higher incidence of SAEs, CRS, CRES and infections in the population older than 65 years.

Sex

Sex has a more significant influence on the number and severity of AEs, as women seem more prone to develop AEs and these AEs are of higher grade, when compared to male study participants. Compared with males, females showed a trend towards a higher incidence of KTE-X19-related SAEs (64% versus 51%), e. g. worst Grade 3 or higher CRS (45% versus 9%), any neurologic events (73% versus 61%), worst Grade 3 or higher neurologic events (64% versus 25%), any grade serious neurologic events (55% versus 28%), any grade thrombocytopenia (82% versus 72%), worst Grade 3 or higher thrombocytopenia (73% versus 47%), any grade anaemia (82% versus 65%), worst Grade 3 or higher anaemia (64% versus 47%), any grade infections (73% versus 53%), and worst Grade 3 or higher infections (45% versus 30%).

This divergence has been also observed for another CAR T cell product and seems to be irrespective of the indication.

AEs by performance status at baseline

Compared with subjects who had a baseline ECOG (Eastern Cooperative Oncology Group) Performance Status of 0, subjects who had an ECOG Performance Status of 1 showed a trend towards a higher incidence of worst Grade 3 or higher CRS (21% versus 11%), worst Grade 3 or higher neurologic events (42% versus 25%), and any grade serious neurologic events (42% versus 27%). Compared with subjects who had a baseline ECOG Performance Status of 1, subjects who had a Performance Status of 0 showed a trend towards a higher incidence of any grade thrombocytopenia (84% versus 54%), any grade neutropenia (93% versus 75%), any grade serious infections (30% versus 17%), and any grade hypogammaglobulinemia (23% versus 13%).

Use during pregnancy and lactation

There is no relevant clinical experience with KTE-X19 therapy in pregnant women, and animal reproductive studies have not been performed. Once infused, CAR T-cells may persist long term and women who plan a pregnancy should consult their physician. This therapy should not be administered to pregnant women. Women of childbearing potential must have a negative pregnancy test prior to enrolment due to the potentially dangerous effects of the preparative chemotherapy on the foetus. Contraception must be used during treatment and for 6 months after receiving lymphodepleting chemotherapy and KTE-X19. This is reflected in SmPC section 4.6.

Paediatric Subjects < 18 Years of Age

No children were included in ZUMA-2 study. Paediatric and adolescent subjects with r/r B-precursor ALL are being treated with KTE-X19 in ZUMA-4; 29 subjects had been treated as of the data cut-off date. KTE-X19 shows preliminary evidence of a manageable safety profile in paediatric subjects. All 29 subjects had at least 1 AE, and 28 subjects (97%) had worst Grade 3 or higher AEs. 28 subjects (97%) had AEs that were related to KTE-X19, 20 subjects (69%) had at least 1 SAE; and 17 subjects (59%) had SAEs that were related to KTE-X19. 25 subjects (86%) had CRS; 8 subjects (28%) had worst Grade 3 or higher CRS. 19 subjects (66%) had neurologic events; 7 subjects (24%) had worst Grade 3 or higher neurologic events. No subject had Grade 5 CRS or neurologic event. Two subjects (7%) had fatal AEs not due to PD; both were infection.

Immunological events

Despite some positive antibody test results in the initial screening assay, the confirmatory cell-based tests did not bring any evidence for the presence of FMC63 antibodies (a CD19 antibody clone). Therefore, immunogenicity does not represent a hazard for the subjects treated with the product.

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to adverse events

There were no discontinuations due to AEs, this is a one-time administered therapy.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

The safety database included a total of 82 subjects treated with KTE-X19 in the ZUMA-2 trial. The overall exposure to KTE-X19 including the supportive trials was 225.

In the ZUMA-2 study in Cohort 1 68 subjects received the intended target dose of 2.0 x 106 anti-CD19 CAR T cells/kg, whereas for Cohort 2 14 subjects received 0.5 x 106 anti-CD19 CAR T cells/kg. There are no significant dose dependent differences with respect to AEs in the two cohorts. The median potential follow-up time from the KTE-X19 infusion for all subjects dosed in Cohort 1 was 16.8 months (range: 7.2 to 37.6 months). The median

potential follow-up time from the KTE-X19 infusion for subjects in Cohort 2 was 16.0 months (range: 13.9 to 18.0 months). The median potential follow-up time from the KTE-X19 infusion for subjects in Cohort 2 was 21.3 months (range: 19.1 to 23.2 months). In the three supportive studies a total of 143 patients were treated with KTE-X19 at various doses (0.5, 1.0 or 2.0 x 106 CAR T cells/kg). Only 13 patients in the supportive studies received the intended dose of 2.0 x 106 CAR T cells/kg.

All patients in ZUMA-2 had at least one AE, 80 subjects (98%) had worst Grade 3 or higher AEs, and 56 subjects (68%) had serious AEs (SAEs). The most common KTE-X19 related AEs reported were pyrexia, hypotension, chills, tremor, anaemia, hypoxia, white blood cell count decrease, encephalopathy and tachycardia. Many of these are symptoms of the most critical AEs, in particular CRS, neurologic AEs, cytopenias and infections. Time to onset was usually a few days and duration was in median 11-12 days, but could last for several months, in particular for neurologic AEs. All CRS and most neurologic AEs were reversible with adequate management according to recommended guidelines (SmPC section 4.4), but four subjects had still ongoing neurologic AEs at cut-off date. One death (caused by staphylococcus bacteraemia) was considered related to conditional chemotherapy and KTE-X19 infusion.

