National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tisagenlecleucel-T for previously treated B-cell acute lymphoblastic leukaemia in people aged 3 to 21 at initial diagnosis [ID1167]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	-	-	-
Wording	Novartis Pharmaceuticals UK Limited	Novartis anticipates that the marketing authorisation for tisagenlecleucel as a treatment for relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (ALL) will be as follows: "Paediatric and young adult patients aged 3 to 25 years with relapsed or refractory B-cell acute lymphoblastic leukaemia" Novartis therefore requests that the wording in the draft remit be updated to reflect this. Novartis are aware that the eligibility criteria for the ELIANA trial specified that patients be of age 3 to 21 years at the time of initial diagnosis.[1] However, although age at diagnosis is up to 21 years in this trial, Novartis considers the age at which patients would receive tisagenlecleucel to be more appropriate when describing the patient population eligible for treatment i.e., time may have elapsed between diagnosis and treatment. In tisagenlecleucel clinical trials which included ALL patients (ELIANA,	Comment noted. Remit has been amended and broadened. The technology will be appraised within its marketing authorisation.

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		ENSIGN and B2101J), [redacted] (hence, the age of 25 years specified in the marketing authorisation application).[1-3] **References** 1. Novartis Pharmaceuticals UK Ltd. Data on File. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Interim Clinical Study Report. 2. Novartis Pharmaceuticals UK Ltd. Data on File. ENSIGN: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Interim Clinical Study Report. 3. Novartis Pharmaceuticals UK Ltd. Data on File. B2101J: A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Patients with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma. Interim Clinical Study Report.	
Timing Issues	Novartis Pharmaceuticals UK Limited	There is a considerable unmet need for new treatment options that can provide sustained remissions, improve health-related quality of life, and provide the hope of a cure for paediatric and young adult patients with r/r B-cell ALL. Current treatment options for these patients are mainly used as a bridge to haematopoietic stem cell transplantation (HSCT), however, responses to these treatments are sub-optimal and not all patients are	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/

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		eligible to receive HSCT, which is itself associated with life-threatening adverse effects. This appraisal is therefore highly relevant to the NHS and should be treated accordingly as a matter of urgency by NICE.	guidance/indevelopment/gid-ta10270. No action required.
Additional comments on the draft remit	Novartis Pharmaceuticals UK Limited	No additional comments	Comment noted. No action required.

Comment 2: the draft scope

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Background information	Novartis Pharmaceuticals UK Limited	The background information section reports the proportion of adult ALL patients that have Philadelphia-chromosome-positive disease as being 20%. Given the 'Population' under consideration in this appraisal (3 to 25 years), Novartis requests that additional information is provided to note that Ph+ ALL is much less prevalent amongst paediatric patients and young adults. Guidelines from the National Comprehensive Cancer Network (NCCN) 2017 presents estimates of 3% and 5–7% for the proportion of Ph+ ALL cases amongst paediatric and adolescent/young adult ALL patients, respectively (the latter defined as patients aged 15–39 years old).[4] **References** 4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukaemia. Version 1. 2017.	Comments noted. The background has been amended to "A specific chromosomal abnormality known as the 'Philadelphia chromosome' is present in 3-7% of paediatric and young adults with ALL."

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The technology/ intervention	Novartis Pharmaceuticals UK Limited	The description of the technology incorrectly states that: "[Tisagenlecleucel] is being studied in a clinical trial compared to placebo in people with…." Novartis requests this to be corrected to: "[Tisagenlecleucel] is being studied in a single-arm clinical trial in people with…" Furthermore, the scope should be updated to note that tisagenlecleucel has also been studied in two other single-arm trials (ENSIGN and B2101J) which have included paediatric and young adult patients with r/r B-cell ALL.[2, 3] The scope provides a summary of inclusion criteria for the ELIANA trial (received previous treatment or be ineligible for allogeneic SCT or tyrosine kinase inhibitor therapy), which refers to how relapsed and refractory disease had been defined (see Table 1 at the end of this document for details from the ELIANA Interim Clinical Study Report). Novartis requests that when referring to patients who are ineligible for tyrosine kinase inhibitor therapy, it should be noted that this is specific to those with Ph+ ALL. Novartis requests that the description of the technology be amended to note that chimeric antigen receptor T-cell (CAR-T) therapy modifies the patient's T-cells (rather than "blood cells"). **References** 2. Novartis Pharmaceuticals UK Ltd. Data on File. ENSIGN: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Interim Clinical Study Report.	Comments noted. This section has been amended to refer to the ELIANA and ENSIGN trials: "It is being studied in single-arm clinical trials in people with relapsed or refractory B-cell ALL who were aged 3 to 21 years at initial diagnosis". The B2101J trial is referred to in the following sentence "It is also being studied in a single arm trial which recruited people age 1 to 24 years." The summary of inclusion criteria for the ELIANA (and ENSIGN) trials have been amended to "… be ineligible to receive an allogeneic stem cell transplant or for Philadelphia-chromosome-positive

