Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value

Evidence Report

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2022/06/ICER_Beta-Thalassemia_Stakeholder-List_060222.pdf

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List of Acronyms and Abbreviations Used in this Report

AHRQ	Agency for Healthcare Research and Quality
BLA	Biologics License Application
DEXA	dual-energy X-ray absorptiometry
dL	deciliter
evLY	equal value life year
EQ-5D-3L VAS	EuroQol visual analog scale
EQ-5D-Y VAS	EuroQol visual analog scale-youth
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplant
FACT-G	Functional Assessment of Cancer Therapy-General
g	gram
Hb	hemoglobin
HLA	human leukocyte antigen
HSC	hematopoietic stem cells
HSCT	hematopoietic stem-cell transplantation
LIC	liver iron concentration
LTF	long-term follow-up
MCID	minimal clinically important difference
Mg	milligram
MRI	magnetic resonance imaging
n	number
N	total number
NC	not calculated
NR	not reported
PDUFA	Prescription Drug User Fee Act
PedsQL	Pediatric Quality of Life Inventory
pRBC	packed red blood cells
QALY	quality adjusted life year
SCD	sickle cell disease
SD	standard deviation
SE	standard error
SF-36 MCS	Short Form-36 Health Survey Mental Component Summary
SF-36 PCS	Short Form-36 Health Survey Physical Component Summary
SMR	standardized mortality ratio
SOC	standard of care
TD	transfusion dependent
TDT	transfusion-dependent beta-thalassemia
TI	transfusion independence
TIF	Thalassemia International Federation

Executive Summary

Beta-thalassemia is a rare blood disorder with the potential for high morbidity and mortality when treated sub optimally. Transfusion dependent thalassemia (TDT), the most severe form of this disease, is managed through lifelong regular blood transfusions and iron chelation therapy to avert the consequences of iron overload. There are likely between 1,000 – 1,500 people in the US living with TDT,[1,2] but there are estimated to be about 1.25 million carriers of the genetic defect that is responsible for thalassemia. Until recently, the only curative option for TDT was allogenic hematopoietic (blood) stem cell transplantation (HSCT) from a matched donor, ideally a sibling. HSCT requires high doses of conditioning chemotherapy and places the recipient at risk of complications associated with HSCT itself (e.g., graft vs. host disease) and finding an HSCT match is difficult as fewer than 25% of patients have access to a suitable match.

Life expectancy still lags far behind population norms even with improved treatments: from 2011 to 2021 the median age of death for a person in the US with TDT was 37.[3] Additionally, patients with TDT still report decreased quality of life due to the impact on physical and mental health.[4,5] Patients and clinicians reported to us that living with severe forms of beta thalassemia requires being "tethered to the health care system" and often to a specific region near a medical center that can provide thalassemia care. Some patients receive transfusions as often as every two weeks, and nearly all patients plan their lives around transfusions. Regular transfusions and chelation can be technically challenging in young children, causing stress in patients and caregivers.

Betibeglogene autotemcel (beti-cel), manufactured by bluebird bio, is a gene therapy that provides an additional potentially curative option for patients with TDT. Beti-cel is manufactured *ex vivo* utilizing an individual's own hematopoietic stem cells (HSCs). A lentiviral vector (BB305) is then used to add functional copies of the β-globin gene ($\beta^{A\text{-}T87Q}$) to patients' HSCs. The modified HSCs (beti-cel) are then infused intravenously back into the individual following conditioning chemotherapy. The Food and Drug Administration (FDA) accepted bluebird bio's Biologics License Application (BLA) of beti-cel for priority review on November 22, 2021, and the revised PDUFA date is set for August 19, 2022 (originally May 20, 2022). Public statements made by the manufacturer suggest that beti-cel pricing will be consistent with an outcome-based payment plan of five equal yearly payments totaling $2.1 million for individuals who achieve and maintain transfusion independence.

The systematic review yielded five studies of beti-cel: two Phase I/II trials, two Phase III trials, and one long-term follow-up cohort study of trial participants. Each of the four trials were open-label single arm designs. A manufacturing change occurred between the Phase I/II and Phase III trials; therefore, we gave greater emphasis to the results from the Phase III trials.

Transfusion independence in the Phase III trials was achieved in 89% of the patients who received beti-cel.[6] Transfusion independence among patients treated in Phase I/II and Phase III trials and who were enrolled in the long-term follow-up study was sustained over a median length of follow-up of 42 months (range 23-87).[7] However, this duration is not long enough to remove uncertainty regarding the durability of effect over a longer time period. Beti-cel infusion is associated with mild side effects, but few patients experienced serious adverse events, and no deaths were reported. Uncertainty remains about the degree of risk of beti-cel infusion in real-world practice, and there are known risks associated with myeloablative conditioning.[8] Because of the questions about these risks and the durability of the clinical benefit, we judge that the evidence demonstrates that beti-cel is superior overall to the current standard of care, but the magnitude of that overall net health benefit is less certain, ranging from incremental to substantial ("B+"). Interestingly, we heard from many stakeholders, including patients with TDT and their families, that even if beti-cel proves to be a durable cure with an excellent safety profile, there are likely to be many patients who choose to continue their current management with transfusion and chelation.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Betibeglogene autotemcel (beti-cel)	Standard of Care	B+

The manufacturer has suggested publicly that beti-cel will be priced based on its clinical value to patients only, rather than its ability to offset costs of current therapy.[9] ICER's single and short-term therapy (SST) value assessment framework includes a scenario analysis where half the cost offsets from an SST are returned to society rather than all being credited to the price of the treatment. While in the base case, no discount is needed from the anticipated price of $2.1 million to achieve typical ICER Health Benefit Price Benchmarks (HBPBs), assuming 50:50 shared savings, the HBPB range is $1.3 to $1.8 million.

In summary, despite remaining uncertainties, the evidence suggests that beti-cel provides net health benefits to patients with TDT. Given the high annual costs of standard care, cost-effectiveness modeling finds that this new treatment meets commonly accepted value thresholds at an anticipated price of $2.1 million with an 80% payback option for patients who do not achieve and maintain transfusion independence over a five-year period. However, if half of the lifetime cost savings from the therapy are returned to society, then discounts between 15% and 38% off the anticipated price are required to meet commonly accepted thresholds.

1. Background

Beta thalassemia is an inherited blood disorder caused by a genetic mutation of the *HBB* gene that leads to reduced or absent synthesis of the β-globin proteins of hemoglobin, components of red blood cells responsible for carrying oxygen. When β-globin is markedly reduced or absent, it leads to ineffective production and increased destruction of red blood cells, manifesting in clinically significant anemia.

