2 September 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Tecartus (brexucabtagene autoleucel)

Treatment of acute lymphoblastic leukaemia

EU/3/20/2344

Sponsor: Kite Pharma EU B.V.

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	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
Other name(s)	-
International Non-Proprietary Name	Brexucabtagene autoleucel
Tradename	Tecartus
Orphan condition	Treatment of acute lymphoblastic leukaemia
Sponsor's details:	Kite Pharma EU B.V. Tufsteen 1 2132 NT Hoofddorp Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Kite Pharma EU B.V.
COMP opinion	10 September 2020
EC decision	19 October 2020
EC registration number	EU/3/20/2344
Type II variation procedural history	
Rapporteur / Co-rapporteur	J. Mueller-Berghaus / R. Kjeken
Applicant	Kite Pharma EU B.V.
Application submission	1 June 2021
Procedure start	19 June2021
Procedure number	EMEA/H/C/005102/II/0008/G
Invented name	Tecartus
Proposed therapeutic indication	Tecartus is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL). Further information on Tecartus can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/tecartus
CHMP opinion	21 July 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Maria Elisabeth Kalland / Bozenna Dembowska-Baginska
Sponsor's report submission	29 June 2021
COMP discussion and adoption of list of questions	14-16 June 2022
COMP opinion (adoption via written procedure)	25 July 2022

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing 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 was considered justified based on clinical data in heavily pre-treated patients showing high rate of durable responses;
- the condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukaemic forms being fatal in a few weeks if left untreated. Symptoms include persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain. The invasion of the bloodstream, the bone marrow and/or the lymphatic system result in lack of normal blood cells, bone marrow failure, and organ damage;
- the condition was estimated to be affecting less than 1.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 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 will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who were relapsed/refractory to the standard of care achieved a high rate of complete and durable responses. This compared favourably to all products authorised in the condition. The Committee considered that this constitutes a clinically relevant advantage".

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Acute lymphoblastic leukaemia (ALL) is a heterogeneous group of lymphoid disorders resulting from clonal proliferation of immature B-cell (75-80%) or T-cell (20-25%) lineages (lymphoblasts or blast cells) in the blood, bone marrow, and other lymphatic- (e.g., lymph nodes and spleen) and non-

lymphatic organs (e.g., central nervous system [CNS], liver, and bones). The leukemic blast cells displace normal healthy blood cells, and white blood cells and/or precursors of these in the bone marrow. Low blood cell counts of white blood cells, red blood cells, and platelets can subsequently cause infections, anaemia, and bleeding.

ALL occurs in a bimodal age distribution, with approximately 60% of diagnosed cases occurring in patients less than 20 years old and over 25% of diagnosed cases occurring in adult patients over 45 years old (National Comprehensive Cancer Network [NCCN], 2020). The condition can be classified in 3 subtypes, explicitly B-cell precursor ALL, mature B-cell ALL, and T-cell ALL. B-precursor ALL represents the most common form of ALL in adult patients characterized by infiltration of bone marrow and peripheral blood by small to medium-sized blast cells typically positive for the B-cell markers such as CD19, CD79a, and CD22. Moreover, 25% of adult patients with ALL have Philadelphia chromosome positive (Ph+) disease, a status which confers a very poor prognosis to the patients (Pullarkat et al., 2008).

ALL is the most common childhood malignancy. It represents 75% of childhood leukaemias and approximately 30% of all childhood cancers {Hoffman 2014, Rizzari 2014}.

The approved extension of the therapeutic indication "Tecartus is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)" falls entirely within the scope of the designated orphan condition "treatment of acute lymphoblastic leukaemia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CAT/CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

There has been no change to the chronically debilitating and/or life-threatening nature of the condition since the orphan designation in 2020.

Clinically, ALL may present as asymptomatic or acute with life-threatening haemorrhage, infection, or episodes of respiratory distress. The most common ALL symptoms reported are often related to bone marrow failure and include fatigue, intolerance of physical activities due to anaemia, easy bruising, and excess bleeding, caused by onset of thrombocytopenia. Other notable symptoms include persistent fever, infections, bone and joint pain, night sweats and weight loss. The invasion of the tumour cells in the bloodstream, the bone marrow, and/or the lymphatic system result in lack of normal blood cells, bone marrow failure, and specific organ damage. In addition, acute leukaemic forms are being fatal in a few weeks if left untreated.

