



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1519 – Tisagenlecleucel (CTL019) for treatment of refractory CD19-positive leukaemia and lymphoma

Applicant: Novartis Pharmaceuticals Australia Pty Ltd

Date of MSAC consideration: MSAC out-of-session Meeting, 9 April 2019
MSAC 75th Meeting, 28-29 March 2019
MSAC 74th Meeting, 22-23 November 2018

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

April 2019 MSAC consideration

The Department of Health and Novartis negotiated the details of a risk share arrangement for tisagenlecleucel (TIS) for the treatment of confirmed relapsed/refractory CD19-positive acute lymphoblastic leukaemia in children and young adults up to 25 years old (ALL), reconsidered out-of-session by the MSAC in April 2019.

March 2019 MSAC consideration

A revised application received from Novartis by the Department of Health for TIS for treatment of confirmed relapsed/refractory CD19-positive ALL in children and young adults up to 25 years old (ALL) was considered by the MSAC in March 2019.

A revised application received from Novartis by the Department of Health for TIS for diffuse large B-cell lymphoma (DLBCL) in adults will be considered at the June 2019 ESC and the August 2019 MSAC.

November 2018 MSAC consideration

An application was received from Novartis by the Department of Health requesting funding of TIS for the treatment of confirmed refractory or relapsed (r/r):

- B-cell acute lymphoblastic leukaemia (ALL) in paediatric and young adult patients (aged 3–25 years) (pALL); and
- diffuse large B-cell lymphoma (DLBCL) in adults.

The application proposed that the new funding program have two distinct components:

- one encompassing those aspects of the proposed therapeutic process performed entirely within an Australian treatment setting; and

- another comprising the totality of the process of transportation of cryopreserved T cells to a centralised manufacturing facility, genetic reprogramming and expansion of the T cells to create TIS, strict quality control and release procedures, and transportation of finished product back to the hospital site for reinfusion into the patient.

2. MSAC’s advice to the Minister- April 2019 consideration

Following the MSAC’s decision to defer its advice on the public funding of TIS for treatment of ALL in children and young adults up to 25 years old at the March 2019 meeting, the Department and the applicant negotiated the details of a risk share arrangement for TIS in the ALL population.

The MSAC reviewed the risk share arrangement in an out-of-session MSAC reconsideration. The MSAC supported the negotiated risk share arrangement, considering it appropriately managed the clinical, economic and financial uncertainty existing in the March 2019 application funding proposal and recommended the public funding of TIS for treatment of ALL in children and young adults up to 25 years old.

Summary of consideration and rationale for MSAC’s advice – April 2019

The MSAC considered the following negotiated risk share agreement between the applicant and the Department for an initial 2 years of public funding, would appropriately manage the uncertainty existing in the applicant’s March 2019 funding proposal:

- a pay only on successful infusion* arrangement;
- **Redacted;**
- **Redacted;**
- **Redacted;**
- **Redacted;**
- treatment to be limited to a single dose of TIS, as there is no evidence currently available informing the effectiveness or safety of multiple doses; and
- a full review of clinical effectiveness, cost- effectiveness and budget impact will be conducted by the MSAC no later than 2 years post the commencement of public subsidy (note: Novartis will provide a submission to initiate this review). **Redacted.**

*successful infusion: patient is infused with Kymriah with a clinically acceptable cell dose which is consistent with the expected cell dose specified prior to apheresis.

Redacted.

3. MSAC’s advice to the Minister– March 2019 consideration

The MSAC considered the revised subsidy proposal for TIS (CTL019 – CAR-T therapy) for treatment of confirmed relapsed/refractory CD19-positive acute lymphoblastic leukaemia (ALL) in children and young adults up to 25 years old received from the applicant.

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its advice on public funding of TIS for treatment of ALL in children and young adults up to 25 years old.

MSAC recognised the large unmet clinical need for a small group of patients and the preliminary supportive evidence of a clinically important treatment effect.

MSAC considered that TIS would be acceptably cost-effective in the ALL population with additional risk share measures in place to those proposed in the application to manage the remaining areas of clinical, economic and financial uncertainty that exist in the funding proposal. These include uncertainty about the proportion of, and durability of, responses in clinical practice; uncertainty about the number of patients going on to stem cell transplantation; uncertainty about the duration of immunoglobulin (intravenous, IVIg, or subcutaneous, SCIg) treatment; and uncertainty in the number of patients who will be selected for treatment, and the number of patients who will ultimately receive treatment. MSAC requested that the detail of a risk share arrangement be negotiated between the Department and the applicant. MSAC further requested that this information be provided to the MSAC Executive for review with MSAC out-of-session reconsideration if considered necessary by the MSAC Executive.

Summary of consideration and rationale for MSAC's advice – March 2019

MSAC noted that the purpose of the application is to seek national funding for TIS for the treatment of refractory or relapsed ALL in children and young adults up to 25 years old. The MSAC recalled it had deferred its decision at the November 2018 MSAC meeting, as the incremental cost effectiveness ratio per quality-adjusted life-year gained (ICER/QALY) was both unacceptably high and underestimated. At that time, the MSAC advised that the economic evaluation for ALL needed to be revised and a price for TIS ascertained at which it is acceptably cost-effective. The MSAC also considered the financial estimates too high.

The MSAC noted that the revised application did not provide any additional clinical data but appropriately endeavoured to address the uncertainties in the economic model and financial estimates and proposed a new lower price.

The MSAC noted that the main changes to economic model were a reduction in the effective price of TIS; an increase in the duration of IVIg use in both the treatment and comparator arms to 36 months; and adoption of blinatumomab as the single comparator. The Critique presented a respecified base case in which 6 years of IV1g use was assumed for all TIS infused patients who do not go on to stem cell transplantation together with a reduced duration of IVIg use in the comparator arm. The Critique also presented the ICER/QALY using a weighted comparator of blinatumomab (75%) and salvage chemotherapy (25%) as per the original version of the application considered at the November 2018 meeting of the MSAC.

The effective price of TIS was lowered by applicant from **\$redacted** to **\$redacted**. The MSAC noted that at the proposed new price, the ICER is **\$redacted** /QALY using the revised application's economic model with a weighted comparator, and **\$redacted** /QALY using the Critique's re-specified model with a weighted comparator. The MSAC was reassured by the concordance of the ICERs from both versions of the model.

The MSAC noted that the high ICER is driven primarily by the high cost of TIS. The MSAC further noted the ICER is only slightly reduced from the base case of **\$redacted** /QALY with a weighted comparator estimated by the economic model considered in November 2018 on

the basis of a price of \$**redacted**. At that time, the MSAC considered the ICER was both unacceptably high and underestimated.

The MSAC advised **redacted** price and to manage the remaining uncertainty that the outcomes observed in the small clinical trials will be achieved in practice, **redacted**. In this context, the MSAC noted **redacted**.

The MSAC noted the applicant had revised its financial estimates for ALL in response to the concerns raised by the MSAC in November 2018. The applicant did not agree with the MSAC suggestion that the estimate should be based on the number of Australians with ALL receiving allo-SCT who subsequently relapsed. The revised application considered that the proposed population criteria is broader than just patients who relapse after receiving allo-SCT and this would therefore be an underestimate. A comparison of the applicant’s patient number estimates from the November 2018 and March 2019 versions of its applications is provided in Table 1.