Beta thalassemia is an autosomal recessive disorder. Individuals who carry a mutation in only one copy of the *HBB* gene are generally asymptomatic or only have mild anemia (beta thalassemia minor or trait, Hb>10.0 g/dL). It is estimated that 1.5% of the global population carries at least one defective copy of the *HBB* gene, with certain geographic areas having a higher local prevalence – primarily in the Mediterranean, Africa, the Middle East, and South Asia.[10-12] However, if both copies of the *HBB* gene have a mutation, there will be a reduction or absence of β-globin. The degree to which β-globin is reduced depends on the specific mutation and how many genes are affected: β0/β0 (completely absent β-globin), β+/β+ (some β-globin production, severity depends on mutation), or β+/β0 (one gene copy produces some β-globin, the other produces none). Patients with completely absent β-globin have a more severe clinical course, typically presenting in the first six to 24 months of life with severe anemia, failure to thrive, and end organ damage; prompt initiation of transfusion therapy is required to prevent early mortality.[13,14] Conversely, patients with some β-globin production have variable clinical presentations with some patients depending on routine transfusions to maintain health and quality of life, while others might have mild symptoms or only receive transfusions in times of stress (e.g., pregnancy, infection, surgery). Historically, patients with absent β-globin were considered to have thalassemia major and those with reduced β-globin were considered to have thalassemia intermedia, but it is clinically preferable to classify thalassemia based on clinical severity and transfusion requirements regardless of the underlying genotype. The 2021 Guidelines published by the Thalassaemia International Federation (TIF) classify beta thalassemia phenotypically into two main groups based: transfusion dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT).[14]

Lifelong, regular blood transfusions and removal of excess iron through chelation are the mainstays of treatment for patients with TDT. Routine transfusions, typically every two to five weeks, aim to keep hemoglobin at a level that suppresses the body's production of its own (abnormal) hemoglobin. However, as excess iron accumulates as a consequence of repeated transfusion and increased gut absorption, chelation is critical for treating and preventing complications from iron overload (e.g., pulmonary hypertension, liver dysfunction, cardiac manifestations), the main source of morbidity and mortality in TDT. In addition, patients with TDT also contend with other disease-related complications such as problems with growth and development, diabetes and other endocrine abnormalities, and fertility and pregnancy-related concerns. There is also the ongoing

risk of transfusion-related side effects and infections, although the latter are rare with modern blood screening procedures. Standard of care may also include treatment with luspatercept-aamt (Reblozyl®, Acceleron Pharma Inc. and Bristol Myers Squibb/Celgene Corp.), a biologic that can enhance erythropoietic maturation and differentiation resulting in increased red cell production, thereby reducing transfusion burden in some patients.

Hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment for TDT. Ideally, HSCT is performed in children younger than 14 years of age with a human leukocyte antigen (HLA)-matched sibling donor. In such candidates, the cure rate is over 90% with a 4% risk of mortality. The cure rate decreases in older patients, those with extensive iron toxicity, and those without a matched donor.[15] Lack of compatible donors is a central limitation of initiating HSCT, not more than 25% of patients have access to compatible related or unrelated donors.[16]

Betibeglogene autotemcel ("beti-cel", bluebird bio), previously marketed in Europe under the brand name Zynteglo™, is an emerging, potentially curative, gene therapy for beta thalassemia. Beti-cel uses a lentivirus vector to insert a functioning version of the *HBB* gene into the patient's own blood cells. This is accomplished by retrieving stem cells from the patient's blood, engineering them outside of the body, and then transplanting cells with functioning *HBB* genes back into the body. The person must receive chemotherapy to prepare the bone marrow to receive the modified cells and to produce new red cells with normal β-globin/hemoglobin. The FDA accepted bluebird bio's Biologics License Application (BLA) of beti-cel for priority review on November 22, 2021, and the revised PDUFA date is set for August 19, 2022 (originally May 20, 2022).

Table 1.1. Intervention of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Betibeglogene autotemcel (beti-cel)	*Ex vivo* genetic modification of autologous HSC using a lentiviral vector encoding the $\beta^{A\text{-}T87Q}$-globin gene	Intravenous infusion following myeloablative conditioning with chemotherapy	To be determined

HSC: hematopoietic stem cells

2. Patient and Caregiver Perspectives

From 2011 to 2021 the median age of death for a person in the US with TDT was 37.[3] Although life expectancy is likely to continue to increase with improved treatments, it still lags behind population norms. Additionally, patients with TDT still report decreased quality of life due to the impact on physical and mental health.[4,5] Patients and clinicians reported that living with severe forms of beta thalassemia requires being "tethered to the health care system" and often to a geographic area with a medical center that can provide thalassemia care. Management of the condition has been described as a part-time job for patients and their caregivers. Patients plan their lives around transfusions, disrupting their ability to travel, take vacations, work, and study. Some patients receive transfusions as often as every two weeks, in addition to regular MRI and DEXA imaging, monitoring of laboratory values, and visits to clinical specialists (e.g., endocrinologists, cardiologists). Regular transfusions and chelation can be technically challenging in young children, causing stress in patients and caregivers. Some patients require semi-permanent catheters (i.e., ports) to facilitate regular transfusions, which carry a risk of infection. Patients and their caregivers also spend hours managing administrative aspects of their condition, such as calling doctors' offices and navigating insurance policies. Patients and caregivers emphasized how quality of life is also markedly impacted by other manifestations of thalassemia (e.g., diabetes, problems with growth or development). Infertility, including as a consequence of HSCT, was highlighted as a particular concern among all groups of stakeholders, including adult patients, caregivers of children, and clinicians.

Social determinants of health may be important drivers of quality of life in patients with TDT. Patients reported needing to have high health literacy and access to major medical centers specializing in thalassemia care. Patients also reported requiring significant flexibility in their work and home lives in order to attend medical appointments and receive frequent transfusions. Patients with "white collar" jobs that allow for remote work may have advantages over patients with more physically demanding jobs (e.g., still being able to work during periods of extreme fatigue between transfusions). Among patients with TDT, women, older age, and those with more disease complications or side effects from management of iron overload (i.e., chelation therapy), on average report lower health-related quality of life.[17] This was echoed in the sentiment of the patients we spoke to – their views about their own quality of life over time related to how well-managed their thalassemia was, with a particular emphasis on iron status/overload. Adherence to iron chelation is associated with better quality of life but using iron chelation therapy as indicated is a problem for many patients.[18] We heard from patients and caregivers that optimizing iron chelation therapy was challenging, particularly during adolescence. The lack of immediate symptomatic decline ("feeling normal for a period of time"), route of administration and dosing, and the side effects of chelation therapy itself were all cited as reasons that someone might not adhere to iron chelation therapy.

While patients we spoke to expressed optimism about the promise of gene therapy, they also raised concerns about barriers to accessing this treatment (e.g., insurance coverage/pre-authorization, needing to live near particular medical centers, eligibility criteria). For instance, some patients highlighted that they had difficulty accessing luspatercept, an adjunct to standard care, even though their treating clinicians recommended it. Overall, patients reported that they will carefully weigh costs, insurance coverage, duration of clinical benefit, and risks once gene therapy becomes available.

We met with representatives from the Thalassaemia International Federation (TIF), the largest global thalassemia advocacy group, about the perspective of patients and caregivers. In a 2020 report by TIF, the majority of survey respondents with thalassemia demonstrated a positive attitude towards gene therapy with a significant proportion interested in gene therapy for themselves or their children. In developed countries (including the US), however, 29% of patients reported that they would accept gene therapy, while the remaining patients reported they would not accept gene therapy (24%) or were uncertain (47.2%). This mirrors what we heard from patients in our stakeholder interviews. While there was general enthusiasm toward the possibility of curing beta thalassemia, some patients whose condition is well-managed with current standard of care thought they might be reluctant to modify their treatment regimen because beti-cel has only been evaluated in small numbers of patients and treatment requires chemotherapy and hospitalization. Other adults we spoke with expressed a strong interest in gene therapy and thought they would pursue it if eligible. We spoke with caregivers of adult children living with TDT and also parents of a child who had undergone a sibling matched HSCT. These caregivers thought there would be a strong interest in gene therapy among parents with young children. When probed about what a cure for TDT would mean, one participant told us "Time… and you just can't put a price on that."