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		3. Novartis Pharmaceuticals UK Ltd. Data on File. B2101J: A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Patients with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma. Interim Clinical Study Report.	disease, tyrosine kinase inhibitor therapy". The technology description has been amended to "Tisagenlecleucel-T (Kymriah, Novartis) is a chimeric antigen receptor (CAR) T cell therapy that changes the patient's T-cells to target a protein called CD19."
Population	Novartis Pharmaceuticals UK Limited	As for the draft remit, Novartis requests that the wording for 'Population' be updated to be consistent with the anticipated wording for the licensed indication. "Paediatric and young adult patients aged 3 to 25 years with relapsed or refractory B-cell acute lymphoblastic leukaemia"	Comment noted. The population has been amended in line with the expected marketing authorisation and NICE's preferred writing style.
Comparators	Novartis Pharmaceuticals UK Limited	Novartis acknowledge the lack of NICE guidance or UK guidelines available for the treatment paediatric and young adult patients aged 3 to 25 years with r/r B-cell ALL. Expert clinician feedback sought by Novartis thus far is that 'established clinical management' could include blinatumomab or salvage chemotherapy. Novartis are still looking into what relevant comparators might be and therefore flexibility is requested from NICE to accept other comparators should it become apparent that there is significant usage.	Comments noted. The comparators have been amended to reflex the possible positioning of tisagenleleucel-T in the treatment pathway of ALL.

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		Whilst there may be differences in the order in which these therapies are tried in clinical practice for patients below 18 years old versus those aged 18-25 years, it is Novartis's understanding that ultimately the same regimens will be tried for both age categories. Therefore, these same therapies are likely to represent comparators for all eligible patients aged 3 to 25 within the indicated population. It is also Novartis's understanding that best supportive care would rarely, if ever, be considered a relevant treatment option and hence may not constitute a part of established clinical management. Novartis would also like to note that the proportion of patients with Ph+ ALL within the eligible population will constitute a significant minority and therefore tyrosine kinase inhibitors are not considered to represent relevant comparators to this submission.	
Outcomes	Novartis Pharmaceuticals UK Limited	Novartis requests that "progression-free survival" be replaced as an outcome with "relapse-free survival" and "event-free survival". Unlike progression free-survival, relapse-free survival and event-free survival were included in the final scope for TA450 and were included as secondary endpoints in the ELIANA trial.[1, 5] Similarly, Novartis requests that "response rates" be changed to "remission rates". **References** 1. Novartis Pharmaceuticals UK Ltd. Data on File. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Interim Clinical Study Report. 5. National Institute for Health and Care Excellence. TA450: Blinatumomab for previously treated Philadelphia-chromosome-	Comments noted. The outcomes have been amended to "progression-free survival (including relapse-free and event-free survival) and response rate (including remission rates)".

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		negative acute lymphoblastic leukaemia. Available at: https://www.nice.org.uk/guidance/ta450 [Last accessed: 05 December 2017].	
Economic analysis	Novartis Pharmaceuticals UK Limited	Novartis considers a lifetime time horizon to be most appropriate for the modelling of tisagenlecleucel, which has the potential to offer a 'cure' for some patients. In accordance with the NICE reference case, a lower annual discount rate of 1.5% may also be explored by Novartis as part of the appraisal.	Comments noted. No action required.
Equality and Diversity	Novartis Pharmaceuticals UK Limited	Novartis has not identified any issues related to equality that should be covered in the remit or scope of this appraisal.	Comments noted. No action required.
Innovation	Novartis Pharmaceuticals UK Limited	Tisagenlecleucel represents a paradigm shift in the management of r/r B-cell ALL for patients aged 3 to 25 years old. Current treatment options for r/r B-cell ALL are associated with suboptimal clinical outcomes and are mainly used as 'bridges' to allogeneic HSCT.[6, 7] Allogeneic HSCT does offer a curative option for some patients but is associated with significant limitations, including: eligibility requirements and waiting times, high rates of treatment-related mortality, and potentially life-threatening adverse events, such as graft-versus-host disease. Tisagenlecleucel is a CAR-T therapy which works via harnessing the body's own immune system to destroy cancer cells, and thus represents a highly innovative and novel approach to treatment. Tisagenlecleucel may offer a potential 'cure' for some patients, returning them to a level of quality of life and life expectancy similar to the general population. As a single treatment infusion, tisagenlecleucel also avoids the need for recurrent cycles of chemotherapy, thus potentially lowering the risk of relapse due to lower adherence in r/r B-cell ALL. Tisagenlecleucel is being considered for	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. In line with NICE reference case, benefits and costs are considered from the NHS and Personal