Table 1 Applicant estimates of numbers of pALL patients infused

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Estimates in the pre-ESC response before the November 2018 MSAC meeting							
Number infused	redacted	redacted	redacted	redacted	redacted	redacted	redacted
Estimates in the revised application to the March 2019 MSAC meeting							
Number infused	redacted	redacted	redacted	redacted	redacted	redacted	redacted

The MSAC considered the revised patient numbers continue to be overestimated and remained of the view that a more realistic estimate of the number of patients eligible for treatment is that provided in Table 2. The MSAC advised that the uncertainty in patient numbers could be managed through a risk share arrangement **redacted** (see below for further detail).

Table 2 MSAC estimates of numbers of pALL patients infused

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
MSAC estimate							
Number infused	redacted	redacted	redacted	redacted	redacted	redacted	redacted

Risk Share redacted

The MSAC noted the applicant agreed to:

- Limit treatment to a single dose of TIS, as there is no evidence currently available informing the effectiveness or safety of multiple doses;
- Only receiving reimbursement for the cost of TIS where patients are ultimately infused with TIS with a clinically acceptable cell dose which is consistent with the expected cell dose specified prior to apheresis.

The MSAC considered these were not the only areas of risk associated with public subsidy of TIS for ALL. The risks identified by the MSAC and methods for mitigating these risks are detailed in Table 3.

Table 3 Risks and mitigations

Issue	Impact	Mitigation
Patient not successfully infused with TIS	Potential to pay for product that is not delivered	Novartis agreed to only invoice on successful infusion of TIS
Patient receives second TIS infusion	Cost-effectiveness less favourable Increase overall spend	Novartis agreed to limit treatment to once per lifetime through guidelines. Redacted
Patient numbers overestimated	Financials redacted too high	Time limited subsidy agreement Redacted
Durability of response	Changes cost-effectiveness	Time limited subsidy agreement Redacted
Proportion receiving stem cell transplant post TIS (model assumed redacted)	Changes cost-effectiveness	Time limited subsidy agreement Redacted
Need for ongoing IVIg (Revised application model assumed 3 years. Department model assumed 6 years)	Changes cost-effectiveness Changes overall spend	Time limited subsidy agreement Redacted

The MSAC advised the following risk share measures be put in place during an initial 2 years of public funding:

- A pay only on successful infusion arrangement;
- A limit of one CAR-T treatment per patient;
- **Redacted** and
- **Redacted**.

The MSAC noted that using the available survival data from the pooled analysis of results from the ELIANA/ENSIGN studies, the proportion of patients surviving at 12 months was estimated to be 71.0% (95%CI: **redacted**). The MSAC considered the **redacted**, such that the resulting ICER from either the applicants or the Critique’s economic model considered at the March 2019 MSAC is no more than \$**redacted** /QALY. The MSAC considered that the **redacted**. The MSAC considered that supplies of TIS for **redacted**.

The MSAC advised these measures be supplemented by a requirement for a full review of the clinical and cost-effectiveness of TIS a maximum of 2 years after the commencement of public funding in Australia. This review should allow for a renegotiation of the conditions of public funding if considered appropriate by the MSAC at that time.

The MSAC considered any future CAR-T therapies that are nationally funded should be required to join the same risk share arrangements.

Patient eligibility, treatment centres and data collection

The MSAC considered patient eligibility for subsidy for ALL should be aligned with the Therapeutic Goods Administration (TGA) registered indication.

The MSAC advised that patients who receive TIS need to be managed at co-located adult/paediatric tertiary public hospital sites so that the patients can be managed in the appropriate clinical setting for that individual. The MSAC also reaffirmed its earlier advice of the need to limit treatment to highly specialised tertiary centres. In keeping with a national program, there needs to be a co-ordinated approach to patient referral and selection to ensure equitable access.

Facilities must meet the requirements set out in the Risk Management Plan agreed between the applicant and the TGA

The MSAC considered that data on the use of TIS in Australia should be recorded by the Australian Bone Marrow Transplant Recipient Registry, with the cost of data collection met by the applicant. This would ensure a single Australia source of data for all CAR-T therapies in all indications and from all treatment centres. The data collected in the registry should align with international data collections to ensure comparability and access and thus contribute to global knowledge. The registry should include the following minimum data:

- patient-reported outcomes;
- leukaemia-free survival (morphological complete remission and complete molecular remission);
- complications, use of high cost medicines, late-onset adverse events and adverse events requiring hospitalisation admission and adverse events including those requiring ICU admission;
- use and duration of immunoglobulin;
- rate of reinfusion with any CAR-T therapy (noting the cost of reinfusion of such therapy will not be funded under the proposed arrangement);
- indication for use of CAR-T – for example bridge to stem cell transplant, following transplant; and
- results for patients infused with non-optimal cell numbers (noting that for the purposes of subsidy, this is considered an unsuccessful infusion).

4. MSAC's advice to the Minister – November 2018 consideration

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC:

- deferred its decision on public funding of TIS for treatment of children and young adults with confirmed relapsed/refractory CD19-positive ALL; and
- did not support public funding for TIS for adults with confirmed relapsed/refractory DLBCL.

For both conditions, MSAC recognised the large unmet clinical need and the preliminary supportive evidence of a clinically important treatment effect, but the incremental cost-effectiveness ratio (ICER) was both unacceptably high and underestimated. For pALL, the economic evaluation needed revisions and a price for TIS ascertained at which it is acceptably cost-effective. For DLBCL, the definition of the appropriate eligible population needed to be redefined, as well as amendments made to the economic evaluation and a reduced price for TIS ascertained at which it is acceptably cost-effective.

MSAC noted the differences in the scope of further work required between the pALL and DLBCL populations, and recommended that the applicant split them into two separate re-applications to allow them to progress at different paces.

The applicant subsequently advised its intention to make a single resubmission for both populations.

Summary of consideration and rationale for MSAC's advice – November 2018

At the hearing, the applicant noted comments from the critique regarding analysis of the population that had received TIS, rather than the intention-to-treat (ITT) population. The applicant claimed that the infused population was more relevant than the ITT population (although data from both populations had been provided to MSAC) because manufacturing capacity had expanded and improved. The applicant's estimate that the manufacturing failure rate is now around 7%, which means that 93% of the "intention to treat" patients are treated.

Redacted.

The independent expert informed MSAC during the hearing that:

- the plateau in the survival curves and the persistence of T cells at 6 and 12 months post-infusion are encouraging; TIS may be an alternative to transplant in some patients, and a bridge to transplant for others
- patients who have had previous CD19 therapy, and infants under 3 years of age, should both be included in the eligible population
- eligible patients should be those with morphological evidence of disease (>5% lymphoblasts) rather than minimal residual disease (0.01–5% lymphoblasts); overseas studies are underway for patients with minimal residual disease
- all pALL patients would require lifelong intravenous immunoglobulin (IVIg) following TIS infusion, and 30% of DLBCL patients would also require IVIg, although it is unlikely that lifelong IVIg treatment will be needed in this group
- the only proven long-term cure for refractory disease is allogeneic stem cell transplant (allo-SCT), and CAR-T therapies could achieve the remission necessary to confirm eligibility for an allo-SCT.

MSAC noted that TIS is a chimeric antigen receptor T-cell (CAR-T) therapy and a Class 4 Biological Product. Prior to MSAC consideration, TIS was deemed to be not suitable for public funding via either the Medicare Benefits Schedule (MBS) or the Pharmaceutical Benefits Scheme (PBS). MSAC was considered the most appropriate channel for the health technology assessment and for advising with reference to a funding mechanism outside the MBS. MSAC noted that a parallel evaluation was being conducted by the Therapeutic Goods Administration (TGA) for the purpose of deciding on marketing approval, and that the TGA Delegate's overview supported registering TIS. MSAC accepted the proposed comparators as being appropriate.