In sum, our stakeholder conversations highlight significant enthusiasm and cautious optimism for a gene therapy cure for TDT.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence on betibeglogene autotemcel (beti-cel) for the treatment of TDT are described in Supplement Section D1. A research protocol is published on Open Science Framework and registered with PROSPERO (CRD42022300138).

Scope of Review

We reviewed the clinical effectiveness of beti-cel versus standard of care for the treatment of TDT. We also intended to compare beti-cel to HSCT but did not identify any evidence directly comparing the two therapies. We sought evidence on patient-important outcomes, including transfusion independence, manifestations of iron overload, health-related quality of life, and adverse events. The full scope of the review is described in Supplement Section D1.

Evidence Base

The evidence informing this review was derived from two Phase I/II trials, two Phase III trials, and one long-term follow-up study of trial participants. Additional safety data were reviewed from a Phase I/II trial of lovotibeglogene autotemcel in sickle cell disease because it was developed and tested together with beti-cel in early phase trials; both therapies insert a functional human beta-globin gene into the patient's hematopoietic stem cells.

Beti-cel was first evaluated in two Phase I/II trials ("HGB-204" and "HGB-205") in patients with TDT of any genotype.[19] These trials enrolled patients who were 35 years of age or younger, with lower age limits of 12 and 5 years in the HGB-204 and HGB-205 trials, respectively. Patients were considered to be transfusion-dependent if they received at least eight transfusions per year, or at least 100 mL/kg of body weight of packed red cells per year, in the two years prior to enrollment.[20,21] Of the 23 enrolled patients in these two trials who underwent mobilization and apheresis, all but one patient continued on to receive beti-cel.[19] Following the Phase I/II trials, the manufacturing process was modified to enhance transduction efficiency in the Phase III trials; due to this change, the Phase III trials are the primary focus of this review.

NorthStar-2 ("HGB-207") and NorthStar-3 ("HGB-212") were identically designed single-arm Phase III trials in patients with TDT. NorthStar-2 enrolled patients with a non-β0/β0 genotype and NorthStar-3 enrolled patients with either a β0/β0 genotype or severe non-β0/β0. Eligible patients were up to 50 years of age, received at least eight transfusions per year for the prior two years, or

at least 100 mL/kg/year of packed red blood cells, and were HSCT eligible. Patients were excluded if they had a previous HSCT or had a known or available HLA-matched family donor.[22,23]

A total of 41 patients in the Phase III trials received beti-cel. These patients had a median age of 13 years, received 11 to 40 transfusions per year prior to enrollment, and had baseline liver iron concentrations above normal levels.[6] There were no apparent clinically important differences in patient characteristics between the two Phase III trials. Additional baseline characteristics can be found in Table 3.1 and Supplement Table D6. Patients remained in the trial for 24 months post-infusion, after which they could enroll in a long-term follow-up study; follow-up is still ongoing for some patients.

A total of 63 patients from Phase I/II and Phase III trials have enrolled in the long-term follow-up study ("LTF-303"), which will follow patients up to fifteen years. Patients have been followed for a median of 42 months and a maximum of 88 months to date.[7] Detailed descriptions of all included trials can be found in Supplement Table D4.

Table 3.1. Overview of Included Studies[7,24,25]

Trial	Study Design	Population	Key Baseline Characteristics
HGB-204	Single arm, multi-site, Phase I/II trial N = 18 Follow-up: 2 years	TDT of any genotype	**Age**, median (range): 20 (12-35) **Transfusions per year,** median (range): NR **Previous splenectomy**, n (%): 6 (33) **LIC†, mg/g**, median (range): 5.7 (0.4-26.4)
HGB-205*	Single arm, multi-site, Phase I/II trial N = 4 Follow-up: 2 years	TDT of any genotype	**Age**, median (range): 18 (16-19) **Transfusions per year,** median (range): NR **Previous splenectomy**, n (%): 3 (75) **LIC†, mg/g**, median (range): 11.2 (3.9-14)
NorthStar 2 (HGB-207)	Single arm, multi-site, Phase III trial N = 23 Follow-up: 2 years	TDT with a non-β0/β0 genotype	**Age**, median (range): 15 (4-34) **Transfusions per year,** median (range): 16 (11.5-37) **Previous splenectomy**, n (%): 4 (17) **LIC†, mg/g**, median (range): 5.3 (1-41)
NorthStar 3 (HGB-212)	Single arm, multi-site, Phase III trial N = 18 Follow-up: 2 years	TDT with β0/β0 and severe non-β0/β0 genotypes	**Age**, median (range): 13 (4-33) **Transfusions per year,** median (range): 17.3 (11-39.5) **Previous splenectomy**, n (%): 3 (17) **LIC†, mg/g**, median (range): 3.6 (1.2-13.2)
LTF-303 (Phase III participants only)	Phase IV multi-center long-term follow-up N = 41 Follow-up: 13 years	TDT previously infused with beti-cel	**Age**, median (range): 15 (5-34) **Transfusions per year,** median (range): 17.5 (11-39.5) **Previous splenectomy**, n (%): 7 (20) **LIC†, mg/g**, median (range): 4.9 (1-41)

g: gram, LIC: liver iron concentration, LTF: long-term follow-up, mg: milligram, n: number, N: total number, NR: not reported, SCD: sickle-cell disease, TDT: transfusion-dependent beta thalassemia

* Patients with TDT and SCD were included in HGB-205; only patients with TDT are presented here

† Normal liver iron concentration reference <1.8

‡ Severe non-β0/β0 genotypes include β0/ $\beta^{+IVS-I-110}$ and $\beta^{+IVS-I-110}/\beta^{+IVS-I-110}$ genotypes

3.2. Results

Clinical Benefits

Transfusion Independence

A total of 63 patients from the Phase I/II and Phase III trials have received an infusion of beti-cel.[6,19] All patients had successful neutrophil and platelet engraftment, which occurred after a median of 26 (range 13-39) days for neutrophil engraftment and a median of 46 (range 13-94) days for platelet engraftment in the Phase III trials. Patients spent a median of 44 (range 29-92) days in the hospital from conditioning through discharge.[6] See Table 3.2 for additional information regarding engraftment outcomes.