MCL is primarily a cancer disease in elderly above 65 years of age and in the pivotal study (ZUMA-2) in total 42 (51% of subjects) were ≥65 years, in cohort 1, 39 (57%) subjects were ≥65 years. There are only minor differences in the two age groups regarding AEs. The older patients seem to have a slightly higher incidence of AEs. Sex could have a more significant influence on the number and severity of AEs, as women seem more prone to develop AEs and these AEs are of higher grade, when compared to male study participants. This divergence has been also observed for Yescarta and seems to be irrespective of the indication.

Pregnant women are not allowed to undergo the therapy, and contraception must be used for 6 months after receiving the therapy. Breastfeeding women were also prohibited in receiving this therapy.

The safety of KTE-X19 has not been investigated separately for subjects with renal or hepatic impairment.

There were no paediatric patients treated with MCL

For the patients included in the pivotal study, the vast majority had CRS of any grade as well as neurologic events, and the majority of the patients also had different grades of thrombocytopenia, neutropenia or anaemia. About half of the patients suffered from an infection episode, and about 16% of the patients had hypogammaglobulinemia.

The important identified risks and the potential risks identified for KTE-X19 are similar to the AEs identified for this product class. The important identified risks are: CRS, neurotoxicity, cytopenias, infections, hypogammaglobulinemia.

CRS and neurologic events had an early onset. Neurologic AEs were often seen as part of the CRS events. All CRS events were resolved at the time of the data cutoff. Neurologic events resolved for all but 6 subjects; 2 of the 6 subjects had ongoing neurologic events at the time of death: 1 subject had ongoing neurologic event not related to KTE-X19, the other subject had 2 ongoing neurologic events related to KTE-X19 (agitation and confusional state). The remaining unresolved neurologic events in 4 subjects were either Grade 1 (tremor and dysaesthesia) or Grade 2 (hypoaesthesia). Data indicates that there can be an association between both tumour burden/disease burden and dose infused (number of CAR-T cells/kg) and the risk for CRS and neurologic AEs. The higher peak blood levels of KTE-X19 correlated well with higher grades of CRS and CRES. The applicant was requested to discuss such data from ZUMA-studies and possible associations with the severity, duration and management of CRS and neurologic AEs for both cohorts. No clear linear relationship between tumour burden

and the incidence of severe CRS or neurologic events, or relationship between dose of CAR-T cells given and incidence of such events was found in the data.

Management plans for CRS and neurotoxicity are included in the SmPC in conjunction with the respective grading guidance. Patients with CRS or neurotoxicity were treated with steroids, tocilizumab, supplemental oxygen and vasopressors: 71% were treated with tocilizumab for any AE, 38% were treated with steroids for neurologic AEs, 56% were treated with both steroids and tocilizumab. 28% of subjects had to be treated with more than two doses of tocilizumab.

Cytopenias and hypogammaglobulinaemias lead to the increased risk of infections. These AEs were managed according to standard protocols and this is also indicated in the SmPC. Cytopenias usually resolved within a few weeks, but in some cases were present at 30 days after infusion. A challenge when assessing the degree of cytopenias related to KTE-X19 is the fact that cytopenias also are frequent AEs following medicines used in the bridging therapy and conditional chemotherapy given the period before KTE-X19 infusion. However, inclusion criteria were "Toxicities due to prior therapy must have been stable and recovered to ≤ Grade 1", which should imply that the worsening of cytopenias observed after KTE-X19 infusion are probably related to lymphodepleting chemotherapy or the CAR-T infusion. Duration of cytopenias is reported as "presence on and after day 30". Twenty-two subjects (32%) were administered gammaglobulines in the pivotal study, cohort 1.

Cardiac AEs were reported following KTE-X19 infusion. There was a trend in lower frequencies of cardiac arrhythmias (57% and 79%) and cardiac failure (4% and 7%) in cohort 1 compared to cohort 2. Cardiac arrhythmias are reported as part of CRS. These cardiac AEs are not considered as direct cardiotoxicity from anti-CD19 CAR T cells. The cardiac elevations seem rather to be associated with CRS or concomitant TLS

There was one case of tumour lysis syndrome in Cohort 1, which resolved upon treatment with rasburicase. In total 16% of subjects in cohort 1 had increase in urate of grade ≥3. This may be associated with the risk of TLS. In SmPC section 4.4 there is a recommendation to administer allopurinol in patients with elevated uric acid and high tumour burden prior to infusion.

There were three subjects who died in the pivotal study due to AEs. One case was deemed related to conditioning chemotherapy but unrelated to KTE-X19, one case was deemed related to conditioning chemotherapy and KTE-X19. The third patient deceased as a consequence of a pre-existing condition, which was not deemed related to the study treatment. In the supportive studies a total of 11 subjects deceased due to AEs. From these cases two were deemed to be KTE-X19 related, a further patient deceased due to a Grade 5 cerebral oedema after the cut-off date.

Interestingly, there are several patients with negative CD19 IHC (6 patients) and with CD19 IHC results unavailable (19 patients). Nonetheless, acknowledging the limited number of these patients, based on the data provided by the applicant no obvious safety risk could be identified for CD19 negative subjects.