MSAC considered that, for both indications, small single-arm studies show promising rates of remission (up to 2 years). MSAC preferred that the ITT approach be adopted for the comparative clinical and economic evaluations on the grounds of this being standard practice, consistency with the reporting of the single-arm studies of the comparators, and, from the pre-MSAC response, **redacted**. MSAC also concluded, in the absence of prospective comparative data on safety, that for many patients TIS causes substantial adverse effects, and an ongoing need for IVIg.

MSAC noted the substantial clinical uncertainties in the application flowed on to the economic evaluation. Data on the duration of response are evolving as the follow-up in the single-arm studies matures. For this reason, the results from the data cut with the longest follow-up of each study are generally preferred. The changes from the current treatment pathway are complex and expensive, and the economic models were unreliable when they were driven by uncertain extrapolations of event-free survival and overall survival. The

revised economic model in the pre-MSAC response and pre-ESC response (for pALL and DLBCL, respectively) adopted a more acceptable lognormal basis for the extrapolation to report high ICERs (**\$redacted** to **\$redacted** per QALY gained for pALL and DLBCL, respectively). These ICERs were likely to be underestimated as the full costs of IVIg were not included for pALL, and the start age of patients in the DLBCL model (**redacted**) is younger than the expected Australian population. The possibility of late onset, severe and expensive adverse effects also could not be excluded given the preliminary nature of the clinical evidence provided.

MSAC noted that the economic model had been through several iterations of critiques and revisions, with significant changes made at each stage. The latest model used a lognormal function for extrapolation beyond the study follow-up, which appeared to be appropriate. However, given the multiple rounds of new data and new analyses over the course of the assessment, MSAC considered that it was unclear whether all relevant changes had been applied appropriately. The model would benefit from a considered re-specification. This should include greater use of IVIg, and could include two-way sensitivity analyses, appropriate extrapolation of event-free survival and overall survival, and less simplistic costing of adverse events.

However, MSAC also noted that the high cost of TIS itself was a major driver of the model. MSAC advised that the cost of TIS would need to be significantly reduced to reach the range of usually accepted ICERs, particularly as the use of TIS would generate a net increase in other costs, particularly when the costs of increased IVIg are included. MSAC considered that new CAR-T therapies were under development and these sought to improve survival and reduce the severity and risk of severe adverse events. These future CAR-T treatments would likely be compared with TIS and hence it was important to have certainty around the conditions of funding TIS.

MSAC noted from the pre-MSAC response that the revised estimated net financial cost to the health system for both populations would be **\$redacted** over 6 years, including substantial flow-on financial implications for the public hospital system, and considered that the likelihood of leakage to a broader group of refractory patients would be high. In relation to the financial estimates, MSAC considered that, as the first product to market, it was not appropriate for the applicant to take a market share approach and claim declining uptake of TIS over time due to future competitors. Reverting to an overall epidemiological approach would increase the financial implications of funding.

MSAC noted the range of considerations in establishing a new funding mechanism for these types of interventions and the importance of making strategic decisions to account for future similar genetically modified autologous cell-based interventions. It was suggested that a standardised economic model could be developed to facilitate data comparisons in future considerations of CAR-T therapies, including adverse event profiles and costs.

MSAC considered that mandatory recording of TIS use on the Australian Bone Marrow Transplant Recipient Registry and related health outcome and healthcare resource use consequences would be preferable to an applicant-administered registry, due to potential issues with data access and control. The data collected in the registry should also align with international data collections to ensure comparability across countries and thus enable a larger sample size for analyses. It was suggested that any register should also include patient-reported outcomes. It was noted that the Therapeutic Goods Administration would mandate a detailed risk management plan.

MSAC considered that it would be appropriate to limit initial funding for the pALL population to two paediatric stem cell transplant centres (one in Sydney and one in Melbourne). **Redacted**. For the DLBCL population, it was suggested that a centre would subsequently be required in every state due to the larger patient numbers.

MSAC noted the differences in the scope of further work required between the pALL and DLBCL populations to inform its reconsideration, and recommended that the applicant split them into two separate re-applications to allow them to progress at different paces.

The applicant subsequently advised its intention to make a single resubmission for both populations.

For the pALL population, MSAC noted that the population was more clearly defined, the number of patients would be small, and the expectation of a prolonged response was more plausible than for the DLBCL population. However, MSAC foreshadowed that, consistent with the independent expert clinical advice at the hearing and the TGA delegate's overview, it would consider advising that i) the lower limit of 3 years of age be omitted as an exclusion from any funding arrangement, ii) patients who have had prior CD19 therapy should be eligible, and iii) the lower limit to define relapse before TIS would be morphological evidence of disease only (i.e not minimal residual disease). MSAC considered that further data and inputs were needed to respecify the base case of the economic evaluation and the financial estimates, particularly to reflect the cost of lifelong IVIg for all patients. MSAC decided to defer its advice for the pALL population to enable the additional modelling and to ascertain whether an arrangement can be made to incorporate the necessary reduction in the effective price of TIS. MSAC advised that the numbers of eligible patients each year are likely smaller than the estimates in the application. The Committee noted smaller estimates accepted for funding in England and Norway when adjusted for the relative size of the country's population, and considered that there was a relatively confident basis for estimating the numbers of Australians with pALL receiving allo-SCT (40) who subsequently relapse (30%) and that this comprises the pathway through which most patients with pALL would become eligible for TIS.

For the DLBCL population, MSAC considered that substantial further work was required. The eligible population was less clearly defined, larger than the pALL population, and there was no clinical evidence to justify the exclusion of certain subgroups which may have more aggressive relapsed or refractory B cell lymphoma. The median age of patients in the two single-arm studies was 56 years, but the average age of diagnosis in Australia is 60–70 years. There are uncertainties regarding clinical effectiveness and persistence of benefit in this population. MSAC also considered that the DLBCL population has other treatment options available to them, and the comparative effectiveness of TIS against these options had not been adequately explored. MSAC concluded that the application for the DLBCL population should not be supported, and that any re-application should clearly specify the patient population, include the additional evidence and economic and financial information. This re-submission would need to be evaluated by ESC.

5. Background

Application 1519 was previously considered at the November 2018 meeting.

6. Prerequisites to implementation of any funding advice

The application stated that, while initially limited to selected tertiary public hospitals, **redacted**.

7. Proposal for public funding

The application requested creation of a new national funding mechanism, suitable for providing equitable and affordable patient access to this highly specialised and individualised hybrid genetic therapeutic process. Funding of TIS was requested for the treatment of confirmed refractory or relapsed (r/r):

- B-cell acute lymphoblastic leukaemia (ALL) in paediatric and young adult patients (aged 3–25 years) (pALL); and
- diffuse large B-cell lymphoma (DLBCL) in adults.

8. Summary of public consultation feedback/consumer issues

Three responses were received in the consultation feedback, one from a professional organisation and two from consumer organisations.

The feedback was supportive of the application. One consumer organisation had concerns about unknown long-term outcomes and medium-to-long-term adverse events and disagreed with limiting the pALL population to the clinical study population (i.e. the upper age limit of 25), as there is little biological rationale behind the age limit. One consumer organisation had concerns about the lack of psychological support and the ongoing administration of intravenous immunoglobulin for the treatment of adverse events.

9. Proposed intervention's place in clinical management

The application stated that the main change envisaged to clinical practice in both indications is substitution of TIS for currently available salvage chemotherapy regimens (including blinatumomab in pALL) administered with the intent of obtaining a response and progressing to allogeneic stem cell therapy (allo-SCT). Although not recommended in either indication, a proportion of patients who achieve a complete response to TIS may elect to undergo subsequent allo-SCT in an effort to consolidate this response. Options for patients who fail to respond or relapse following TIS infusion include best supportive care (BSC), clinical studies, further allo-SCT or further attempts at salvage therapy using alternative approaches. For purposes of clarity, TIS was developed as a single, one-time treatment, and there is no evidence currently available informing the effectiveness or safety of multiple infusions.