The primary efficacy endpoint in the Phase III NorthStar-2 and -3 trials was transfusion independence (TI), defined as a weighted average hemoglobin ≥9 g/dL without any packed red blood cell (pRBC) transfusions for a continuous period of ≥12 months, and beginning within 12 to 24 months of beti-cel infusion.[22,23]

Among 38 participants from the NorthStar-2 and -3 trials with sufficient follow-up to evaluate the primary endpoint, 34 (90%) achieved TI (Table 3.2).[6] Over a median follow-up of 42 months (range 23-87) across Phase I/II and Phase 3 studies, no patients who achieved TI have lost TI.[7]

Weighted average hemoglobin during the period of TI (weighted by time), was also used to assess treatment efficacy. The median hemoglobin levels presented in NorthStar-2 and -3 remained stable over at least 24 months of follow-up (Supplement Table D9).[26]

Table 3.2. Key Trial Results[7,19,27,28]

	Pooled Phase I/II	Pooled Phase III
Follow-Up, median months (range)	42 (23-88)	
Enrolled, N	23	43
Infused, N	22	41
Successful Engraftment, n (%)	22/22 (100)	41/41 (100)
Time to Neutrophil Engraftment, median days (range)	18 (14-30)	25.5 (13-39)
Time to Platelet Engraftment, median days (range)	36 (19-191)	46 (13-94)
Duration of Hospitalization†, median days (range)	40 (27-69)‡	44 (29-92)
Transfusion Independence, n/N (%)	15/22 (68)	34/38 (89.5)*
Hb level during TI, g/dL, median (range)	10.3 (9.1-13.2)	11.3 (9.3-13.7)

dL: deciliter, g: grams, Hb: hemoglobin, n: number, N: overall number, TI: transfusion independence
* Evaluable patients (i.e., surpassed at least 12-months of follow-up)
† From conditioning through discharge
‡ Reported for HGB-204 only

Quality of Life

Patients in NorthStar-2 and -3 who achieved TI were assessed for improvements in health-related quality of life (HRQoL) using several instruments: Pediatric Quality of Life Inventory (PedsQL), EuroQol visual analog scales (EQ-5D-Y and EQ-5D-3L VAS), Short Form-36 Health Survey: Physical and Mental Component Summaries (SF-36 PCS and SF-36 MCS), and Functional Assessment of Cancer Therapy-Bone Marrow Transplant and -General (FACT-BMT and FACT-G). All instruments assessed physical, emotional, and social functioning, with higher scores indicating better HRQoL.[26] The instruments are described in more detail in Supplement Section A1.

Adolescents evaluated with the EQ-5D-Y VAS and adults evaluated with the EQ-5D-3L VAS instruments had high mean HRQoL at baseline (scores of 81 and 85 respectively out of a best possible score of 100), which improved 24 months after receiving beti-cel (see Table 3.3). On the

PedsQL scale, pediatric and adolescent patients experienced a mean improvement of 9 points 24 months after receiving beti-cel, which exceeded the minimally clinically important difference (MCID) of 4.36. Small improvements were reported in adults assessed with the SF-36 PCS, SF-36 MCS, FACT-BMT, and FACT-G instruments.[26] More details on HRQoL instruments and outcomes can be found in Table 3.3 and Supplement Table D14.

Table 3.3. HRQoL Outcomes[26]

Instrument (score range)	Baseline, mean score (SE)	Month 24, mean score (SE)	Change from Baseline to Month 24	Instrument MCID
EQ-5D-Y VAS (0-100)	81.4 (SD: 19.2)	92.4 (SD: 6.0)	11.0	NC
EQ-5D-3L VAS (0-100)	85.2 (SD: 10.5)	94.2 (SD: 4.8)	9.0	NC
PedsQL (0-100)	77.4 (3.6)	86.4 (1.7)	9.0	4.36
SF-36 PCS (0-100)	53.8 (1.4)	55.4 (1.3)	1.6	2.0
SF-36 MCS (0-100)	51.0 (1.7)	53.5 (2.1)	2.5	2.0
FACT-BMT (0-196)	125.8 (3.4)	128.9 (3.0)	3.1	NC
FACT-G (0-108)	94.2 (2.6)	95.8 (2.1)	1.6	NC

EQ-5D-3L VAS: EuroQol visual analog scale, EQ-5D-Y VAS: EuroQol visual analog scale-youth, FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow, FACT-G: Functional Assessment of Cancer Therapy-General, HRQoL: health-related quality of life, MCID: minimal clinically important difference, NC: not calculated, PedsQL: Pediatric Quality of Life Inventory, SD: standard deviation, SE: standard error, SF-36 MCS: Short Form-36 Health Survey Mental Component Summary, SF-36 PCS: Short Form-36 Health Survey Physical Component Summary

Changes in Chelation Therapy and Iron Overload

Patients discontinued iron chelation therapy 7 to 25 days prior to myeloablative conditioning and could resume treatment approximately three months after beti-cel infusion. The decision to resume or discontinue therapy was at the discretion of patients and their physicians, rather than achievement of reference levels of iron indicators. Among 49 participants from the Phase I/II and Phase III trials who achieved TI, 33 (67%) discontinued iron chelation post-infusion; of these 33 patients, 12 never resumed chelation and 21 restarted chelation for a median of 25 months (range 0.2-62.3 months) and have since stopped.[29]

Indicators of iron overload improved following beti-cel infusion (Table 3.4, Supplement Tables D8-10), although some patients who restarted and then stopped chelation in the long-term follow-up study experienced increases in iron levels. It is uncertain how iron fluctuations affected decisions to stop or restart chelation therapy.

Overall, serum ferritin levels declined by approximately 50% during the first two years of follow-up in the Phase III trials; longer-term follow-up of four patients from the Phase I/II HGB-205 trial suggested ferritin levels continued to fall, with two patients reaching a normal level by 48 months of follow-up and a third reaching a normal level by 60 months.[7,25,28] In this latter study, one of the

four participants stopped chelation after 17 months, while the remainder continued chelation and phlebotomies.[28]

Declines in liver iron concentrations accrued over time. While there was no appreciable decline in participants of the Phase III NorthStar-2 trial during the first 24 months of follow-up, three patients for whom longer follow-up data were available reached the normal range by 36 months. Over a median of 44 months follow-up, the median concentration of liver iron in patients who achieved TI fell from a baseline of 5.3 mg/g of dry weight (range 1.0-41.0) to 4.5 mg/g (range 1.4-20.3).[25]

Myocardial iron levels did not change over the first 24 months of follow-up in the NorthStar-2 trial, and remained within the normal range for all but one patient whose T2*-weighted MRI measurement decreased below the normal range of >20 msec at 12 and 24 months.[25] Results from the Phase I/II HGB-205 trial were only reported between 24 and 72 months of follow-up, but remained within the normal range during that time.[28]

Table 3.4. Iron Status in the Phase III NorthStar-2 (HGB-207) Trial[25]

	Baseline	24 Months	36 Months
Median serum ferritin level, ng/ml (range)	1826 (349 - 5978) n=20	862 (94-8443) n=18	698 (126 - 2134) n=8
Median liver iron concentration, mg/g of dry weight (range)	5.1 (1.0 - 41.0) n=20	4.9 (1.4 - 20.3) n=17	2.0 (1.4 - 2.2) n=3
Median T2*-weighted MRI measurement of myocardial iron, msec (range)	36.5 (21 - 57) n=20	35.1 (15 - 47) n=17	33.5 (29 - 41) n=7

g: gram, mg: milligram, ml: milliliter, MRI: magnetic resonance imaging, n: number assessed, ng: nanogram
Liver iron concentration reference <1.8
Myocardial iron reference >20
Serum ferritin reference range 30-400

Harms

All patients who underwent myeloablative conditioning and beti-cel infusion during the Phase III trial NorthStar-2 trial experienced at least one adverse event (AE).[25] There have been no deaths in patients with TDT across the beti-cel clinical development program, although serious AEs have been reported. Serious AEs were deemed likely related to myeloablative conditioning and included five cases of veno-occlusive liver disease, stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, pyrexia, and heart failure (Table 3.5).