In paediatric population, for the 20% of patients who relapse after an initial response, re-induction can yield remission in 65% to 85% of patients; however, long-term survival rates are significantly lower (40% to 50%) in relapsed patients than in non-relapsed patients (5-year overall survival [OS] of 90%) (Malard 2020). Outcomes are also worse in patients who are primary refractory, relapse after first salvage and beyond setting or relapsed or refractory (r/r) after SCT (Gaynon 1998, Hoffman 2014, Malempati 2007, Nguyen 2008).

Although ALL is less common in adults, both the prognosis and outcome are worse in adults when compared to children. While initial complete remission (CR) rates in adults are high (80-90%) and median duration of first remission in most studies is 18 months or more, most patients eventually

relapse. For example, in patients treated with chemotherapy, CR rates were approximately 20% to 40% lower in patients who relapsed within 12 months of an initial response and OS was approximately 6 months with a median survival time ranging from 2 to 8 months {Fielding 2007, Gokbuget 2012, Kantarjian 2010, O'Brien 2008, Oriol 2010, Tavernier 2007}.

The condition can be considered both chronically debilitating and life threatening.

Number of people affected or at risk

At the time of designation, the prevalence figure accepted led to the conclusion that ALL was affecting less than 1.4 in 10,000 people in the EU. The sponsor does not discuss this but seem to use a different methodology and possible some different references and suggest a 1-year prevalence of 3.46 per 10,000 based on data from the Global Burden of Disease database (GBD; EU28; 2019 data). It is not clear why a 1-year prevalence has been used as in general the disease duration is longer, and in the orphan designation a 5-year duration was used. The sponsor seems also to have used data from all of Europe while only data for the EU27 plus the EEA countries are to be used for the prevalence estimate. Furthermore, there is no explanation of the GBD, what sources it uses, and the methodology used to come to this conclusion. Neither does the sponsor provide a discussion on the outcome of the claimed literature search.

It is not agreed with the sponsor that there is a paucity in data sources reporting the incidence or prevalence in the EU. GLOBOCAB, NORDCAN, and ECIS are all relevant sources and there are several national cancer registries. In case a prevalence figure cannot be found, the prevalence can be calculated by using the incidence times duration (I*D) as suggested in the https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/points-consider-estimation-reporting-prevalence-condition-orphan-designation_en.pdf

Although it is acknowledged that ALL affects less than 5 in 10,000 people in the EU, the sponsor should recalculate the prevalence estimate based on more relevant and comprehensive data sources on ALL, including ECIS for indirect estimation. The sponsor should specifically describe the methods used for the estimation and present the different sources used for the reported calculations in a tabular format. Improvements in survival due to current treatment options for ALL and better treatment outcomes should be considered and updated European survival data should be used for the estimate. In addition, sensitivity analyses of the reported calculations should be performed to reflect the variability and uncertainties from the different sources used.

The sponsor provided an updated prevalence calculation based on a direct method and an indirect approach, the latter which uses the standard formula of Prevalence = Incidence x Duration of disease, as a response to a list of question from the COMP.

For the direct method, a review of published literature and relevant online databases was conducted to search for 5-year or higher ALL prevalence estimates from studies published during January 1, 2012, through June 6, 2022. Only studies examining individuals residing in EU countries were considered. The reported ALL prevalence estimates ranged from 0.11 to 0.66 per 10,000 for a 5-year prevalence and 0.76 to 1.12 per 10,000 for a 10-year prevalence (Table 3, from sponsors answers to the list of questions).

Table 1. Sources of data for direct prevalence estimates of ALL

Source	Country	Time Period	5-year prevalence (per 10,000)	10-year prevalence (per 10,000)
The Haematological Malignancy Research Network (HMRN)[1]	UK	2006-2016	0.44	0.76
GLOBOCAN[2]	EU	2006-2015	0.52	NR
NORDCAN	Nordic countries[3]	2011-2020, Female	0.44	0.83
		2016-2020, Male	0.66	1.12
REDECAN[4]	Spain	2016-2020, Female	0.11	NR
		2016-2020, Male	0.15	NR

[1]age and sex-standardized
[2]computed by assuming that 15% of all leukemia cases are ALL (Bassan *et al.*); leukemia 5-year prevalence (2020)(3.49) estimated using age-specific ratios of incidence to 5-year prevalence from Nordic countries during 2006-2015 period
[3]includes Sweden, Denmark, Finland, Norway, and Iceland
[4]computed by assuming that 15% of all leukemia cases are ALL (Bassan *et al.*); leukemia 5-year prevalence (2020): 0.76 (female) and 1.03 (male)