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		regulatory approval in Europe as part of the PRIME scheme and was awarded 'Priority Review' status by the US Food and Drug Administration, in acknowledgement of the potential for tisagenlecleucel to help address a considerable unmet need. Evidence of the benefit of tisagenlecleucel as a treatment for paediatric and young adult patients with r/r B-cell ALL (in terms of remission rates, relapse-free survival, overall survival, and QoL) will be available from three single-arm trials (ELIANA, ENSIGN and B2101J).[1-3] Given the age of patients (3 to 25 years old), the potential for a one-time treatment to offer sustained remission and a 'cure' with tisagenlecleucel is also likely to provide additional health benefits (such as reduced carer burden), as well as non-health benefits (such as attainment of education and employment) which would not be captured in the QALY estimates. **References** 1. Novartis Pharmaceuticals UK Ltd. Data on File. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Interim Clinical Study Report. 2. Novartis Pharmaceuticals UK Ltd. Data on File. ENSIGN: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Interim Clinical Study Report. 3. Novartis Pharmaceuticals UK Ltd. Data on File. B2101J: A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Patients with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma. Interim Clinical Study Report.	Social Services perspective. The committee, at its discretion, may request non-reference case analyses if appropriate. No action required.

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		6. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol 2006;24:1917-23. 7. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. J Clin Oncol 2016;34:4381-4389.	
Other considerations	Novartis Pharmaceuticals UK Limited	No comment	Comment noted. No action required.
Questions for consultation	Novartis Pharmaceuticals UK Limited	Comments have been provided above with regards to the population, comparators and outcomes specified in the draft scope, as well as issues related to equality, and the innovativeness of tisagenlecleucel. In addition: Novartis does not consider there to be any clinically-relevant subgroups of patients for whom tisagenlecleucel will be more clinically- or cost-effective when compared to the overall population covered by the indication.[1] Novartis expects that tisagenlecleucel will be positioned within the existing NICE pathway according to the anticipated licensed indication, i.e. as a treatment for paediatric and young adult patients aged 3 to 25 years with r/r B-cell ALL. Novartis accepts that the Single Technology Appraisal process is suitable for this appraisal. Finally, CAR-T therapy represents an entirely novel type of treatment, the delivery of which will require sites to have specific capabilities and facilities (e.g. for performing leukapheresis and also handling, storing, and disposing of human cells that have been genetically modified with a lentivirus). Novartis is therefore	Comments noted. Please see specific sections for response to comments on population, comparators, outcomes, equality and innovation. No action required.

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		[redacted] and hopes to work with NICE and NHS England going forwards in order to support the introduction of CAR-T therapy into the NHS. **References** 1. Novartis Pharmaceuticals UK Ltd. Data on File. ELIANA: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Interim Clinical Study Report.	
Additional comments on the draft scope	Novartis Pharmaceuticals UK Limited	Novartis requests that the draft scope be updated throughout to reflect the proposed change to the remit and 'Population' for the appraisal (i.e. to change '21' to '25' for all instances where the population age of '3 to 21' or '18 to 21' is referred to).	Comment noted. Remit and population have been amended.

Table 1: ELIANA inclusion criterion for relapsed or refractory paediatric B-cell ALL

a) 2nd or greater bone marrow relapse or

b) Any bone marrow relapse after allogeneic SCT and was ≥6 months from SCT at the time of tisagenlecleucel infusion or

c) Primary refractory as defined by not achieving a CR after 2 cycles of a standard chemotherapy regimen or chemo-refractory as defined by not achieving a CR after 1 cycle of standard chemotherapy for relapsed leukaemia or

d) Patients with Philadelphia chromosome positive ALL were eligible if they were intolerant to or had failed two lines of tyrosine kinase inhibitor therapy, or if tyrosine kinase inhibitor therapy was contraindicated or

e) Ineligible for allogeneic SCT because of:

- Comorbid disease
- Other contraindications to allogeneic SCT conditioning regimen

- Lack of suitable donor
- Prior SCT
- Declined allogeneic SCT as a therapeutic option after documented discussion about the role of SCT with a bone marrow transplantation physician not part of the study team

Abbreviations: CR: complete remission; SCT: stem cell transplantation.
Source: ELIANA Interim Clinical Study Report[1]

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Leukaemia Care