Grade ≥3 AEs were common, with 96% of trial participants experiencing grade ≥3 thrombocytopenia and ≥50% experiencing grade ≥3 neutropenia, anemia, leukopenia, and/or stomatitis (Table 3.5). Other commonly reported grade ≥3 AEs included febrile neutropenia, epistaxis, decreased appetite, and mucosal inflammation.

AEs deemed by investigators to be possibly related to beti-cel include two cases of grade 3 thrombocytopenia, three cases of abdominal pain, and one case each of leukopenia, neutropenia, mild thrombocytopenia, tachycardia, and pain in an extremity.

Table 3.5. Pooled Safety Data from Clinical Trials of Beti-cel[*7,24,25]

	Serious Adverse Events n/N (%)	Grade ≥3 Adverse Events n/N (%)
Veno-occlusive liver disease	5/42 (12)	3/34 (9)
Pyrexia	4/38 (11)	4/23 (17)
Stomatitis	2/41 (5)	23/42 (55)
Thrombocytopenia	3/41 (7)	22/23 (96)
Neutropenia	2/41 (5)	18/23 (78)
Anemia	NR	14/23 (61)
Leukopenia	NR	13/23 (57)
Lymphopenia	NR	2/23 (9)
Febrile Neutropenia	2/41 (5)	17/38 (45)
Congestive cardiac failure	1/15 (7)	NR
Epistaxis	NR	5/23 (22)
Decreased appetite	NR	6/38 (16)
Pharyngeal inflammation	NR	4/38 (11)
Mucosal inflammation	NR	3/15 (20)

n: number, N: total number, NR: not reported

*Safety data are still emerging on beti-cel. Data reported in this table were pooled from a combination of publications and conference abstracts and should be interpreted with caution

Oncogenesis and Malignancies

Insertional oncogenesis has been identified as a potential risk with transgene integration. There has been no evidence of insertional oncogenesis and no malignancies in the TDT trials of beti-cel. However, cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been reported in gene therapy trials that use a lentiviral vector to treat other conditions. An early-phase trial of lovotibeglogene autotemcel in patients with sickle cell disease reported one case of MDS and one case of acute myeloid leukemia (AML); the MDS diagnosis was subsequently revised to transfusion-dependent anemia and the European Medicines Agency judged that the viral vector was unlikely to be the cause of either case.[30,31] However, three cases of MDS have also been reported in patients with cerebral adrenoleukodystrophy treated with elivaldogene autotemcel; at least one case is considered to have been mediated by the lentiviral vector insertion.[32]

Fertility

Trial participants were offered fertility preservation (sperm or testicular tissue banking for males or oocyte aspiration following ovarian stimulation and cryopreservation for females) at the discretion of the patient, their legal guardian, and the investigator.[25] During the long-term follow-up study,

two male patients, one of whom underwent fertility preservation, reported healthy births.[7] There was one case of gonadotropic insufficiency, one ectopic pregnancy, and one fetal death that resulted from a spontaneous miscarriage that occurred after at least two years of follow-up.

Subgroup Analyses and Heterogeneity

Two Phase III trials of beti-cel were conducted in patients with TDT: NorthStar-2 evaluated patients with non-β0/β0 genotypes and NorthStar-3 evaluated patients with either β0/β0 or severe non-β0/β0 genotypes. NorthStar-2 reported transfusion independence in 20/22 (91%) of patients and NorthStar-3 reported transfusion independence in 12/14 (86%) of patients.[24,25]

Pooled analysis of NorthStar-2 & -3 phase III trials evaluated transfusion independence by age groups of: <12, ≥12 - <18, and >18. At a maximum follow-up of 35.5 months transfusion independence was achieved by 9/11 (81%) of patients in the <12 subgroup, 10/10 (100%) of patients in the ≥12 - <18 subgroup, and 11/13 (85%) of patients in the >18 subgroup. At a maximum follow-up of 41.5 months 20/22 (91%) of patients <18 years had achieved transfusion independence.[33]

We were not able to draw conclusions about heterogeneity of treatment effect by genotype or age due to small sample size.

Uncertainty and Controversies

As discussed in ICER's Value Assessment Framework Modifications for Ultra-Rare Diseases, there are important challenges to generating high quality evidence for emerging treatments of ultra-rare diseases. The small sample sizes of the trials of beti-cel creates uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Given the magnitude of the benefit (e.g., proportion of patients achieving transfusion independence) consistently observed across the trials, there is high certainty that beti-cel is successful in treating TDT. There is however much more uncertainty around significant harms such as myelodysplastic events and even mortality. Some serious harms are likely rare occurrences and as such may not be observed in small trials. Although no deaths were observed in any of the trials, the risks associated with myeloablative chemotherapy confer a non-zero risk of mortality. Other adverse events such as infertility may require more than a decade to assess. Lastly, adverse events often occur more frequently when a therapy is used outside the careful monitoring of a clinical trial.

Two patients with sickle cell disease who were treated with a product nearly identical to beti-cel had serious bone marrow events, including one case of leukemia. However, patients with sickle cell disease are felt by some experts to be at higher risk of such events, both at baseline and after myeloablative conditioning, than patients with TDT. Further examination of the events in sickle cell disease did not establish evidence of insertional oncogenesis. However, the mechanism of action of

beti-cel via a lentiviral vector could theoretically introduce the risk of malignancy through this mechanism. Although no events were noted in any of the trials, additional real-world data may be required to fully assess this risk.

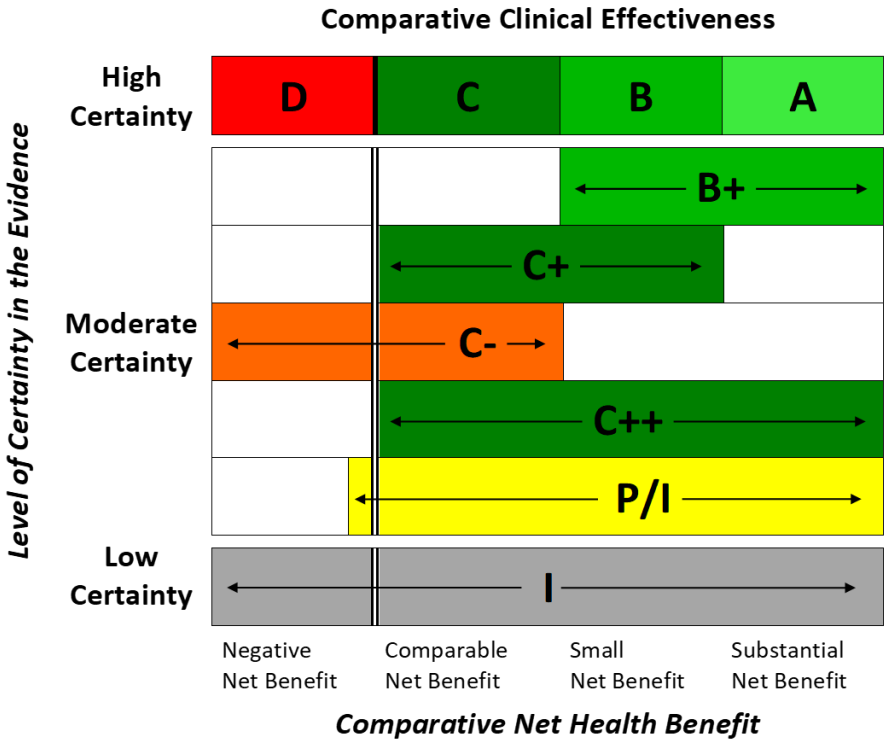
In addition to a small sample, the length of follow-up translates into uncertainty of the durability of treatment effect. To date, no trial participants that became transfusion independent have reverted to becoming transfusion dependent. The first trial participants have now completed approximately seven years of follow-up, yet others are only one year out from receiving beti-cel. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect.