For the indirect estimate, the sponsor used data from the European Cancer Information System (ECIS) to calculate the incidence. The 2020 crude incidence of leukaemia in the 27 EU member states (EU27) was reported to be 1.49 per 10,000 persons (ECIS, 2022). In the initial maintenance report, the sponsor estimated that 15% of leukaemia cases in adults are ALL as reported by Bassan and colleagues (Bassan et al., 2004). The sponsor conducted upon request a more recent literature search of epidemiology data on ALL and identified a study published by Dong and colleagues (Dong et al., 2020) which reported that ALL comprises 21.3% of all leukaemia cases in Western Europe, 25.7% of leukaemia cases in Eastern Europe, and 23.8% of leukaemia cases in Central Europe based on data from 2017. Since the percentage of ALL among all leukaemia cases reported in the literature varied, the sponsor calculated a range of ALL incidence estimates based on the lowest (15%) and highest (25.7%) reported values. The estimated incidence of ALL, which was calculated using Incidence of leukaemia multiplied by Proportion of leukaemia presented as ALL, thus ranged from 0.224 (1.49 x 15%) to 0.383 (1.49 x 25.7%) per 10,000 persons in the EU.

Concerning the estimate for the disease duration of the condition, the sponsor reviewed real-world studies from the literature, which revealed that the 5-year OS for adult patients diagnosed with ALL ranges from 32%-43.4% (Maheswaran and Morley, 2018; Lennmyr et al., 2019). Since the data found on OS was considered limited by the sponsor, studies examining relative survival were also included. Still, disease duration based on relative survival was regarded as more conservative as it represents cancer survival in the absence of other causes of deaths. According to the sponsor, all 5-year survival rates reported in the literature were found to be less than 50%. The median survival for patients diagnosed with ALL was therefore anticipated by the sponsor to be less than 5 years.

Using the formula P=I*D, and both the low and high estimates for the ALL incidence, the updated prevalence of ALL was estimated to span between 1.12 per 10,000 (0.224 x 5 years) and 1.92 per 10,000 (0.383 x 5 years) persons in the European community.

The upper range of the revised estimate of 1.9 in 10,000 persons could be accepted for this maintenance procedure and is also in line with the 10-year prevalence from NORDCAN and prevalence figures recently considered by the COMP.

Article 3(1)(b) of Regulation (EC) No 141/2000

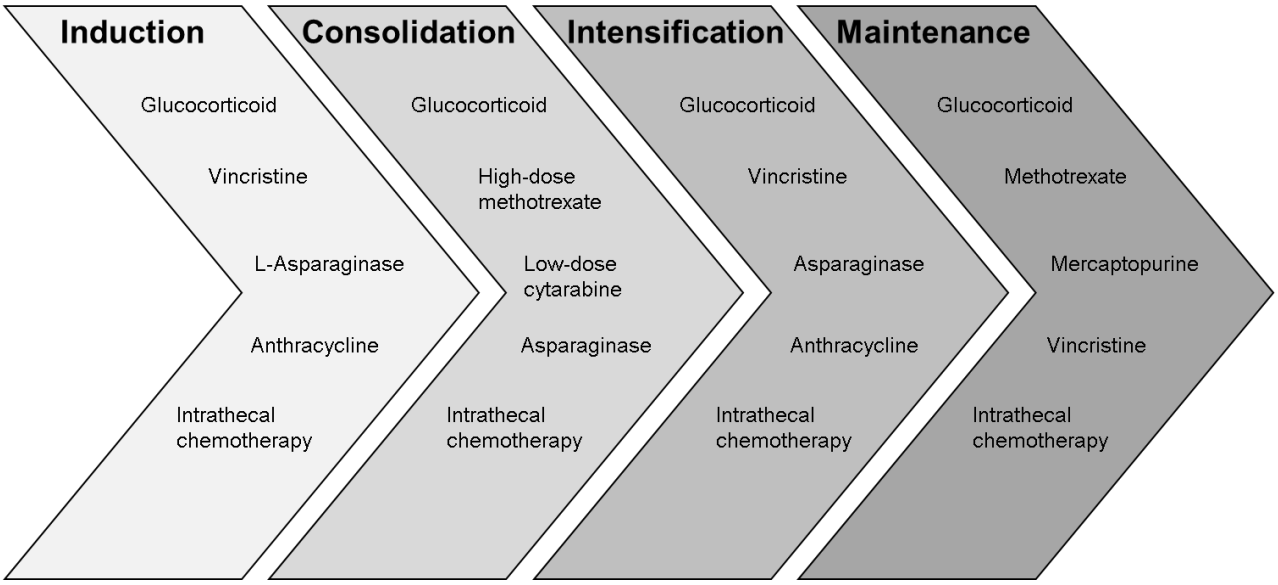
Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor provided a detailed description of both EU and nationally approved therapies used for treatment of adult patients with ALL. Targeted therapies that have been approved more recently include tisagenlecleucel (Kymriah), blinatumomab (Blincyto), and inotuzumab (Besponsa). Other medicinal products authorized in the community for the treatment of ALL are cyclophosphamide (Sendoxan), cytarabine (generics), fludarabine, clofarabine (Evoltra and generics), daunorubicin (Cerubidine), doxorubicin (generics), idarubicin (Zavedos and generics), asparaginase (Spectrila), pegaspargase (Oncaspar), crisantaspase (Erwinase), melphalan (Phelinun), mercaptopurine (Xaluprine and generics), methotrexate (Jylamvo and generics), nelarabine (Atriance), liposomal vincristine sulphate, imatinib (Glivec and generics), dasatinib (Sprycel), and ponatinib (Iclusig).