10. Comparator

For the r/r pALL population, the proposed comparator is salvage chemotherapy regimen (SCR), with the most relevant specific SCR being blinatumomab (BLN) with the intention to proceed to allo-SCT; the alternative comparator is conventional salvage chemotherapy with the intention to proceed to allo-SCT.

For the r/r DLBCL population, the proposed comparator is SCR. Salvage chemotherapy regimens which are frequently used in DLBCL include various combination regimens, including but not limited to (R)-DHAP, (R)-Gem-Ox, (R)-IVE, and (R)-ESHA. R-DHAP was nominated as a reasonable proxy for all current regimens for costing purposes.

11. Comparative safety

Two parallel clinical evaluations were presented which considered the comparative effectiveness and safety of TIS and the nominated main comparator BLN/SCR in the respective pALL and DLBCL patient populations. Updates of some of the TIS studies were

provided with the pre-ESC response in the form of Kaplan-Meier plots; these updates are not reported here.

The pALL evaluation presented details of the design and results from three single-arm TIS studies (B2101, B2202/ELIANA and B2205/ENSIGN). An individual patient pooled analysis of results from the most recent data cut of the ELIANA and ENSIGN studies available at the time the application was finalised was also presented.

For the main comparator, the evaluation presented details of the design and results of one small single arm study of BLN in a relevant pALL population, identified via a systematic literature search (NCT01471782/(Von Stackelberg, Locatelli et al. 2016)).

These four studies enrolled overlapping r/r pALL patient populations, employed generally similar study designs and assessed comparable outcomes. The studies were all of similar quality, but the comparison across the single-arm studies remains subject to a high risk of bias.

No formal indirect comparison was presented due to the absence of a common reference group across the studies, however a matched adjusted indirect comparison (MAIC) analysis was provided as an attachment to the application.

A similar approach was taken for the DLBCL evaluation, reporting two single-arm TIS studies (UPEN and JULIET) and three single-arm SCR studies, one of which reported two additional phases of follow-up.

The application stated that all patients in the combined ELIANA/ENSIGN safety analysis experienced at least one adverse event (AE) (see Table 4). The most frequently reported post-infusion serious adverse events (SAEs) were CRS (64.4%), febrile neutropenia (24.0%), and hypotension (11.5%). The majority of SAEs were reported within the initial 8 weeks post-infusion. Similar results were reported for the DLBCL studies (see Table 5).

12. Comparative effectiveness

Note: results reported in this section are on an intention-to-treat (ITT) basis for the comparator interventions, but for TIS, are limited to those infused only.

pALL population

The application stated all three TIS studies in pALL met their primary endpoint (B2101: safety, feasibility of administering and persistence of TIS; ELIANA: independent review committee (IRC) assessed overall remission rate (ORR) during 3 months infusion of TIS from all manufacturing sites; and ENSIGN: IRC assessed ORR during 6 months after infusion). Specifically, in ELIANA, the ORR at 3 months was 82.0% (95% confidence interval (CI): 68.6, 91.4); in ENSIGN, the ORR at 6 months was 69.0% (95% CI: 43.6, 88.1); and in B2101, the ORR was 94.6% (95% CI: 85.1, 98.9) (see also Table 4, which reports results of the most recent data cut available at the time the application was finalised). In the December 2017 data cut of the ELIANA study, in which median follow up was 10.5 months, the ORR remained at 81.8%, and median EFS and OS had not yet been reached. In the pooled analysis of results from the ELIANA/ENSIGN studies, the ORR was 76.4% (95% CI: 68.0, 83.5). Median EFS was estimated at 13.0 months (95% CI: **redacted** and the proportion of patients surviving at 12 months was estimated to be 71.0% (**redacted**).

Table 4 Summary results from the pALL studies*

Outcome	B2101	ELIANA	ENSIGN	NCT0141782 ^a
Efficacy outcomes	N=56	N=77	N=42	N=70
ORR, n (%) [95% CI]	53 (94.6) [85.1, 98.9]	63 (81.8) [71.4, 89.7]	29 (69.0) [52.9, 82.4]	27 (38.6) [27, 51]
Median EFS (months) [95% CI]	redacted	NE [9.2, NE]	redacted	4.4 [2.3, 7.6]
Median OS (months) [95% CI]	37.9 [22.7, NE]	NE [NE, NE]	23.8 [8.8, NE]	7.5 [4.0, 11.8]
Safety outcomes	N=56	N=79	N=58	N=70
Adverse events, n (%)	redacted	75 (94.9)	redacted	70 (100)
Grade 3/4, n (%)	redacted	58 (73.4)	redacted	61 (87)
Drug-related, n (%)	redacted	NE	redacted	NR
Serious AEs, n (%)	redacted	61 (77.2)	redacted	NR
Deaths, n (%)	redacted	23 (29.1)	redacted	NR
CRS (any grade), n (%)	redacted	61 (77.2)	47 (81.0)	8 (11.0)

* Results for TIS (B2101, ELIANA, ENSIGN) are not reported on an intention-to-treat (ITT) basis.

Abbreviations: ORR = overall remission rate; EFS = event free survival; OS = overall survival; AE = adverse event; CRS = cytokine release syndrome; NE = not evaluable; NR = not reported; CI = confidence interval; TIS = tisagenlecleucel

Study notes: ELIANA = Dec 2017 data cut; ENSIGN = Oct 2017 data cut

^a Primary endpoint: ORR per investigator during the first two cycles of blinatumomab treatment

The safety outcomes for B2101 and ENSIGN that have been redacted from Table 4 are consistent with those for ELIANA, except that there were numerically higher proportions of patients in B2101 who experienced serious adverse events or who died.

DLBCL population

The application stated both TIS studies in DLBCL also comfortably met their primary endpoint (UPEN: overall response rate (ORR) with radiologist review; and JULIET: ORR by IRC at the pre-planned interim analysis, with median duration of follow-up of 3.5 months): the overall response rate (ORR) in JULIET was 58.8% (95% CI: 44.2, 72.4) while in UPEN, the ORR in the subgroup of patients with DLBCL specifically was 50% (95% CI: 23, 77) (see also Table 5, which reports results of the most recent data cut available at the time the application was finalised).

The ORR rate for TIS treated patients in the 12-month follow-up of the key JULIET study was 51.6% (95% CI: 41.0%, 62.1%) and the median duration of response had not yet been reached. Median (PFS) in this highly relapsed/refractory patient population was 2.9 months (95% CI: redacted) and median OS 11.7 months (95% CI: 6.6, not evaluable).