Within the observed AEs some can be directly linked to the conditioning chemotherapy (cytopenias), and other AEs are directly linked to the administration of KTE-X19. CRS and neurological adverse reaction are likely caused by KTE-X19, while cytopenias might also be related to conditioning chemotherapy or previous therapies even though most laboratory values should be of grade ≤1 before KTE-X19 infusion. The AEs described here are in line with the AEs of CAR T cell products and are a direct consequence of the mode of action of these products. These AEs are expected to occur based on the previous experience with this product class. Though the safety data is limited for any firm conclusion, the safety profile of KTE-X19 appears to be in accordance with the expected known class effects.

No further risks and AEs could be identified which would be specific for KTE-X19 or for the indication to be treated with KTE-X19. The important identified risks in the RMP are: CRS, neurotoxicity, cytopenias, infections, hypogammaglobulinemia. There are some potential risks linked to the use of this product: secondary malignancy, immunogenicity, RCR, tumour lysis syndrome, and aggravation of GvHD. These risks will be followed part of the pharmacovigilance activities described in the RMP.

Essentially, these AEs and risks are similar to what has been described for other CAR T cell therapies. No further risks and AEs could be identified which would be specific for KTE-X19 or for the indication to be treated with KTE-X19. The risk mitigation measures are presented in the SmPC and are in line with the general management plans for this product class.
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Additional safety data needed in the context of a conditional MA

The imposed specific obligations in the frame of the conditional Marketing Authorisation will provide long-term and per-population subgroups efficacy data and will also collect long term safety data for the product.

2.6.2. Conclusions on the clinical safety

Therapy with KTE-X19 is associated with a high incidence of AE/ADR and a clinically relevant fraction of these AE/ADR is of a severity of grade ≥ 3 and/or serious. However they are consistent with the safety profile of the product class and generally manageable with SmPC recommendations.

The CAT considers the following measures necessary to ensure the follow-up of safety:

- A long term follow up: In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory Mantle cell Lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.

The CAT furthermore considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.
- In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2.

The CHMP endorse the CAT conclusion on clinical safety as described above

2.7. Risk Management Plan

Safety concerns

Important Identified Risks	Serious neurologic events, including cerebral oedema
	CRS
	Cytopenias
	Infections
	Hypogammaglobulinaemia
Important Potential Risks	Secondary malignancy
	Immunogenicity
	RCR
	TLS
	Aggravation of GvHD
Missing Information	New occurrence or exacerbation of an autoimmune disorder
	Long-term safety

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Non-interventional prospective long-term efficacy and safety study based on data from a registry Planned	Further evaluation of efficacy, additional characterization of the identified risks, further evaluation of potential risks and missing information. This study will be designed as an efficacy and safety long-term follow up.	Identified risks, potential risks, and missing information	Protocol submission	Protocol submission within 3 months of marketing authorization
			Annual report for first 5 years, followed by report once every 2 years	Annual
			Progress updates in the nearest PSUR to the annual anniversary	Annual
			Safety reports	Every 6 months Additional reports every 3 months if new safety concern is

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
				identified
			Study Completion	Q2 2041
			Final study report	Q2 2042
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Prescriber Survey Planned	Assess the prescribers' understanding of the risks of KTE-X19. Evaluate the effectiveness of risk minimization activities: HCP educational materials, and Patient Alert Card.	Serious neurologic events including cerebral oedema CRS	Protocol submission	Protocol submission within 6 months of marketing authorization
			Final study report	Q3 2023
KTE-C19-103 (ZUMA-3) Phase 1/2, multienter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r B-precursor ALL Ongoing	To evaluate efficacy and safety of KTE-X19 in relapsed/refractory adult ALL subjects	Serious neurologic events including cerebral oedema CRS Cytopenias Infections Hypogammaglobulinaemia Secondary malignancy Immunogenicity RCR TLS Aggravation of GvHD New occurrence or exacerbation of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary	Annual
			Final study report	Jul 2033
KTE-C19-108 (ZUMA-8) Phase 1 multicenter, open-label study evaluating the safety and tolerability of KTE-X19 in adult subjects with r/r CLL and SLL	To evaluate the safety and tolerability of KTE-X19 in adult subjects with relapsed/refractory CLL and SLL	Serious neurologic events including cerebral oedema CRS Cytopenias Infections	Safety updates in the nearest PSUR to the annual anniversary	Annual

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Ongoing		Hypogammaglobulinaemia Secondary malignancy Immunogenicity RCR TLS Aggravation of GvHD New occurrence or exacerbation of an autoimmune disorder Long term safety	Final study report	Dec 2036

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
Serious neurologic events including cerebral oedema	Routine risk minimization measures: SmPC sections: 4.2, 4.4, 4.8 PL: 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for monitoring and management of serious neurologic events, including treatment algorithms, are included in the SmPC sections 4.2, 4.4 Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers. Additional risk minimization measures: HCP educational material Patient Alert Card (PAC) Controlled distribution program	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event Follow-up Questionnaire Additional pharmacovigilance activities: Registry study, prescriber survey, and studies ZUMA-3 and ZUMA-8
CRS	Routine risk minimization measures: SmPC sections: 4.2, 4.4, 4.8 PL section: 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for monitoring and management of CRS, including treatment algorithms, are included in the SmPC sections 4.2, 4.4 Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event Follow-up Questionnaire Additional pharmacovigilance activities: Registry study, prescriber survey, and studies ZUMA-3 and ZUMA-8