Several of the anti-neoplastic agents used for treatment of ALL are given in varying doses and schedules, based on patient tolerability and regional preferences, that can be separated in four distinct phases after initial diagnosis: induction (1–2 months), consolidation (6–8 months), late intensification (re-induction) and long-term maintenance (i.e., 2.5–3 years is optimal and usually recommended) (Figure 1).

Figure 1. Overall concept of Front-line treatment of ALL.



Adapted from {Malard 2020}

Allogeneic stem cell transplantation (allo-SCT) remains the standard consolidation treatment for adults and high-risk patients, in particular Ph+ ALL patients who are biologically fit and have an according donor. The continuous improvement in supportive care has significantly reduced transplant-related mortality {Malard et al., 2014}. In addition, the outcome of Ph+ ALL patients have significantly improved with the introduction of tyrosine kinase inhibitors (TKIs).

The sponsor is specifically targeting an adult population and refer to the ESMO treatment guidelines for adults with ALL {Hoelzer et al., 2016}. Age and frailty are both considered during customization of treatment regimens. For young adult ALL patients (≤ 35 to 40 years), increased drug intensity is recommended, without SCT. For the older adult ALL patients (> 35 to 40, but ≤ 55 to 60 years), doses similar to younger patients are recommended, but with an increased role of allo-SCT. Elderly ALL patients (> 55 to 60 years), on the other hand, receive less intensive therapy to reduce early treatment-related death. This is often accomplished by avoiding anthracyclines and alkylating agents. Lastly, frail patients (> 70 to 75 years), typically not considered candidates for major intensive therapy, may also potentially benefit from less intensive therapies.

The indication extension of Tecartus is intended to include treatment of adult patients with r/r B-cell precursor ALL. A table overview with a list of medicinal products authorised in the EU for the treatment of adult patients with r/r B-precursor ALL and whether they are considered relevant for a discussion on the significant benefit of brexucabtagene autoleucel (hereinafter referred to as brexu-cel; Tecartus) in ALL is presented below.

Table 2. Approved products for the treatment of adults with r/r B-precursor ALL in the EU

EU Centralised number	**Product name (INN)**	**Approved therapeutic indication**	**Significant benefit discussion needed**
EMEA/H/C/004119	Besponsa (inotuzumab ozogamicin)	Besponsa is indicated as monotherapy for the treatment of adults with r/r CD22+ B-cell precursor ALL. Adult patients with Ph+ r/r B-cell precursor ALL should have failed treatment with at least 1 TKI.	Yes, there is a complete overlap between the two indications
EMEA/H/C/003731	Blincyto (blinatumomab)	Blincyto is indicated as monotherapy for the treatment of adults with CD19+ r/r B-precursor ALL. Patients with Ph+ B-precursor ALL should have failed treatment with at least 2 TKIs and have no alternative treatment options. Blincyto is indicated as monotherapy for the treatment of adults with Ph- CD19+ B-precursor ALL in first or second CR with MRD greater than or equal to 0.1%.	Yes, there is a complete overlap between the two indications
EMEA/H/C/004090	Kymriah (tisagenlecleucel)	Kymriah is indicated for the treatment of paediatric and young adult patients up to and including 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.	No, covers only young adult patients up to 25 years of age