The trials of beti-cel lacked a control group for reasons of both ethics and feasibility. There is therefore no head-to-head comparator with the only curative treatment – allogenic HSCT. As such sibling matched allogenic HSCT is likely to remain the first line treatment, with beti-cel indicated in patients that do not have sibling matched donor as an option. Clinician experts with whom we spoke expressed an interest in knowing if gene therapy should be the first line curative option (over sibling matched allogenic HSCT), but this is a shortcoming of available trial data given a lack of direct comparison to HSCT.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here. As discussed elsewhere in the report, ICER acknowledges that generating high-quality evidence for emerging treatments for ultrarare diseases can be challenging.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

In this review, we set out to compare the clinical effectiveness and safety of beti-cel to standard of care for individuals with transfusion-dependent beta-thalassemia.

We evaluated data from two open-label, single-arm Phase III trials on successful neutrophil and platelet engraftment, transfusion independence, hemoglobin levels during transfusion independence, and indicators of iron overload. Safety outcomes that were evaluated included hepatic veno-occlusive disease, pyrexia, stomatitis, thrombocytopenia, neutropenia, anemia and leukopenia. Evidence for efficacy outcomes was significant enough to suggest that the gene therapy provides a substantial net health benefit. Given the novelty of gene therapies and lack of significant long-term evidence, we are unable to assess the long-term durability of treatment effect for this intended cure. Safety outcomes have been consistent with those generally expected from

myeloablative conditioning and there have been no deaths in the trials. Although there have been no oncogenic events in beti-cel trials, there have been some occurrences in other gene therapy trials utilizing lentiviral vectors. Therefore, it is not possible to dismiss concern about the possibility of oncogenic events with beti-cel. We judge beti-cel to be incremental or better with moderate certainty of a small or substantial net health benefit ("B+") for this comparison.

Additionally, given what we heard from many stakeholders, including patients with TDT and their families, it is likely that even if beti-cel is a durable cure and has an excellent safety profile, there are likely to be a proportion of patients who choose to continue their current management with transfusion and chelation.

Table 3.6. Evidence Rating

Treatment	Comparator	Evidence Rating
Betibeglogene autotemcel (beti-cel)	Standard of Care	B+

4. Long-Term Cost Effectiveness

4.1. Methods Overview

The primary aim of this analysis was to estimate the cost effectiveness of beti-cel for the treatment of TDT. We developed a de novo decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models.[34] Our analysis reports results from a health care system perspective (i.e., focus on direct medical care costs only) and a modified societal perspective (i.e., including patient productivity and/or education impacts, caregiver productivity impacts, caregiver quality of life). The modified societal perspective was included as a co-base case given that patient and caregiver productivity costs are high relative to direct health care costs, and the impact of beti-cel treatment on these costs (i.e., by achieving transfusion independence) is substantial.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients living with TDT being treated with beti-cel and, separately, with SOC alone entering the model. Model cycle length was one year, based on what was observed in prior published economic models,[35,36] with the first yearly cycle representing a decision tree when patients would receive the beti-cel intervention (Figure 4.1). After the first-year decision tree, the Markov model consisted of health states including transfusion dependent (TD), transfusion independent (TI), and dead (Figure 4.2). Patients entering the Markov model in the TI health state were based on clinical trial data (i.e., hemoglobin [Hb] ≥9g/dL without any red blood cell [RBC] transfusions for a continuous period of ≥12 months after infusion) and remaining in that state was defined by no requirement for RBC transfusions. A cohort of patients transitioned between states during annual cycles over a lifetime time horizon, modeling patients from treatment initiation until death. All patients who achieved transfusion independence from beti-cel in the decision tree entered the Markov model in that state. No additional patients transitioned from the TD to TI health state for the remainder of the model and retransplant with beti-cel was not modeled. Patients reverting to the TD health state remained in that state until death. Cost effectiveness was presented across different time horizons to gain further understanding of the relationship between durability, time horizon, and cost effectiveness. Costs and outcomes were discounted at 3% per year.

Patients remained in the model until death. The model tracked iron overload and corresponding complications within each of the living health states. In addition to all-cause mortality, probability of death varied based on transfusion health state (i.e., standardized mortality ratio for TD and TI) and iron overload complications.

Cost effectiveness was estimated using the incremental cost-effectiveness ratios (cost per life year, QALY, and evLY gained), with incremental analyses comparing beti-cel to SOC alone. We also present a cost per transfusion independent year gained.

Beti-cel met the criteria for the ICER Value Framework adaptations for high-impact "single and short-term therapies" (SST) and for treatments of serious, ultra-rare conditions as outlined in our Revised Background and Scoping Document. We have assessed beti-cel under these framework adaptations which include additional scenario analyses such as optimistic and conservative scenarios regarding the benefit of treatment with beti-cel, a 50/50 shared savings analysis, and a cost-offset cap scenario. Additional detail regarding these scenarios is provided in Section 4.3.

In response to public comments and internal model validation processes, changes to the economic evaluation between the draft Evidence Report and the Evidence Report included:

- Updates to the beti-cel payment plan and payback option: for ease of communication, our base case analysis was revised to assume a full upfront payment of beti-cel with an 80% payback option if transfusion independence was not achieved. Payback for patients who die was only applied if death was due to beti-cel. Our draft report assumed a 5-year payment plan with payment occurring only if transfusion independence was achieved and maintained. Given our draft report assumption that beti-cel acquisition costs would not be discounted under a multi-year payment model, this change had minimal impact on findings.

- Update to the base-case value for the percentage of patients achieving TI from treatment with beti-cel: based on updated data from the manufacturer, two additional patients had achieved TI between the posting of the draft Evidence Report and the Evidence Report. Consequently, the percentage of patients achieving TI was changed from 32/36 (88.89%) to 34/38 (89.47%).

- Changes to model code for the calculation of disutility values: based on internal model validation processes, our formula to calculate disutility values within each model trace (i.e., for beti-cel and SOC) was updated to appropriately account for health state specific disutility. This error in the draft report resulted in an approximately 3.8% increase in base case health system incremental cost per QALY gained.