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: HCP educational material PAC Controlled distribution program	
Cytopenias	Routine risk minimization measures: SmPC sections: 4.4, 4.8 PL section: 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for blood count monitoring will be included in SmPC section 4.4 Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8
Infections	Routine risk minimization measures: SmPC sections: 4.4, 4.8 PL section: 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for monitoring the signs and symptoms of infection before, during and after KTE-X19 infusion are included in SmPC section 4.4 Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8
Hypogammaglobulinaemia	Routine risk minimization measures: SmPC sections: 4.4, 4.8 PL section: 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for monitoring immunoglobulin levels and management using infection precautions, antibiotic prophylaxis and immunoglobulin replacement are included in SmPC section 4.4 Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important potential risk(s)		
Secondary malignancy	Routine risk minimization measures: SmPC section: 4.4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for life-long monitoring for secondary malignancies is included in SmPC section 4.4 Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8
Immunogenicity	Routine risk minimization measures: SmPC section: 4.8 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8
RCR	Routine risk minimization measures: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
TLS	Routine risk minimization measures: SmPC section: 4.4 PL section: 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8
Aggravation of GvHD	Routine risk minimization measures: SmPC section: 4.4 PL section: 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8

Missing information

New occurrence or exacerbation of an autoimmune disorder	Routine risk minimization measures: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long-term safety	Routine risk minimization measures: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study and studies ZUMA-3 and ZUMA-8

Conclusion

The CHMP, CAT and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP and CAT considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 24 July 2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that autologous peripheral blood t cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured has not been previously authorised in a medicinal product in the European Union.

The CAT/CHMP, based on the available data, considers autologous anti-CD19-transduced CD3+ cells to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a

bridging report making reference to Yescarta. The bridging report submitted by the applicant has been found acceptable.

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Based on art. 63(3), the applicant requested the use of minimum particulars on the label to be included on the ethylene-vinyl acetate cryostorage infusion bag. Even if the bag contains approximately 68mL of cell dispersion, the company claimed there was insufficient space for full particulars. They proposed to display the name of the medicinal product, route of administration, expiry date, batch specific information (lot number, patient ID, patient name, patient DOB), volume, information on autologous use and need to verify patient identity. The use of minimum particulars would also allow for the batch specific information to be clearly inserted by hand.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tecartus (autologous anti-CD19-transduced CD3+ cells) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is a biological product that is not covered by the previous category and authorised after 1 January 2011;
- It is approved under a conditional marketing authorisation [REG Art 14-a].

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin lymphoma (NHL) with distinctive clinical, biological, and molecular characteristics and a generally aggressive, albeit heterogeneous, clinical course. The lymphoma cells in MCL are thought to originate from antigen-naive pre-germinal centre B cells within the mantle zone of the lymph node and typically express several surface markers including CD19 and CD20. The molecular hallmark of MCL is the chromosomal translocation t(11;14)(q13;q32), which results in overexpression of the cell cycle regulator cyclin D1.

MCL patients are often diagnosed with advanced disease (Stage III or IV), characterised by an aggressive clinical course. Patients present with generalised lymphadenopathy and extranodal involvement of the blood, bone marrow, spleen and gastrointestinal (15% to 30%). Prognostic factors include the (simplified) MIPI risk score (performance status, age, LDH levels > upper limit of normal, and white blood cell count), which can be further improved by adding the Ki-67 proliferative index. Morphological variant also impacts outcome, with blastoid and pleomorphic cytomorphology being associated with a poorer prognosis.

MCL accounts for approximately 5% to 7% of malignant lymphoma in Western Europe. The estimated annual incidence of MCL is approximately 1 to 2 per 100,000 in Europe. MCL is more likely to affect men than women, and the median age at diagnosis is 68 years

3.1.2. Available therapies and unmet medical need

In the r/r situation in MCL, the treatment concepts comprise immunochemotherapy followed by autologous/allogeneic SCT, BTK inhibitors (ibrutinib and acalabrutinib; both approved in the US; only ibrutinib is approved in the EU), the immunomodulatory (and thalidomide analogue) agent lenalidomide, the m-TOR inhibitor temsirolimus and the BCL-2 antagonist venetoclax. Bortezomib is approved in the EU for use in combination with R-CHOP for the treatment of newly diagnosed MCL, and it has also been investigated as a monotherapy in relapsed/refractory MCL. An optimal sequence of treatments for r/r MCL has not been established. Choice of regimen is influenced by response duration to frontline therapy, comorbidities, tumour chemo-sensitivity, and overall risk-benefit evaluations.

Responses to ASCT in relapse are inferior to those in first-line and there is no consensus on the benefit of its use in relapsed/refractory disease (Ketterer et al, 1997; Robinson et al, 2015). By contrast, allo-SCT has the potential to be curative in relapse/refractory MCL (Vose 2015), in younger patients (i.e. <65 years) while few patients with r/r MCL are candidates for allo-SCT . However, high treatment-related mortality rates of up to 40% following allo-SCT were also reported, primarily due to graft-versus host disease, and the majority of patients still did not achieve durable remissions.

Maintenance regimens with rituximab in the r/r situation have a favourable safety profile and prolong PFS and OS, however, second-line maintenance in patients relapsing after front-line maintenance is not recommended which implies a restriction of a therapeutically approach in the r/r situation of MCL a priori.

Despite promising high rates of ORR (68%) for BTK inhibitors (ibrutinib SmPC) in the relapsed setting, they are not considered as curative treatments since all patients will eventually have progressive disease after receiving a BTK inhibitor.