Table 5 Summary results from the DLBCL studies*

Outcome	UPEN	JULIET	NCIC-CTG ^a	CORAL_R ^a	SCHOLAR	CORAL_E1	CORAL_E2
Efficacy outcomes	N=28	N=111	N=619	N=396	N=523		
ORR, n (%) [95% CI]	7 (50) [23,77]	48 (51.6) [41.0, 62.1]	276 (44.6) [40.6, 48.6]	245 (61.9) [56.9, 66.7]	134 (26.0) [21.9, 29.6]	79 (38.9) [32.2, 46.0]	33 (44.0) [32.5, 55.9]
Median PFS (months) [95% CI]	3.2 [0.9, NE]	2.9 redacted	≈ 8.0 [NR]	≈ 12.0 [NR]	NR	NR	NR
Median OS (months) [95% CI]	22.2 [NR]	11.7 [6.6, NE]	≈ 15.0 [NR]	≈ 36.0 [NR]	6.3 [5.9, 7.0]	4.4 [NR]	10.0 [NR]
Safety outcomes							
Adverse events, n (%)	NR	111 (100)	Not systematically or comparably reported				
Grade 3/4, n (%)	NR	99 (89.2)					
Drug-related, n (%)	NR	99 (89.2)					
Serious AEs, n (%)	NR	72 (64.9)					
Deaths, n (%)	NR	53 (47.7)					
CRS (any grade), n (%)	16 (57.0)	64 (57.7)					

* Results for TIS (UPEN, JULIET) are not reported on an intention-to-treat (ITT) basis.

Abbreviations: ORR = overall response rate; PFS = progression-free survival; OS = overall survival; AE = adverse event; CRS = cytokine release syndrome; NE = not evaluable; NR = not reported; CI = confidence interval; TIS = tisagenlecleucel

Study notes: JULIET = Dec 2017 data cut; CORAL_R = Coral 1st randomised phase; CORAL_E1 = CORAL observational extension phase (chemo refractory patients); CORAL_E2 = CORAL observational phase (relapsed post auto-SCT patients)

^a Primary endpoints for salvage chemotherapy arms (SCR): NCIC-CTG Ly.12: ORR after 2 cycles of chemotherapy; and CORAL: mobilisation adjusted response rate after 3 cycles of chemotherapy

Clinical claims

The respective clinical claims across the two proposed populations were that:

- for patients with r/r pALL, TIS provides superior efficacy to BLN +/- allo-SCT, with respect to all key patient relevant outcomes including overall remission rates, duration of remission, event-free survival and overall survival, with predictable and acceptable safety; and
- for patients with r/r DLBCL, TIS provides superior efficacy to a mixed SCR +/- SCT with respect to all key patient relevant outcomes including overall response rate, duration of response, progression-free survival and overall survival, with predictable and acceptable safety.

13. Economic evaluation

March 2019 MSAC consideration

The application summarised the revisions to the respecified base case economic evaluation of treating eligible patients with r/r pALL (Table 6).

Table 6 Summary of economic issues raised and how they have been addressed

Issue	Response
Effective Price of TIS	The proposed effective price for TIS has been reduced from \$redacted to \$redacted .
Comparator	The evaluation now considers a single main comparator (BLN), with the comparison to other standard chemotherapy regimens (SCR) included only as a sensitivity analysis.
Naïve indirect comparisons of single arm trials	No change, with the revised base case continuing to be informed by a naïve indirect comparison of results from the pooled ELIANA and ENSIGN trials with those of the Von Stackelberg 2011 study of BLN. No direct or indirect randomised trials have (or are likely to) become available which would facilitate a more formal comparison. Results of an updated MAIC analysis are available but considered an experimental approach and would require an assumption of proportional hazards in order to be incorporated in the economic evaluation.
Maturity of evidence from TIS trials	The revised base case is informed by pooled results from most recent available analyses of the ELIANA (April 2018) and ENSIGN (October 2017) trials.
Intention to treat analysis	Whilst Novartis maintains the infused population is most appropriate, acknowledging the strong views expressed by the evaluators, the resubmission adopts the ITT population in the base case analysis. The revised base case is informed by PFS and OS outcomes for the total enrolled population from the above analyses of ELIANA and ENSIGN, under a conservative assumption that observed rates of non-infusion in those trials will be replicated in the real-world commercial setting. Estimated costs for this proxy ITT cohort are adjusted for the proportion of patients who do not receive TIS, under the reasonable assumption that such patients would likely receive an alternative standard chemotherapy regimen.
Unclear/uncertain extrapolation of survival curves	The revised base case is informed by data from the pooled ELIANA and ENSIGN trials only; excluding the less applicable B2101J. Furthermore, model selection is based on the best fitting parametric model for each PFS/OS dataset for TIS and SCR, as opposed to the probability weighted approach presented in the original submission. Based on these criteria, lognormal models have been used to extrapolate outcomes from the observed trial period of approximately redacted until the assumed application of a common long-term mortality rate from redacted .
Consideration of SCT following TIS	Costs and potential quality of life effects of subsequent SCT following either TIS or BLN were included in the original model and have been retained here. Comparative rates of SCT have been obtained from the respective clinical trials. Survival outcomes drawn from the same trials are by definition inclusive of any additional effects from these downstream procedures. However, there are insufficient data with which to separately model the effects of alternative rates of subsequent SCT post TIS or BLN.
Underestimation of IVIg use	The assumed mean duration of IVIg use has been increased from redacted to 3 years based on expert clinical advice that patients would continue to receive this intensity of treatment only for as long as they remain in a paediatric treatment setting. Given the extended duration of treatment assumed, these costs have also been more formally integrated into the calculation of ongoing costs and discounted accordingly.
Underestimated costs for progressive disease	In the absence of reliable long term cost data pertaining to management of pALL patients, more robust estimates from the DLBCL setting have been used as reasonable proxy values.
Oversimplified and underestimated costs for adverse events	Additional sensitivity analyses performed to assess the impact of any potential underestimation on the cost effectiveness based on the approach used to estimate the costs for adverse events. The simplified approach has been maintained on the basis that many individual events would be experienced concurrently, often within the context of a hospital admission for administration of TIS.
Number of eligible patients	An epidemiological approach has been maintained, and is considered the most suitable approach to determining the eligible population based on eligibility criteria aligned to the clinical trials. A proportion of patients who relapse after allo-SCT, as well as a prevalent pool of patients has been factored into the revised estimates.

Source: 1519 pALL Resubmission

Abbreviations: BLN = blinatumomab; DLBCL = diffuse large B-cell lymphoma; IVIg = intravenous immunoglobulin; LY = life year; PFS = progression-free survival; OS = overall survival; QALY = quality-adjusted life-year; pALL = paediatric acute lymphocytic leukaemia; SCR = salvage chemotherapy regimen; SCT = stem-cell transplant TIS = tisagenlecleucel

Results of the revised base case of the economic evaluation, incorporating these changes and the reduced price of TIS as previously discussed, are summarised in Table 7.

Table 7 Results of the base case economic evaluation

Outcome	TIS	BLN	SCR	TIS v. BLN	TIS v. SCR
Median EFS	9	5	3	4	6
Median OS	28	7	3	21	25
Discounted costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Discounted Life Years	7.450	2.250	0.621	5.200	6.829
Discounted QALYs	4.972	1.269	0.224	3.703	4.748
Discounted Cost/LY				\$redacted	\$redacted
Discounted Cost/QALY				\$redacted	\$redacted

Source: 1519 pALL Resubmission

Abbreviations: BLN = blinatumomab; EFS = event free survival; LY = life year; OS = overall survival; QALY = quality-adjusted life-year; SCR = salvage chemotherapy regimen; TIS = tisagenlecleucel

The application presented results from deterministic sensitivity analysis of key model parameters: TIS cost per infusion **redacted**; TIS-related adverse events **redacted**; and IVIg: **redacted** (Table 8).

Table 8 One-way sensitivity analysis results (discounted)

Analysis	Base Case	Worst case	Best case		
	Value	Value	Cost/QALY	Value	Cost/QALY
Base case ICER = \$redacted					
TIS cost per infusion	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total TIS related AE costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
IVIg duration	redacted	redacted	redacted	redacted	redacted

Source: 1519 pALL Resubmission

Abbreviations: AE = adverse events; BLN = blinatumomab; IVIg = intravenous immunoglobulin LY = life year; QALY = quality-adjusted life-year; TIS = tisagenlecleucel

November 2018 MSAC consideration

Using a cost-utility framework, the application presented parallel economic evaluations which considered the likely costs and consequences of treating eligible patients with r/r pALL or r/r DLBCL with either TIS or BLN/SCR.