Figure 4.1. Model Structure – Decision Tree

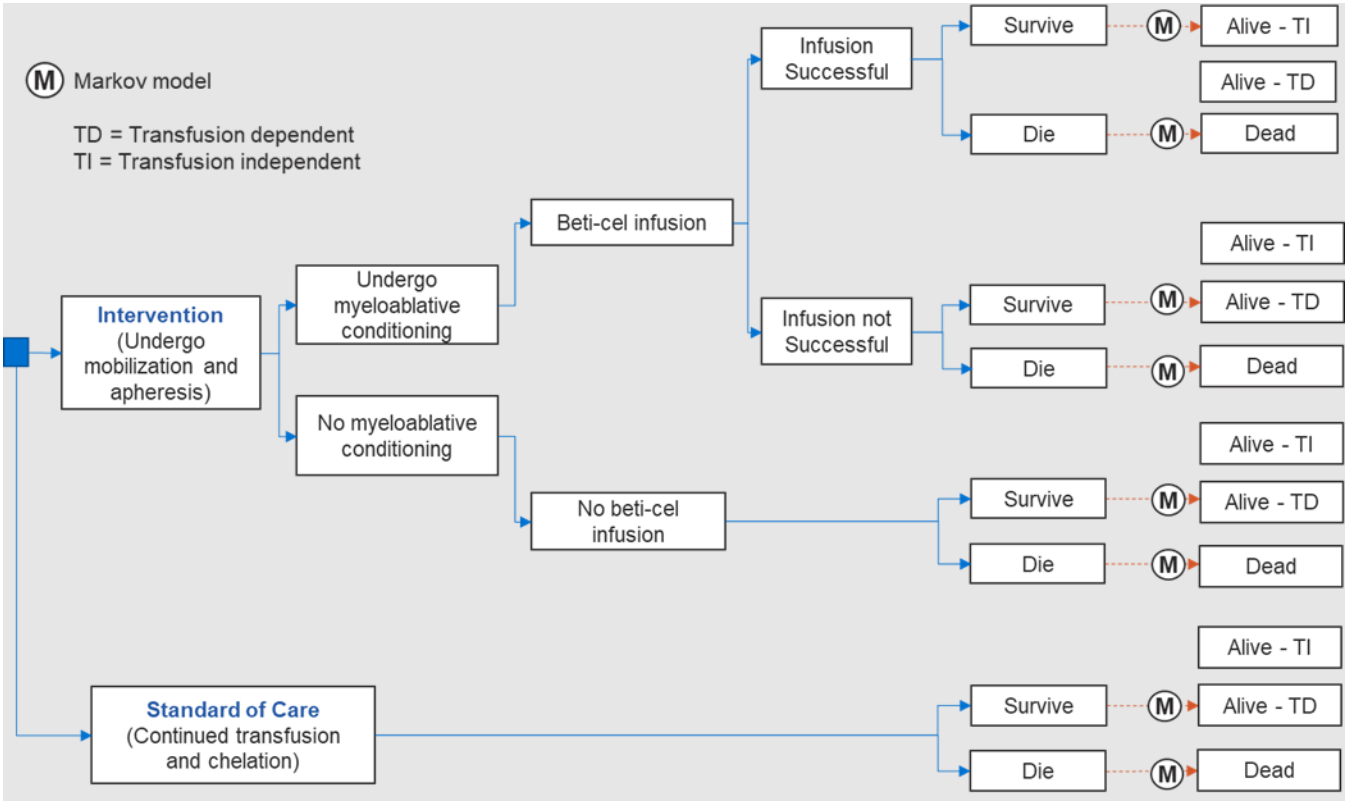
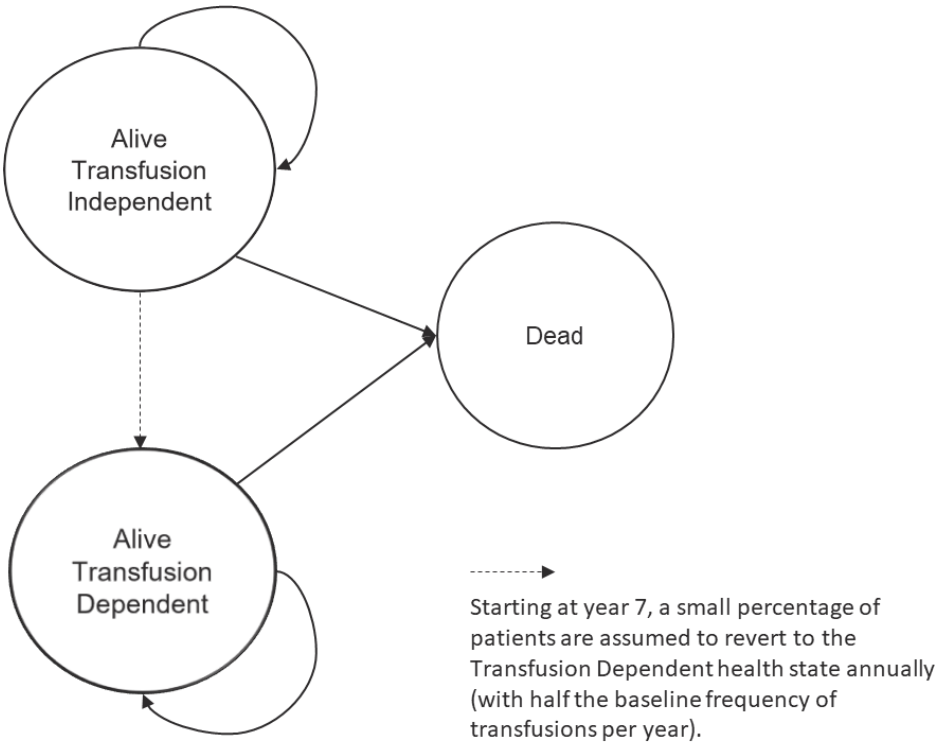


Figure 4.2. Model Structure – Markov Model



4.2. Key Model Assumptions and Inputs

Our model includes several key assumptions stated in Table 4.1. Additional assumptions are found in Supplement Table E2.1.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Real world cohort study sources were used to characterize the model cohort.	Larger sample sizes were available from cohort studies and experts suggested wider possible age bands will consider beti-cel therapy, if available.
The baseline distribution of iron overload risk categories was consistent between beti-cel and SOC arms. Patients entering the model in the transfusion dependent health state retained this distribution of iron overload for the duration of the model. Patients entering the model in the transfusion independent health state progressed through an iron normalization period of five years for cardiac iron, liver iron, and serum ferritin where a disutility aligned with the TD state was applied. At the end of the iron normalization period, patients aged 2 to 11 years of age were considered at no risk of complications and patients ≥12 years were considered at "low risk" of complications.	Manufacturer submitted data and longitudinal cohort studies suggest no strong evidence of increases in the proportion of iron overload severity over time. A five-year iron normalization period was deemed reasonable based on data suggesting that the median time to achieve target ferritin levels (<300ng/mL or <500ng/mL) for individuals with baseline ferritin levels of ≥2500ng/mL was 64 months and 65 months, respectively.[37] Finally, after a normalization period, evidence suggests serum ferritin may remain above the reference range. This risk is likely to vary by age, and thus, we assigned "low risk" of complications rather than zero risk for patients aged ≥12 years.[25,38]
Complications modeled included cardiac, liver, diabetes, and hypogonadism. Annualized risks were derived from real world evidence and contingent upon baseline iron levels.	Cardiac, liver and endocrine complications are primary comorbidities resulting from high iron associated with beta thalassemia.[14,25]
The base case risk of death from beti-cel infusion was 1.4% and tested in sensitivity and scenario analyses.	Experts suggested that mortality seen with autologous HSCT would be the best proxy for what may be expected with beti-cel in clinical practice. Literature-based estimates for acute risk of death from autologous HSCT was found to be 2.8%;[39] however, this estimate was derived from a population with a more severe disease. Input from clinical experts suggested that acute risk of death from beti-cel for TDT is likely to be 1-2%. Consequently, an estimate of 1.4% was deemed a reasonable estimate based on the available evidence and clinical expert opinion. We explored alternate assumptions in sensitivity and scenario analyses.
At year seven 0.271% of patients reverted to the TD health state (with half the baseline frequency of transfusions per year) and continued at a rate	The long-term durability of beti-cel treatment effect is unknown. Trial data suggest that all patients who have achieved TI from beti-cel have