EMEA/H/C/000406	Glivec (imatinib)	Imatinib is indicated for adult patients with newly diagnosed Ph+ ALL integrated with chemotherapy and adult patients with relapsed or refractory Ph+ ALL as monotherapy.	No, covers only adults with Ph+ ALL
EMEA/H/C/000709	Sprycel (dasatinib)	Sprycel is indicated for the treatment of adult patients with Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior therapy.	No, covers only adults with Ph+ ALL
EMEA/H/C/002695	Iclusig (ponatinib)	Ponatinib is indicated for adult patients with Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.	No, covers only adults with Ph+ ALL

For the purpose of the orphan regulation, a satisfactory method has to overlap completely with the target patient population for Tecartus. This means that TKIs will have been used before treatment with Tecartus, they are also only indicated for Ph+ ALL and there is no such restriction for Tecartus.

Inotuzumab ozogamicin has an indication for a similar patient population, however, according to the SmPC section 4.1 of this product it is states that "When considering the use of BESPONSA as a treatment for relapsed or refractory B cell ALL, baseline CD22 positivity of > 0% using a validated and sensitive assay is required prior to initiating treatment (see section 5.1)." However, as all patients with B-cell precursor ALL are expected to be CD22 positive (ZM van Zelm et al., 2005), this specification does not preclude the target patient population for Tecartus to be treated with inotuzumab ozogamicin.

Tisagenlecleucel is indicated for children and young adults up to and including 25 years of age which is a different target population as compared to that for Tecartus which will be used only in adults over 25 years of age with ALL.

The conclusion is that blinatumomab and inotuzumab ozogamicin can be considered as satisfactory methods for the treatment of the same patient population as Tecartus.

Significant benefit

The clinical development programme for the indication expansion of brexu-cel to include treatment of adult patients with r/r ALL is based on data from an ongoing, open-label, single-arm, multicenter, phase 1/2 study called ZUMA-3. The study is designed to evaluate the safety and efficacy of brexu-cel in adult patients with r/r B-precursor ALL with morphological disease in the bone marrow (>5% blast cells). Patients with Ph+ disease were eligible if they were intolerant to TKI therapy or if they had r/r disease despite treatment with at least two different TKIs.

The pivotal part of the study is the phase 2 portion, where all patients (n=55) have been treated with the recommended phase 2 dose (RP2D), a single intravenous infusion of brexu-cel, after completion of lymphodepleting chemotherapy for ALL. The primary endpoint for the phase 2 part is the overall complete remission (OCR) rate, defined as the proportion of patients treated with brexu-cel who achieved either a CR or a CR with incomplete hematologic recovery (CRi) as per an independent review committee (IRC). Secondary efficacy endpoints included minimal residual disease (MRD) status, duration of remission (DOR), relapse-free survival (RFS), and OS.

Efficacy and safety data from the adult ALL population from the phase 1 portion of ZUMA-3 was submitted as part of the initial application for orphan designation for KTE-X19 for treatment of ALL and formed the basis of the designation. For the maintenance report, data from the pivotal phase 2 portion of ZUMA-3, up to the data cut-off (DCO) of 9 Sep 2020, is provided to support significant benefit.

The arguments on significant benefit are based on an improved efficacy of brexu-cel over approved therapies for adult patients with r/r B-precursor ALL. The sponsor provides a comparative discussion on the key efficacy results from the pivotal phase 2 portion of ZUMA-3 (DCO: 09-Sep-2020and the pivotal studies for blinatumomab (TOWER) and inotuzumab (INO-VATE) as summarized below.