Table 9 Key elements of the economic evaluations

Component	Description
Intervention	Single episode of tisagenlecleucel (TIS) treatment with curative intent
Comparators	pALL: BLN +/- allo-SCT; OR conventional SCR (FLA-IDA) +/- allo-SCT DLBCL: Conventional SCR (R-DHAP) +/- allo- or auto-SCT
Perspective	Societal health care
Type of evaluation	Cost utility analysis
Sources of evidence	Naïve indirect comparison of extrapolated outcomes from predominantly single-arm studies of TIS and relevant comparators as described in Sections 10 and 11
Methods used	Three-state partitioned survival analysis
Health states	Event-free survival (pALL) / progression-free survival (DLBCL) Progressive disease Dead
Time horizon	Lifetime: 88 years for pALL; 50 years for DLBCL
Cycle length	One month (30.44 days)
Discount rate	5% annual for costs and outcomes
Transition probabilities	Implicit based on analyses of event/progression free and overall survival
Software	Microsoft Excel

Summary results of the respective base case analyses in the application are presented in Table 10. Revised economic evaluations were provided in the pre-ESC and pre-MSAC responses to address concerns raised by the critique and the ESC report, respectively; these revisions increased the incremental cost-utility ratios.

Table 10 Discounted incremental results and cost effectiveness ratios in the application

pALL	TIS	BLN	SCR	TIS v. BLN	TIS v. SCR
Costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
LYs	7.924	2.452	0.678	5.473	7.246
QALYs	5.639	1.556	0.267	4.083	5.372
Cost/LY				\$redacted	\$redacted
Cost/QALY				\$redacted	\$redacted
DLBCL	TIS	SCR		TIS vs. SCR	
Costs	\$redacted	\$redacted		\$redacted	
LYs	6.090	3.005		3.084	
QALYs	4.990	2.230		2.760	
Cost/LY				\$redacted	
Cost/QALY				\$redacted ^a	
Weighted	Assumed weights			Cost/QALY	
pALL comparators	redacted			\$redacted ^b	
Indications	redacted			\$redacted	

^a redacted

^b redacted

Abbreviations: BLN = blinatumomab; DLBCL = diffuse large B-cell lymphoma; LY = life year; QALY = quality-adjusted life-year; pALL = paediatric acute lymphocytic leukaemia; SCR = salvage chemotherapy regimen; TIS = tisagenlecleucel

The application stated that one-way sensitivity analysis showed that both models were relatively sensitive to the key event-/progression-free and overall survival modelling approaches and parameters, the total cost of the intervention/comparator, and the discount rate and time horizon.

14. Financial/budgetary impacts

March 2019 MSAC consideration

An epidemiological approach used in the original submission has been maintained and is considered the most suitable method to estimate the numbers of eligible patients with r/r pALL:

- A conservative estimate of prevalent patients has been included in the eligible population, noting the MSAC's view that the overall numbers of eligible patients in the original submission were likely overestimates;
- The proportion of patients who relapse after receiving allo-SCT is explicitly modelled within the total eligible population, based on estimates provided by MSAC in the PSD;
- The proportion of patients with relapsed disease is increased to the upper estimate from Nguyen 2008 (25%), in order to better reflect the expected relative proportion of relapsed patients that do not receive an allo-SCT versus those that do based on the estimates provided by MSAC;
- The rate of successful infusion applied to the eligible population has been changed from **redacted**;
- The rate of CAR-T uptake after Year 3 has been increased to better reflect the expected uptake of a potentially curative treatment addressing a large unmet clinical need;
- The costs of prolonged IVIg administration have been incorporated, consistent with the revised economic evaluation; and
- Cost estimates have been refined to separately consider infused and non-infused patients, explicitly assuming that Novartis will not receive any funding for the latter group.

Population criteria

Novartis agrees with the MSAC that, consistent with independent expert clinical advice at the hearing for the November 2018 meeting and the TGA delegate's overview:

1. the lower limit of 3 years of age should be omitted as an exclusion from any funding arrangement
2. patients who have had prior CD19 therapy should be eligible, and
3. the lower limit to define relapse before TIS would be morphological evidence of disease only (i.e not minimal residual disease)

The criteria above are not expected to significantly change the financial estimates.

Financial estimates

Taking into account the changes above, as well as a reduction in the effective price of TIS, the estimated net cost to government of funding TIS for the pALL indication has reduced from \$redacted over 6 years.

Table 11 Applicant estimated net financial implications for the Australian Government

Total Patients	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Total infused patients	redacted	redacted	redacted	redacted	redacted	redacted	redacted
TIS costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Other program costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost offsets	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Source: 1519 pALL Resubmission
Abbreviations: TIS = tisagenlecleucel

November 2018 MSAC consideration

The financial analysis employed a mostly top-down epidemiological approach to estimate the budget implications of the proposal for public funding. Revised financial analyses were provided in the pre-ESC and pre-MSAC responses to address concerns raised by the critique and the ESC report, respectively; these revisions increased the initially estimated net financial costs, particularly for DLBCL (Table 12).

Table 12 Estimated financial impact for treated and non-infused patients (from the Applicant's pre-MSAC response)

Total patients	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
pALL indication							
Expected utilization	redacted	redacted	redacted	redacted	redacted	redacted	redacted
Total program cost	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net budget impact	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
DLBCL indication							
Expected utilization	redacted	redacted	redacted	redacted	redacted	redacted	redacted
Total program cost	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net budget impact	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total							
Expected utilization	redacted	redacted	redacted	redacted	redacted	redacted	redacted
Total program cost	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net budget impact	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Source: Extracted from excel spreadsheet: 'Applicant preMSAC response_TIS Section E Workbook (ESC)'
Abbreviations: DLBCL = diffuse large B-cell lymphoma; pALL = paediatric acute lymphocytic leukaemia

15. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Clinical uncertainty	The available Phase I and II clinical studies include inadequate intention to treat analysis, inadequate comparative safety data, different endpoints, small patient numbers, dissimilar patient characteristics and short follow-up times.
Limitations of clinical evidence	Consider whether the presented clinical evidence is sufficient to inform the economic model, considering naive comparisons, short follow-ups for a lifetime model, and limited applicability to the Australian setting.
Uncertainty in economic model	Consider whether the overall uncertainty is acceptable given the choice of comparators, issues around costs and health state utilities, and a simple model structure not reflecting the stepwise preparation for CAR-T or SCT following CAR-T.
Inputs to economic model	ESC requested that the assessment group check the updated model to inspect whether ITT analyses and other modifications were correctly incorporated. The use of modelled shadow prices different than the proposed single effective price is not conventional. This has a moderate impact on the ICERs but in light of other issues does not dramatically change overall findings.
Economic policy issues	Consider the appropriate national funding mechanism, use of the proposed intervention in the outpatient setting, reliance on foreign jurisdictions, and broader implications of decisions given advancements in this class of treatments.

ESC discussion

ESC noted that MSAC advice was being sought in the context of the establishment of a new national funding and service delivery mechanism for TIS.