Although the clinical outcome at MCL generally improved in the last years, the r/r situation and disease progress during or after treatment with BTK inhibitors mean rather limited further treatment options for the patient. Thus, novel therapy strategies resulting in durable response rates are required.

3.1.3. Main clinical studies

The single pivotal trial is ZUMA 2, an ongoing Phase 2 open label multicentre clinical trial (with data cut-off point of 24th July 2019) to evaluate efficacy and safety of KTE-X19 at a target dose of 2x106 cells/kg in the pivotal Cohort 1. The study population were adults with r/r MCL after ≤ 5 lines of prior therapy including anthracycline or bendamustine, anti-CD20 mABs and BTK inhibitors.

Inclusion criteria were confirmed r/r MCL (documented by either overexpression of cyclin D1 or presence of t(11;14)). Patients were to have received up to 5 prior regimens for MCL, including an anthracycline or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody as well as a BTKi. Patients with a central nervous system lymphoma and a history of allogeneic SCT, prior anti-CD 19-targeted therapy, CAR or other genetically modified T-cell therapy were excluded.

Subjects were considered enrolled at the time of leukapheresis. Bridging therapy with dexamethasone or a BTKi was allowed at the discretion of the investigator and subjects receiving bridging therapy were to have a repeat diagnostic PET-CT scan prior to conditioning chemotherapy.

The non-myeloablative conditioning regimen consisted of fludarabine (30 mg/m2/day) and cyclophosphamide (500 mg/m2/day) administered for three days and could be repeated if the KTE-X19 infusion was delayed by > 2 weeks.

The primary and secondary endpoints in ZUMA 2 were ORR (CR and PR), DOR and PFS. The applicant defined the first 60 subjects treated with KTE-X19 (inferential analysis set) as the primary efficacy population. However, the Cohort 1 full analysis set FAS (n=74) was used as the primary basis for the efficacy assessment by central assessment and investigator assessment, respectively.

3.2. Favourable effects

Per data cut-off date 24 July 2019, observed favourable effects for FAS were the ORR rate of 85 % (95% CI: 75.0%, 92.3%), while CR was 59% (95% CI: 47.4%, 70.7%). The response rates were generally consistent across various evaluable subgroups, with the point estimate for ORR ranging from 75% to 100% in individual subgroups, compared to 93% (CI: 84%-98%) which was observed for all subjects (inferential analysis set).

Regarding efficacy per data cut off 31 December 2019, the figures on ORR and CR are considered comparable to the results per data cut-off 24 July 2019 for the FAS. The rates for the primary efficacy endpoint of ORR per central assessment (85%) and for the secondary efficacy endpoint of DOR per central assessment (43% in ongoing response, DOR 13.8 months and median DOR not reached) are confirmed.

3.3. Uncertainties and limitations about favourable effects

The population for efficacy evaluation is limited to 74 patients with ECOG performance status O and 1 at baseline. It is likely that the recruited population is a selected population. Only 14 women were recruited to this trial, even though the point estimate for ORR is comparable the CI indicate that efficacy is less well characterised. Patients with bulky disease also had considerably lower rate of response, again the patient number is very low. These observations indicate this dataset is very limited and there are uncertainties as regards the external validity of the trial.

While the response to treatment is indicative of activity of a medicinal product, time-related endpoints which are regarded as a standard prerequisite for assessment of patient benefit are lacking for KTE-X19. The combination of a high rate of complete responders with durable responses may alleviate this concern, however in the present case long term efficacy data are not available yet and median DOR FU is 8.6 months. Moreover, the single arm open label design is leading to potentially biased estimates for efficacy.

The uncertainties and limitation reported above will be captured by the commitments imposed in the frame of the long term follow up study (see Annex II and RMP). In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory mantle cell lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol. The specific obligation is imposed as per the conditional marketing authorisation (see section 3.7.3).

3.4. Unfavourable effects

The unfavourable effects for patients treated with KTE-X19 do not only occur as a consequence of KTE-X19 treatment, but the bridging therapy and conditioning chemotherapy may also induce such effects.

The most common KTE-X19 related AEs reported in the phase II study, ZUMA-2, were pyrexia, hypotension, chills, tremor, anaemia, hypoxia, white blood cell count decrease, encephalopathy and tachycardia. Many of these are symptoms of the most critical AEs, in particular cytokine release syndrome (CRS), neurologic AEs, cytopenias and infections. Time to onset was usually a few days and duration was in median 11-12 days, but could last for several months, in particular for neurologic AEs. A list of unfavourable effects are expected and regarded as class effects for CAR-T cell-based therapies.

Cytokine release syndrome (CRS) observed in clinical study subjects treated with KTE-X19 has generally been manageable and reversible with supportive care measures, tocilizumab, and/or corticosteroids. In ZUMA-2 Cohort 1, 62 subjects (91%) had CRS. Fifty-two subjects (76%) had worst Grade 1 or worst Grade 2 CRS, 8 subjects (12%) had worst Grade 3 CRS, and 2 subjects (3%) had worst Grade 4 CRS. No subject had Grade 5 CRS. The median time to onset of CRS was 2 days after the KTE-X19 infusion. As of the data cutoff date, CRS had resolved in all subjects; the median duration of CRS was 11 days. CRS can be managed with standard supportive care (see SmPC).