Table 3. Comparison of key efficacy data from ZUMA-3, TOWER and INO-VATE

	KTE-X19		**Blinatumomab**	**Inotuzumab**
	ZUMA-3 mITT Analysis Set (N = 55)	**ZUMA-3 FAS (N = 71)**	**TOWER (N= 405[a])**	**INO-VATE (N=218[b])**
OCR (CR + CRi) rate (95% CI)	70.9%) (57%, 82%)	54.9% 43%, 67%	32%[c] (28%, 37%)	Not comparable to ZUMA-3
CR rate (95% CI)	56.4% (42%, 70%)	43.7% (32%, 56%)	33.6% (28%, 39.5%)	35.8% (26.8%, 45.5%)
MRD negative rate Overall [d] (95% CI)	76%[e] (63%, 87%)	59%[e] (47%, 71%)	29.9% (24.5%, 35.7%)	Not comparable to ZUMA-3
MRD negative rate among OCR (CR or CRi) subjects[d,f,](95% CI)	97% (87%, 100%)	97% (87%, 100%)	76.3% (66.6%, 84.3%)	78.4% (68.4%, 86.5%)
KM median (95% CI) DOR (months)	12.8[g] (8.7, NE)	12.8[g] (8.7, NE)	7.3 (5.8, 9.9)	5.4 (4.2, 8.0)
KM median (95% CI) OS[h] (months)	18.2[h] (15.9, NE)	19.2[h] (10.4, NE)	7.7 (5.6, 9.6)	7.7 (6.0, 9.2)

Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of remission; KM, Kaplan-Meier; mITT, modified intent-to-treat; MRD, minimal residual disease; NE, not estimable; OCR, overall complete remission; OS, overall survival; RFS, relapse-free survival.

Note: 95% CIs are based on the Clopper-Pearson method.

a 271 subjects treated with Blinatumomab

b 164 subjects treated with Inotuzumab

c Pooled OCR from TOWER. The number of OCR responders across the two randomized arms were combined and divided by the total sample size across the arms to calculate the OCR proportion. Methods as per Meta-analysis report.

d MRD status is determined by the central laboratory. Numerators for MRD negative rate are based on an MRD-negative finding at any postinfusion visit.

e Percentage is based on the number of subjects in the mITT analysis set.

f Percentage is based on the number of subjects with OCR (CR or CRi). Disease response is based on central assessment.

g DOR is defined as the time from the first complete remission (CR or CRi) to relapse or death from any cause in the absence of documented relapse. 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, new anticancer therapy (excluding resumption of a TKI) start date, or SCT date, whichever was earlier.

h OS for the mITT analysis set is defined as the time from the KTE-X19 infusion date to the date of death from any cause. OS for the full analysis set is defined as the time from the enrollment date to the date of death from any cause.

g RFS for the mITT analysis set is defined as the time from the KTE-X19 infusion date to the date of relapse or death from any cause. Subjects who received KTE-X19 but did not achieve CR or CRi as the best overall response were counted as events on the KTE-X19 infusion date. RFS for the full analysis set is defined as the time from the

enrollment date to the date of relapse or death from any cause. Subjects who received KTE-X19 but did not achieve CR or CRi as the best overall response and subjects who were enrolled but not dosed were counted as events on the enrollment date.

The median number of prior lines of therapy in the phase 2 portion of ZUMA-3 was 2 (range: 1-8) and almost half of the patients (47%; 26/55) had received at least 3 prior therapies. Among the patients who received brexu-cel, 55% (30/55) were naïve to blinatumomab therapy and 78% (43/55) were naïve to inotuzumab therapy, while 42% (23/55) had previously received an allo-SCT. Most patients (78%; 43/55) had r/r disease after 2 or more lines of therapy, 33% (18/55) had primary refractory disease, and 29% (16/55) experienced a first relapse to their first CR ≤ 12 months. In addition, 27% (15/55) of the patients in the modified intention-to-treat (mITT; all infused) population were Ph+.

Comparative discussion of brexu-cel versus blinatumomab

The bispecific CD19-directed CD3 T-cell engager blinatumomab (Blincyto) was granted approval in the EU as monotherapy, for the treatment of adults with Ph- CD19+ r/r B-precursor ALL, in first or second CR. Full approval in adult patients was granted based on results form a randomised, open-label, multicentre, phase 3 study called TOWER. Patients were randomized 2:1 to receive blinatumomab (n=271) or investigator-selected, standard of care (SOC) chemotherapy (n=134). The primary endpoint was OS. The median OS was 4.0 months (95% CI: 2.9, 5.3) in the SOC chemotherapy arm compared to 7.7 months (95% CI: 5.6, 9.6) in the blinatumomab arm. The OCR rates achieved in the blinatumomab and SOC chemotherapy arm were 43.9% (119/271; 95% CI: 37.9, 50.0) and 24.6% (33/134; 95% CI: 17.6, 32.8), respectively. The stand-alone CR rates for those who were treated with blinatumomab versus chemotherapy were 33.6% vs. 15.7%. The MRD–negative status among patients who achieved a CR/CRi was more frequent for patients treated with blinatumomab than chemotherapy (76.3% vs. 48.5%). Among patients who achieved a CR/CRi, the median DOR with blinatumomab and chemotherapy were 7.3 months (95% CI: 5.8, 9.9) and 4.6 months (95% CI: 1.8, 19.0), respectively. A total of 24% of the patients in both treatment arms underwent a subsequent allo-SCT.