The overall intervention with TIS is a complex multistep process. It involves leukapheresis to extract peripheral blood T-cells, which are then cryopreserved and shipped to a cell processing facility in the US. The facility enriches for T-cells and transduces the cells with a lentiviral vector containing an anti-CD19 CAR transgene. The cells are expanded, prepared, cryopreserved and shipped back to the patient. The patient receives lymphodepleting chemotherapy for 2–14 days before receiving the TIS infusion. The entire process from leukapheresis to infusion can take 2–4 weeks, although the applicant’s pre-ESC response indicated this would likely be 28–30 days for patients in Australia. Patients must remain within 2 hours of the treating hospital for 1 month after TIS infusion to monitor for and manage adverse events.

Eligibility criteria/comparators

ESC noted that the comparator for the pALL population had changed from the original PICO confirmation. The applicant provided the following rationale:

- Segmentation of the proposed population into further subgroups is not feasible (subgroups are not mutually exclusive and the available clinical data are too sparse).

- The majority of patients likely to access TIS under the proposed criteria are expected to otherwise be candidates for some form of active or ‘salvage’ therapy rather than best supportive care.
- BLN is currently TGA indicated and PBS subsidised for treatment of r/r B-precursor cell ALL and would therefore be the most likely alternative treatment option for most patients within the proposed population.
- Prior BLN treatment was an exclusion criterion in the TIS studies, and there are no data on sequential use of these two therapies (in either direction); hence they will tend to be viewed as alternatives/substitutes rather than complements/supplements.
- Alternative salvage chemotherapy regimens, using either clofarabine or combinations of conventional chemotherapy agents may also be potentially informative comparators, but
 - clofarabine is TGA approved as a third-line treatment for r/r pALL patients but it is not currently available via the PBS
 - specific conventional salvage chemotherapy regimens are not well defined, with multiple approaches recommended, based on limited and mixed clinical evidence, against which meaningful comparisons of effectiveness, safety and cost-effectiveness are challenging.

ESC agreed that this was an adequate rationale for changing the comparator, but noted that previous BLN treatment should therefore be an exclusion criterion for accessing TIS.

ESC identified the following key issues for MSAC:

- The eligible populations and comparators need to be properly defined and aligned with populations recruited into supporting clinical studies or extrapolated from them.
- Subgroup analyses of requested subpopulations in the pALL group have not been presented, so it is unclear whether there are subgroups for which there is little or no data. However, data provided from the ELIANA study include small numbers in each group, so it may be better not to split this study population into subgroups.
- For the pALL population, it is unclear whether the comparator should be the last-line (salvage) setting (i.e. all other alternatives not applicable) or earlier (i.e. whether chemotherapy or stem cell transplant are relevant comparators).
- ESC queried the clinical justification for the proposed age limits (3–25 years) for the pALL population. ESC noted that the Australasian Leukaemia and Lymphoma Group disagreed with the upper age restriction of 25 years for this population. The applicant explained that this reflected the draft regulatory indication that was defined based on eligibility criteria for the studies. The applicant may also consider dropping the lower age limit, but will likely leave the upper age limit due to dosing differences in the adult population, with studies evaluating safety and efficacy ongoing.
- ESC noted that the application specifies the morphological evidence of disease as >5% blasts, but it was not clear what would happen with patients who had minimal residual disease (0.01–5% blasts).

Equity

- Access to services would (initially) be through three centres in Sydney and Melbourne, and patients need to be within 2 hours of the treating hospital for 1 month after TIS infusion.
- The age cutoffs for pALL may present ethical and equity challenges.

Safety

ESC noted the potential for serious adverse events associated with TIS in a significant proportion of patients, which include:

- cytokine release syndrome (CRS), a life-threatening condition that requires prolonged ICU admission, anticytokine therapy and vasopressor support;
- neurological events such as encephalopathy and delirium, which can be life-threatening;
- infections and febrile neutropenia;
- prolonged cytopenias and hypogammaglobulinaemia, which require immunoglobulin therapy; and
- tumour lysis syndrome.

ESC noted there was no presentation of comparative safety for the pALL population in the application. However, a combined safety analysis of the ELIANA and ENSIGN studies showed the most common serious adverse events were CRS (64.4% of patients), febrile neutropenia (24.0%) and hypotension (11.5%). Most adverse events were reported in the 8 weeks after infusion.

Similarly, ESC noted there was no presentation of comparative safety for the DLBCL population in the application.

ESC identified the following key issues for MSAC:

- No comparative safety data were provided.
- The therapy is based on genetic modification in humans, and nothing is known about the genotoxicity or carcinogenicity of TIS (or any CAR therapy). There is a potential risk to health care professionals handling and disposing of the product.
- The adverse event profile (and management) should be acceptably clear for each proposed population given potential for both short- and longer-term complications.
- Given the pALL population is mainly children who cannot directly give informed consent, a robust risk–benefit ratio is needed

Effectiveness

ESC noted the data on clinical effectiveness of TIS for the pALL population, which included three single-arm studies of TIS, a pooled analysis from two of these studies, and a single-arm study of BLN. ESC noted that the TIS clinical studies did not use intention to treat (ITT) analysis, and only included patients who received TIS. This was considered a major limitation, and resulted in a comparison against BLN, which was analysed according to the conventional ITT approach, that erroneously favoured TIS. However, the applicant included overall survival curves with ITT analysis in its pre-ESC response. ESC noted that there was no formal indirect comparison with BLN due to lack of a common control group, but a matched adjusted indirect comparison (MAIC) was provided. ESC noted that the MAIC results using the ITT populations in the TIS studies presented in the pre-ESC response were correctly not as favourable to TIS. ESC also noted that the studies had small patient numbers, different endpoints, dissimilar patient characteristics and short follow-up times (20–32 months). ITT analysis estimated the overall remission rate following TIS to be 66% for the ELIANA study and **redacted**% for the ENSIGN study.

ESC noted that TIS is a new class of therapy, and it is unclear how overall remission rates or overall response rates will translate to patient-relevant outcomes such as overall survival or quality of life, or event- or progression-free survival. ESC considered that the best approach

for comparative effectiveness would be to include all patients undergoing cell collection, regardless of receiving TIS (i.e. ITT population) to minimise selection bias. ESC considered that the outcomes should be measured at the equivalent duration of follow-up as comparator studies (time from study entry).

ESC considered there was weak evidence to claim superior effectiveness of TIS for the pALL population. The application included a naive indirect comparison with potential for selection bias. The included studies were small, had short follow-up times, and differed in their inclusion and exclusion criteria. The applicability of the studies may be limited because they were international multicentre studies and it is not clear whether Australian patients' outcomes were similar to those overall.

ESC noted the data on clinical effectiveness of TIS for the DLBCL population, which included two single-arm studies of TIS, no pooled analysis and three single-arm studies of SCR. As for the pALL population, there was no ITT analysis of the TIS studies, but the applicant provided additional survival curves in the pre-ESC response. There was similarly no formal indirect comparison due to lack of a common control group, but an MAIC was provided. ESC noted that the MAIC results using the ITT population in the TIS studies presented in the pre-ESC response were correctly not as favourable to TIS. ESC also noted the studies had small patient numbers, dissimilar patient characteristics and short follow-up times (19–29 months).

ESC considered there was weak evidence to claim superior effectiveness of TIS for the DLBCL population. The application included a naive indirect comparison, which may be subject to confounding and significant selection bias. The included studies were single-arm Phase I and II studies with limited follow-up, and the overall response rate has uncertain long-term clinical relevance. The applicability of the studies may be limited because they were international multicentre studies and it is not clear whether Australian patients' outcomes were similar to those overall.

ESC recognised the challenges of collecting evidence for low-prevalence refractory conditions, but considered that the issues in the application were not a unique consequence of the innovative nature of the therapy. Similar issues are often assessed by the PBAC for oncology products. ESC advised that differences in patients, outcome definitions and setting across the single-arm studies may lead to substantial transitivity issues.