Serious neurologic events (CART-related encephalopathy syndrome (CRES)) including cerebral oedema observed in clinical study subjects treated with KTE-X19 have generally been manageable and reversible with supportive care measures, corticosteroids, and, in the setting of CRS, with tocilizumab. In ZUMA-2 Cohort 1, 43 subjects (63%) had neurologic events. Twenty-two subjects (32%) had worst Grade 1 or worst Grade 2 neurologic events, 15 subjects (22%) had worst Grade 3 neurologic events, and 6 subjects (9%) had worst Grade 4 neurologic events. No subject had a Grade 5 neurologic event. The median time to onset of a neurologic event was 7 days. Neurologic events had resolved in 37 of 43 subjects (86%) as of the data cutoff date, and the median duration of neurologic events for those 37 subjects was 12 days. Neurologic AEs can be managed with standard supportive care and as provided in the adult Neurologic Toxicity Grading and Management Guidance included in the Summary of Product Characteristics (SmPC).

Infections are often seen in subjects treated with KTE-X19. The risk of infection may be increased by neutropenia due to preparative lymphodepleting chemotherapy, pre-existing or treatment induced hypogammaglobulinemia, prior cancer treatments, and underlying B-cell malignancy in subjects who receive KTE-X19 therapy. In ZUMA-2 Cohort 1, under the SOC of infections and infestations, 38 subjects (56%) had AEs of any grade. Of those subjects with AEs of infection, 17 subjects (25%) had worst Grade 3, 4 subjects (6%) had worst Grade 4, and 1 subject had a Grade 5 AE (staphylococcal bacteraemia). Compared with subjects who were < 65 years of age, subjects who were ≥ 65 years of age showed a trend toward a higher incidence of worst Grade 3 or higher infections (38% versus 24%).

One subject in Cohort 1, had worst Grade 3 Tumour lysis syndrome (TLS), related to KTE-X19occurring concurrently with Grade 2 CRS, Patients are monitored for signs and symptoms of TLS and events are managed according to local guidelines.

Cytopenias (thrombocytopenia, neutropenia, or anaemia) were critical AEs, in particular febrile neutropenia as this represents a high risk of infections (see above). In ZUMA-2 (combined cohorts) 93% of subjects had cytopenia of any grade; thrombocytopenia (70% of subjects), neutropenia (85% of subjects) and anaemia 65% of subjects). Compared with subjects who were < 65 years of age, subjects who were ≥ 65 years of age showed a trend toward a higher incidence of worst Grade 3 or higher thrombocytopenia (56% versus 45%). Compared with females, males showed a trend toward a higher incidence of any grade neutropenia (89% versus 73%) and worst Grade 3 or higher neutropenia (88% versus 73%).

Hypogammaglobulinemia was identified in 13 subjects (19%) in cohort 1.

In ZUMA-2 (combined cohorts) 61% of subjects had any grade cardiac arrhythmias and there were 5% of subjects that had cardiac failure.

The most common increased laboratory values are glucose, AST and ALT. Four subjects met initial laboratory criteria for Hy's law. Upon clinical review, an alternate explanation for liver dysfunction was noted in all subjects. Thus, no subject was considered to have met criteria for Hy's law. All subjects had decreased laboratory values for haemoglobin, neutrophils, leukocytes, and lymphocytes, and all but 1 subject had decreased laboratory values for platelets. The other most common decreased laboratory values observed were calcium, phosphate and albumin.

Overall, the unfavourable effects are in line with the experience made with this drug class.

3.5. Uncertainties and limitations about unfavourable effects

The major limitation for safety assessment of KTE-X19 is the limited sample size in the pivotal study ZUMA-2 including 82 subjects, of which only 68 subjects were administered the recommended dose and with rather short follow up limited to a median of 16.8 months (range: 7.2 to 37.6 months) for cohort1. The applicant has estimated that based on the ZUMA-2 study adverse drug reactions with a frequency greater than 1 in 27 could be detected if there were no background incidence. This means that only common AEs have been captured and that the knowledge about long-term safety is limited.

However, since the unfavourable effects are in line with the experience made with this drug class, there are no major concerns arising from these uncertainties and limitations. Nevertheless, there are certain limitations of the safety data which need to be followed up. These limitations relate in particular to the influence of age and sex on the incidence and severity of ADR. Long-term safety data in the study subjects are not available. The applicant committed to further characterise the long-term safety of KTE-X19 including secondary malignancies within the post-authorisation obligations.

The applicant agreed to provide additional at least 24-months long-term efficacy and safety data for full analysis set treated patients in the ongoing ZUMA-2 trial on order to allow a more comprehensive evaluation of the results of pivotal Cohort 1 in the ZUMA-2 study.

There is no safety data for use in pregnant and lactating women, in patients with important comorbidity like renal and hepatic impairment or for use in patients with cardiovascular disease and in immunocompromised

patients (patients with history of HIV infection, patients with primary immunodeficiency or patients with history of autoimmune disease). There is no safety data for subjects with history of CNS lymphoma, brain metastases or history of CNS disorders. The above is reflected in the SmPC.

Based on the submitted data the neurological events are generally reversible, though in a few cases there have been lingering minor symptoms. Longer term follow-up will be helpful in addressing if neurological adverse reactions are fully reversible or if there are long-term sequelae. Similarly, aspects regarding secondary malignancies, replication competent retrovirus analysis will be appropriately assessed in the follow-up study.