Blinatumomab was also evaluated in an open-label, multicentre, single-arm phase 2 study (MT103-211) of 189 adult patients with Ph- r/r B-precursor ALL, which was the basis for the EU conditional approval in 2015. The primary endpoint was the CR/CRi rate within 2 cycles of treatment with blinatumomab. In total, 42.9% (81/189; 95% CI: 35.7, 50.2) of the patients achieved a CR/CRi and 33.3% (63/189) a CR within the first 2 treatment cycles, with most of the responses occurring within 1 cycle of treatment. A total of 17% (32/189) underwent allo-SCT while still in CR/CRi induced by blinatumomab. The median OS was 6.1 months (95% CI: 4.2, 7.5) (Blincyto SmPC).

The efficacy and safety of blinatumomab in adult patients with r/r Ph+ B-precursor ALL (N=45) were evaluated in an open-label, multicentre, single-arm phase 2 study (ALCANTARA). Eligible patients were r/r to at least 1 second generation or later TKI or intolerant to second generation TKI, and intolerant or refractory to imatinib. The primary endpoint was the CR/CRi rate within 2 cycles of treatment with blinatumomab. In total, 35.6% (16/45; 95% CI: 21.9, 51.2) of the treated patients achieved a CR/CRi and 31.1% (14/45) a CR within the first 2 treatment cycles. A total of 11.1% (5/45) of the patients underwent allo-SCT while still in CR/CRi induced by blinatumomab. The median OS was 7.1 months (95% CI: 5.6, NE) (Blincyto SmPC).

The response rates observed in the phase 2 portion of ZUMA-3 compare favourably to those observed with blinatumomab in the pivotal TOWER study. In ZUMA-3, an OCR rate of 70.9% (95% CI: 57, 82) was demonstrated in the mITT analysis set and 54.9% (95% CI: 43, 67) in the FAS. The confidence interval (CI) for the OCR rate in the mITT population of ZUMA-3 did not overlap with the CI for the OCR rate in the TOWER study. The median DOR observed in ZUMA-3 (12.8 months for both the mITT and FAS) also demonstrated a more durable response compared to that observed in the blinatumomab

arm in the TOWER study. In addition, nearly half (45%) of the patients in the mITT analysis set of ZUMA-3 had previously received blinatumomab and the OCR rate in these patients, even after blinatumomab failure, remained high at 60%.

In conclusion, the efficacy results of brexu-cel in adult patients with r/r B-precursor ALL from ZUMA-3 appear to be considerable better than the efficacy results reported from the three pivotal studies for blinatumomab (Blincyto).

Comparative discussion of brexu-cel versus inotuzumab ozogamicin

The anti-CD22 antibody-drug conjugate inotuzumab (Besponsa) was approved in the EU (MA in 2017) as monotherapy for the treatment of adults with r/r CD22+ B-precursor ALL, where patients with Ph+ ALL should have failed treatment with at least 1 prior second or third generation TKI. The approval was granted based on results from a randomized, open-label, multicentre, phase 3 study called INO-VATE. The patients enrolled were randomised to receive either inotuzumab (n=164) or investigator's choice of chemotherapy (n=143 mITT/162 ITT), specifically fludarabine plus cytarabine plus granulocyte colony-stimulating factor (FLAG; n=93 mITT/102 ITT), mitoxantrone/ cytarabine (MXN/Ara-C; n=33 mITT/38 ITT), or high dose cytarabine (HIDAC; N=17 mITT/ 22 ITT). A total of 85% (276/326) of the randomized patients had Ph- ALL, whereas 15% (49/326) had Ph+ ALL.