Costs and funding

- Funding is dependent on the TGA-registered populations, but there is a risk of use earlier in the clinical management pathways for both pALL and DLBCL.
- Other autologous products of gene editing are likely to become available in the near future.
- It is unclear how cases will be handled when the patient is prepared for TIS but is not able to receive the infusion, and who will bear the costs of this preparation, even if there are no costs for the TIS, no matter how far the TIS process has progressed to the point of being ready for infusion.
- Funding would be primarily for the inpatient setting, although some care may be provided through the outpatient setting leading up to and after the TIS infusion.
- It may therefore be desirable to assign separate episodes of care for provision of health care resources to assist with costings by the Independent Hospital Pricing Authority (i.e. confirming the patient's eligibility for TIS, harvesting the patient's T-cells, preparing the

patient for TIS, administering TIS, monitoring and management of the patient after TIS [including adverse events]).

Manufacturing and supply arrangements

- **Redacted**, it is unclear whether the applicant will increase capacity in a timely way if TIS demand rises rapidly across the globe.
- It is unclear whether cell survival rates would be similar in regular practice.
- The application claimed 2–4 weeks from leukapheresis to receipt of TIS. **Redacted**.

Economic evaluation

ESC reviewed the economic evaluation, which was a cost-utility analysis from the Australian health care system perspective. ESC noted that stem cell transplant, salvage therapy or supportive treatment after failed TIS had not been explicitly modelled. ESC noted the high cost of TIS treatment, which was mainly driven by the high cost of the product (**redacted**). ESC also noted the unusual approach in the application of using two different shadow prices for each population in the model, but then taking a weighted average of those (**redacted**) to calculate the proposed effective price of \$**redacted**. ESC considered that these assumptions may differ in reality, and if the DLBCL population was more than **redacted**, the government would effectively be overpaying. ESC noted that this would have implications for overall cost-effectiveness, and advised that this approach therefore carried some risk for the payer.

ESC considered that the simplified approach to costing adverse events adopted for the models was unlikely to be accurate, and sensitivity analysis was required. ESC considered that the simplified approach magnified the uncertainty associated with the absence of a formal comparison of adverse events between TIS and the comparators. The adverse event profile of CAR-T is not benign, and ESC considered that the impact of adverse events in the economic models had not been sufficiently explored. The simplified approach takes no account of different time-courses of adverse events and the possibility of multiple admissions per patient for different adverse events, or the increased management required for concurrent adverse events.

In the application, the base case incremental cost-effectiveness ratio (ICER) for the pALL population was \$**redacted**, and for DLBCL was \$**redacted**. ESC noted that the ICER was highly sensitive to the time horizon in the models. If the models were truncated at time points equivalent to the duration of the observed data (2 years for ALL, and 3 years for DLBCL), the ICERs were \$**redacted** for ALL, and \$**redacted** for DLBCL. ESC considered that extrapolations of survival curves were uncertain because of limited clinical data and difficult to interpret due to unclear pooling of clinical study data.

ESC noted the ITT analyses in the revised economic models presented with the pre-ESC response, but that these revisions resulted in some unexpected effects on the model outputs.

ESC considered that the economic models did not allow exploration of the impact of different assumptions about implementation and technical efficacy. ESC recommended that a useful alternative model structure would be an initial decision tree that steps out each subprocedure of the TIS process, with transition probabilities applied at each step, before ‘response’ is modelled via the Markov health states.

Other key issues identified with the economic evaluation were as follows:

- The TIS arm modelled patients who were treated, while the comparator arms modelled the ITT population. ESC noted that the TIS infusion was not provided to 19% of patients

in the ELIANA study and 33% in the JULIET study. The preparation costs for these patients (for leukapheresis, cryopreservation, bridging therapies) were therefore not included, nor were estimates of reduced treatment effectiveness.

- The clinical evidence and inputs are from naive comparisons of single-arm studies, which had baseline differences, and potential confounding and selection bias.
- The maturity of the evidence was low due to short follow-up times, leading to uncertainty regarding lifetime extrapolations (particularly extrapolation of survival benefit). The assumption of a sustained benefit to overall survival may have been too optimistic, and the application did not address whether multiple or repeat doses might be required to maintain the effect.
- The model should include consideration of an allo-SCT following TIS, because CAR-T therapy can be used as a conditioning therapy to improve the likelihood of successful allo-SCT.
- The applicability to the Australian patient population and Australian clinical practice was not clear.

Financial analyses

ESC noted the financial impacts presented in the application. ESC noted the applicant's pre-ESC response, which clarified that **redacted**. This would be relevant in case of patient death during the manufacturing process, for example. **Redacted**.

ESC considered that leakage to other types of cancer was unlikely, given the high cost of TIS. The use of TIS earlier in the clinical management pathway may be possible however, and this adds uncertainty to the financial estimates. ESC noted that utilisation estimates were uncertain as the projections were incidence based and did not account for eligible prevalent cases.

ESC noted that the applicant argued that including a market share approach within its uptake assumptions was appropriate, as other CAR-T therapies are expected to be 'listed' in coming years. ESC considered that, as the first to market, TIS needs to account for the *total* expected market of CAR-T therapies. Subsequent applications by other manufacturers for the same indications could then adopt a market-share approach for their financial estimates.

The estimates provided in the application were therefore highly uncertain and a significant underestimate of the likely total cost of TIS to the Australian health system.

ESC noted that use of TIS in the outpatient setting was unlikely, given that, currently, only three tertiary facilities can provide the service, and patients must remain within 2 hours of the treating hospital for 1 month after TIS infusion.

A risk-sharing arrangement would be essential. ESC considered that any funding mechanism should preclude payment for more than one TIS therapy per patient, as this would be outside the TGA-approved indication, and contrary to the applicant's proposed use, and economic and financial modelling.

Further comments and options for possible next steps

ESC noted the range of considerations in establishing a new funding mechanism for these types of interventions and the importance of making strategic decisions to account for future similar interventions. It would be important to define which governments, authorities, schemes and schedules would participate; whose costs should be included; and how this

could be coordinated between governments. Considerations for conditions of use would include eligible patient populations and criteria for participating facilities. ESC queried whether advice was required from the Office of the Gene Technology Regulator.

Overall, ESC considered that the discrepancies in data and model inputs between treated and ITT populations were important limitations. ESC noted that the intervention process is complex and includes many steps, including international transport, and each of these steps has associated risks. ESC recommended that each step in the process should be accounted for and have transition probabilities included in the model. ESC considered that the short follow-up times in the studies were insufficient to determine whether the intervention is curative.

ESC recommended that the applicant submit further details of its methods to derive the weighted treatment price, and adjust the proportion of patients receiving TIS to **redacted**. It was not clear if the methods used by the applicant overestimate or underestimate the treatment costs and ICERs when non-infused patients are accounted for. This revised model should then be reviewed by an assessment group. In particular, ESC queried whether the weighted treatment cost appropriately captured costs that would accrue to the health system before TIS infusion is aborted, and whether the downstream costs for non-infused patients were appropriately captured (e.g. whether non-infused patients would avoid all the costs associated with CRS but instead accrue costs associated with another treatment, or whether they die without accruing any further costs).

16. Other significant factors

Nil

17. Applicant's comments on MSAC's Public Summary Document

Novartis thanks the Medical Services Advisory Committee for evaluating this innovative and highly complex therapy. We are committed to working with the Medical Services Advisory Committee and the Australian Government to ensure reimbursement for all eligible patients as soon as possible.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)