3.6. Effects Table

Effects Table for KTE-X19 (data cutoff date: 31 December 2019)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Complete response	Per central assessment in accordance to Lugano Classification (Cheson 2014)	%	FAS population (n=74): 59% (44 of 74 (95% CI: 47.4%, 70.7%)	N/A	Uncertainties: -Single arm trial -Non long-term efficacy data -Impact of high number and category of protocol deviations	
Duration of Response	DOR per central assessment in accordance to Lugano Classification (Cheson 2014)	Months	Responders in FAS population (62 of 74) Median DOR not reached Median follow up time: 13.8	N/A	Strength of evidence: Reached by 43.3% (n=32 of 74 subjects) as of data cutoff in the FAS	
Unfavourable Effects*						
Death/ fatal AE	Death any time post-infusion	fraction	22/84 (26.1%)	NA	18 deceased due to PD, 1 due to AE related to conditioning chemotherapy, 1 due to AE related to conditioning chemotherapy and KTE-X19, 1 case uncertain, 1 other	
Cytokine release syndrome (CRS)	≥ Grade 3	fraction	11/84 (13.1%)	NA	Strong evidence for relationship to the treatment with KTE-X19	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
CART-related encephalopathy syndrome (CRES)	≥Grade 3	fraction	27/84 (32.1%)	NA	Strong evidence for relationship to the treatment with KTE-X19	
Infections	≥Grade 3	fraction	25/84 (29.8%)	NA	Possibly related to conditioning chemotherapy	
Tumour lysis syndrome	≥Grade 3	fraction	1/84 (1.2%)	NA	Strong evidence for relationship to the treatment with KTE-X19	

Abbreviations: NA= not available

Notes: * data in the unfavourable effects table part are presented from the combined cohorts 1 and 2 from the ZUMA-2 pivotal study including all patients receiving conditioning chemotherapy.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Relapsed or refractory mantle cell lymphoma remains a major cause of morbidity since patients have either limited or have exhausted treatment options. As such, this patient population has a clear unmet medical need for novel therapies.

In Cohort 1, the target dose of 2 x 10^6 cells/kg demonstrated an ORR of 85% where the lower confidence interval of 75% was significantly higher than the historical control rate of 25% at a one-sided significance level of 0.025 ($p<0.001$). While ORR is reflective of activity of the medicinal product it carries no clinical relevance by itself. However, achieving CR i.e. the disappearance of all measurable evidence of disease is on the other hand considered relevant for the patient and therefore indicative of a relevant favourable effect. The majority of responders (40/56 subjects in the inferential analyses set) achieved a CR, for which durable remissions were observed (median DOR NR, 95% CI: 13.6, NE, vs DOR in all responders of NR (95% CI: 8.6, NE)). This duration of response compares favourably to the DOR reported in the historical cohort. Achieving relevant CR in conjunction with a relevant duration of response is considered clinically meaningful and relevant for the patient and therefore important for decision making in the context of a single arm trial.

While surrogacy of achieving sustained remission for OS in CAR T cell therapy is some indication that patients may achieve cure or at least long-term remission, follow-up duration is currently too short to conclude on this issue.

Results from secondary endpoints are consistent with the primary endpoint, with median PFS and OS not being reached. Again, this compares favourably to that reported in the literature and indicates the high response rates may translate into a survival benefit.

The main uncertainties regarding the benefit/risk assessment relate to the non-comparative nature of the data, the limited sample size and the short duration of follow up.

Although a historical control group was used to determine the ORR cut-off, there are uncertainties surrounding the way the historical controls were selected and the representativeness of the historic ORR for the ZUMA-2 study population. Furthermore, the ZUMA-2 study had numerous amendments and interim analyses, and these may have affected the integrity of the study to a certain extent. However, considering the compelling efficacy estimates for KTE-X19, it is not expected they will significantly impact the benefit/risk balance.

All subjects in the ZUMA-2 study received BTK inhibitors. This was also an inclusion criterion in the historical cohort. The benefit of KTE-X19 in patients that have not received BTK inhibitors is therefore unknown. The indication has been worded to reflect the study population.

The safety profile of KTE-X19 was mostly consistent with that reported for other CAR-T products. The unfavourable effects primarily are cytokine release syndrome, CART-related encephalopathy syndrome, infections and tumour lysis syndrome. Cytokine release syndrome (CRS) was observed in the majority of subjects (91%) and in subjects >65 years of age, there was a trend towards a higher incidence of worst Grade 3 CRS. Furthermore, in subjects >65 years there was also a worst Grade 3 or higher neurological events, and worst Grade 3 or higher infections. These unfavourable effects are characteristic to the product class and are considered reversible and manageable with appropriate precautions and treatments. The unfavourable effects are in line with the experience with this product class. However, the short duration of follow-up raises an uncertainty whether long-term effects are fully reversible, particularly regarding neurological events and needs to be followed up.

The uncertainties and limitation reported above will be captured by the commitments imposed in the frame of the long term follow up study (In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory mantle cell lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol) and the specific obligation imposed as per the conditional marketing authorisation (see section 3.7.3).

3.7.2. Balance of benefits and risks

The overall benefit/risk balance of KTE-X19 for the treatment of r/r MCL in patients which had received more than 2 prior therapy regimens including BTK inhibitors is favourable. The benefits for this heavily pre-treated patient population outweighs the unfavourable effects and risks which may be addressed by adequate risk mitigation measures in the RMP. The clinical data are regarded to be not comprehensive due to the uncertainties, not yet addressed by the available data, arising from the short follow-up duration and the limited sample size in view of the non-comparative data. As the benefit of the immediate availability of the ATMP outweighs the risks associated with the given uncertainties, there is agreement on granting of a conditional MA (see below).