The study had two co-primary endpoints: 1) CR/CRi as assessed by BIRC and 2) OS (ITT). The secondary endpoints included MRD negativity, DOR, SCT rates, and PFS. The OCR rates achieved in the inotuzumab, and chemotherapy treatment arms were 80.7% (88/109; 95% CI: 72.1, 87.7) and 29.4% (32/109; 95% CI: 21.0, 38.8), respectively. The stand-alone CR rates for patients who were treated with inotuzumab versus chemotherapy were 35.8% vs 17.4%. The MRD−negative status among those who achieved a CR/CRi was more frequent for patients treated with inotuzumab than chemotherapy (78.4% vs 28.1%). The median DOR among patients who achieved a CR/CRi with inotuzumab and chemotherapy were 5.4 months and 4.2 months, respectively. The study's co-primary endpoint of improvement in OS with inotuzumab compared to chemotherapy was 7.7 months versus 6.2 months (HR 0.75 [95% CI: 0.59, 0.96]). A total of 48.2% (79/164) in the inotuzumab arm and 22.2% (36/162) in the chemotherapy treatment arms had a follow-up SCT. The approval for inotuzumab was granted based on CRs, DOR, and MRD−negative rates observed with inotuzumab (Besponsa SmPC).

The sponsor highlighted that all randomized patients in the pivotal phase 3 study INO-VATE for inotuzumab (Besponsa; ITT population) had received either one (66%; 215/326; salvage 1) or two (33%; 108/326; salvage 2) prior lines of antineoplastic therapies for ALL, and that almost none had three or more prior therapies. Among the 55 patients who received brexu-cel in the phase 2 portion of ZUMA-3 (mITT population), 18.2% (10/55) had received one line of prior therapy, 34.5% (19/55) had received two lines of prior therapy, and 47.3% (26/55) had received at least 3 lines of prior therapy. The studied patient population in the INO-VATE study thus appear to be less heavily pre-treated than those enrolled into the phase 2 portion of ZUMA-3.

The efficacy results presented for the patient population in the phase 2 portion of ZUMA-3 appear to be lower in terms of OCR rates than reported in the pivotal study for inotuzumab (Bensponsa) in patients with r/r B-precursor ALL (70.9% in the mITT and 54.9% in the FAS vs. 80.7%). Nevertheless, the responses observed to brexu-cel in r/r ALL patients appear to be better in terms of the CR rates than for inotuzumab (56.4% in the mITT and 43.7% in the FAS vs. 35.8%), and the median OS was longer for those treated with brexu-cel in ZUMA-3 with 18.2 months in the mITT and 19.2 months in the FAS compared to 7.7 months for patients treated with inotuzumab.

Considering that outcomes in ALL significantly decrease with each line of therapy (Gokbuget et al, 2016), the efficacy data for brexu-cel in ZUMA-3 provides evidence for an improved benefit in heavily

pre-treated patients compared to inotuzumab, for which benefits have only been demonstrated for a much less heavily pre-treated patient population. The median DOR in patients treated with brexu-cel in the phase 2 portion of ZUMA-3, defined as the time between CR/CRi to relapse or any death in absence of documented relapse, was 12.8 months (95% CI: 8.7, NE). In the INO-VATE study, the median DOR among patients who achieved a CR/CRi with inotuzumab was 5.4 months (95% CI: 4.2, 8.0). Based on these results, it could be concluded on a significant benefit of brexu-cel over inotuzumab (Besponsa) in adult patients with r/r B-precursor ALL patients based on the clinical data obtained from ZUMA-3.

In general, the comparison across different clinical studies is technically not very informative in terms of quantifying the effects observed. However, taking into consideration that brexu-cel overall appeared to perform better than both blinatumomab and inotuzumab in terms of higher CRs and longer DOR, the arguments of significant benefit over currently authorised methods of treatment for the target r/r ALL population could be accepted based on improved efficacy.

4. COMP position adopted on 25 July 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of acute lymphoblastic leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.9 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukaemic forms being fatal in a few weeks if left untreated. Symptoms include persistent fever, infections, anaemia, fatigue, breathlessness, and bone and joint pain. The invasion of tumour cells in the bloodstream, the bone marrow and/or the lymphatic system result in lack of normal blood cells, bone marrow failure, and organ damage;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Tecartus may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical study data which demonstrated improved and sustained complete remission rates after treatment with Tecartus as compared to both Blincyto and Besponsa in heavily pre-treated adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Tecartus, 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, brexucabtagene autoleucel for treatment of acute lymphoblastic leukaemia (EU/3/20/2344) is not removed from the Community Register of Orphan Medicinal Products.