To summarise, the following issues remain:

- Small population of treated patients (n=68)
- Limited proportion of women (n=14)
- Possibility of differences in efficacy and safety with regard to gender, age and severely diseased patients.
- Missing results on long-term efficacy and safety
- Possible age and gender differences in the pharmacology of KTE-X19 and lack of analyses on population pharmacokinetics

The applicant agrees to provide additional at least 24-months long-term efficacy and safety data for the full analysis set treated patients in the ongoing ZUMA-2 trial post-authorisation. This is considered an acceptable approach to complete the clinical data and allow a more comprehensive evaluation of the positive benefit-risk balance.

The post-authorisation measurements and obligations within a registry in the scope of a granted conditional approval are deemed adequate to provide information and results concerning the remaining uncertainties on efficacy and safety of the product as described above.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was proposed by the CAT/CHMP during the assessment, after having consulted the applicant who requested consideration for its application for a conditional marketing authorisation in accordance with Article 14-a of the above mentioned Regulation.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Furthermore, the CAT/CHMP considers that the product fulfils the requirements for a conditional marketing authorisation, as follows:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data:
    - Long-term follow-up data from ZUMA-2: In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2. Expected date for submission of the final data is 31 March 2022
    - A registry-based study: In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol. Expected date for submission of the final data is 30 September 2025.

  These post authorisation studies will provide longer term data as well as further efficacy and safety information on important subgroups (elderly, females, patients with severe disease) which are not fully represented in the pivotal study submitted for this procedure. The provision of this data post authorisation will complement the dossier in order have a comprehensive understanding of efficacy and safety and to confirm the positive benefit risk balance of the product.
- An unmet medical need will be addressed, as an additional and novel therapeutic option is given for patients with r/r MCL after having received at least two prior lines of systemic therapy including a BTK-inhibitor. Patients with mantle cell lymphoma who are refractory or who relapsed after two or more lines of approved systemic therapy including Bruton's kinase inhibitors have an overall poor prognosis as few authorised treatment options with established efficacy and safety remain. Usually, these patients are

treated by therapy regimens or modifications thereof, they have already received and on which they have relapsed at some point. Tecartus provides a treatment option for which a clinically meaningful benefit was demonstrated with respect to complete response, overall response rate and duration of response. Thus, the availability of Tecartus represents a major therapeutic advantage vis-à-vis existing treatments.

- The benefits to public health of the immediate availability outweigh the risks inherent to the fact that additional data are still required. As benefit-risk balance on basis of the current data is regarded positive, an additional therapy option for Mantle cell lymphoma patients with two or more previous systemic therapies is considered beneficial.

In addition, the CAT considers the following measures necessary to ensure the follow up of safety and efficacy:

In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory Mantle cell Lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.

3.8. Conclusions

The overall B/R of Tecartus is positive, subject to the specific obligations and conditions imposed in order to obtain further clinical data to generate a comprehensive clinical data set and inform the long-term efficacy and safety profile of the product.

The CHMP endorse the CAT conclusion on Benefit Risk balance as described above

4. Recommendations

Similarity with authorised orphan medicinal products

The CAT by consensus is of the opinion that Tecartus is not similar to Imbruvica within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appended similarity report.

Outcome

Based on the CAT review of data on quality, safety and efficacy, the CAT considers by consensus that the benefit- risk balance of Tecartus is favourable in the following indication:

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's tyrosine kinase (BTK) inhibitor.

The CAT therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Based on the draft CHMP opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tecartus in the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor is favourable and therefore recommends the granting of the conditional

marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Key elements:

Availability of tocilizumab and site qualification

To minimise the risks associated with the treatment of Tecartus, the MAH must ensure that hospitals and their associated centres that dispense Tecartus are specially qualified in accordance with the agreed controlled distribution program.

The MAH must ensure on-site, immediate access to at least 1 dose of tocilizumab for each patient as cytokine release syndrome (CRS) management medication prior to treating patients. Hospitals and their associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Tecartus will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals (HCP) involved in the treatment of a patient have completed the educational program.

Educational program – Prior to the launch of Tecartus in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP Educational program

The MAH shall ensure that in each Member State where Tecartus is marketed, all HCPs who are expected to prescribe, dispense, and administer Tecartus shall be provided with a guidance document to:

- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study
- facilitate identification of CRS and serious neurologic adverse reactions
- facilitate management of the CRS and serious neurologic adverse reactions
- ensure adequate monitoring of CRS and serious neurologic adverse reactions
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- ensure that detailed instructions about the thawing procedure are provided
- before treating a patient, ensure that at least 1 dose of tocilizumab for each patient is available on site. The qualified treatment centre must have access to additional doses of tocilizumab within 8 hours

Patient Educational program

To inform and explain to patients:

- the risks of CRS and serious neurologic adverse reactions, associated with Tecartus
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where Tecartus was received for at least 4 weeks following Tecartus infusion
- the need to carry the patient alert card at all times

Obligation to conduct post-authorisation measures>

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory Mantle cell Lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	30 June 2042

E. Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation.

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to	30 September 2025

Description	Due date
characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.	
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2.	31 March 2022

The CHMP endorse the CAT conclusion on the obligation to conduct post-authorisation measures as described above.

New Active Substance Status

Based on the CAT review of the available data, the CAT considers that autologous peripheral blood t cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured autologous anti-CD19-transduced CD3+ cells is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

The CHMP endorse the CAT conclusion on the new active substance status claim