of 0.271% per year. This rate of reversion resulted in approximately 10% of patients reverting to TD by the end of the lifetime time horizon.	remained TI; however, these data are based on a limited number of patients (n=32 in Phase III trials) and limited duration of time (7 years of data for three patients receiving beti-cel).[7] We heard from an expert in gene therapy that it would be theoretically possible for patients to revert to TD if the population of infused stem cells that were not genetically modified became clonally dominant; it was estimated that over a lifetime post-treatment, approximately 10% of patients would revert to TD. Other expert opinion suggested assuming 0% reversion and this was explored in a scenario analysis.
Percentage of patients adherent to chelation therapy was dependent on the type of chelator used and did impact the cost of treatment. No impact on treatment effectiveness or patient utility was anticipated for patients who are not 100% adherent but remain within a range of good adherence (e.g., 95%). Adherence less than 100% is meant to represent the duration of time where the chelation prescription is not filled by the patient.	Evidence suggested that adherence to chelation therapy varies by type of chelator (3% for patients taking combination therapy to 23% for patients taking deferasirox).[40] Lack of 100% adherence to chelation therapy was expected to be intermittent and not substantially affect patient outcomes given the assumption (above) that iron overload status remains constant for TD patients.

HSCT: hematopoietic stem cell transplant, SOC: standard of care, TD: transfusion dependent, TI: transfusion independent

Key model inputs are described in Table 4.2. The population of focus for the economic evaluation included patients with TDT and a mean age of 22.2 years (45.0% between 2 and 17 years old with an average age of nine years old in this subset) in the base-case analysis. The patient characteristics that informed the model's base-case cohort were primarily informed by the Thalassemia Longitudinal Cohort (TLC) study. To explore the impact of alternate baseline population characteristics, we conducted a scenario analysis using data from Phase III beti-cel trials.

Transfusion independence was the primary measure of clinical efficacy and was achieved by 34/38 (89.47%) of the patient population. Beti-cel is currently under regulatory review in the US and therefore does not have a published price. The anticipated acquisition cost of beti-cel ($2.1 million US) was based on a published press release estimate shared by the manufacturer of beti-cel.[9] This cost is based on a single intravenous infusion of at least 5.0 × 106 CD34+ cells/kg[41] and was modeled in the base case using a payment plan consisting of a full upfront payment of $2.1 million US with an outcomes-based agreement communicated by the manufacturer in response to our draft Evidence Report consisting of an 80% payback option for patients who do not achieve transfusion independence. The 80% payback was undiscounted, including when presented within discounted results to represent a payback of 80% of $2.1 million in today's dollars.

Table 4.2. Key Model Inputs

Parameter	Input	Source
Transfusion Independence, n/N (%)	34/38 (89.5)	Data on file[41]
Risk of Death in First Year	1.4%	Jantunen et al., 2006[39] (Assumptions)
SMR for TD Health State	3.9	Kansal et al., 2021[34]
SMR for TI Health State	1.25	Kansal et al., 2021[34]
Mean number of transfusions/year	-	-
< 18 years	14.95	Marketscan and Kansal et al., 2021[34]
≥ 18 years	16.1	Marketscan and Kansal et al., 2021[34]
Iron Overload, Risk of Complications		
Cardiac Complications*, low/ moderate/high	0.0023/0.0177/NA	NERI[42] and Kansal et al., 2021[34]
Liver Complications†, low/ moderate/high	0/0/0.0198	Marketscan and Kansal et al., 2021[34]
RR of TD Diabetes	8.929	Ang et al., 2014[43] (Assumptions)
RR of TD Hypogonadism	2.202	Ang et al., 2014[43] (Assumptions)
Disutility Values		
TD Health State	-0.22 (age ≥16 years) -0.18 (age <16 years)	Shah et al., 2021 [40] (Assumptions)
TI Health State	-0.02	Kansal et al., 2021[34] (Assumption)
Bet-cel Infusion (one year)	-0.31	Matza et al., 2021[44]
Complications from Iron Overload - Cardiac	-0.03	Seyedifar et al., 2015[45]
Complications from Iron Overload - Liver	-0.03	Seyedifar et al., 2015[45]
Complications from Iron Overload - Diabetes	-0.04	Seyedifar et al., 2015[45]
Complications from Iron Overload - Hypogonadism	-0.04	Seyedifar et al., 2015[45]
Caregiver (Patient ≤26 years)	-0.03	Shah et al., 2021[40]
Cost of Beti-cel	$2.1 Million (upfront payment with 80% payback if patients do not achieve success)	Kansal et al., 2021[34]; manufacturer comment

NA: not available, RR: relative risk, SMR: standardized mortality ratio, TD: transfusion dependent, TI: transfusion independent

* low iron, >20 ms; moderate iron, 10–20 ms; high iron, <10 ms

† low iron, <7 mg/g; moderate iron, 7–15 mg/g; high iron, ≥15 mg/g

Detail on all inputs used in the model, along with their respective reference, can be found in Supplement E.

4.3. Results

Base-Case Results

The total discounted costs, TD years, QALYs, life years and evLYs over the lifetime time horizon for the health care system perspective and modified societal perspective are detailed in Table 4.3. Beti-cel transplant incurred additional costs but resulted in fewer transfusion dependent years and more QALYs, life years, and evLYs. Additional results (undiscounted and disaggregated) are presented in Supplement E3.

Table 4.3. Results for the Base Case for Beti-cel Compared to SOC

Treatment	Anticipated Treatment Cost*	Transfusion and Chelation Costs†	Total Cost	TD Years	QALYs	Life Years	evLYs
Health Care System Perspective							
Beti-cel	$1,900,000	$220,000	$2,730,000	2.95	18.70	24.90	18.97
SOC	--	$1,820,000	$2,260,000	22.07	13.76	22.07	13.76
Modified Societal Perspective							
Beti-cel	$1,900,000	$220,000	$2,910,000	2.95	18.58	24.90	18.86
SOC	--	$1,820,000	$2,740,000	22.07	13.65	22.07	13.65

evLY: equal value life year, QALY: quality adjusted life years, SOC: standard of care, TD: transfusion dependent

* Only includes beti-cel acquisition cost and outcomes-based payback plan (i.e., excludes workup, preparation, transplant, post-transplant monitoring and normalization period costs).

† Only includes transfusion costs and chelation acquisition costs (i.e., excludes chelation administration and monitoring costs).

Table 4.4 presents the incremental cost-effectiveness ratios from the base-case analysis (for the health care system perspective and modified societal perspective), which includes estimates for the incremental cost per QALY gained, incremental cost per life year gained, incremental cost per evLY gained, and incremental cost per transfusion dependent year averted.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD Year Averted
Health Care System Perspective					
Beti-cel	SOC	$95,900	$90,800	$167,600	$24,700
Modified Societal Perspective					
Beti-cel	SOC	$35,100	$33,300	$61,400	$9,000

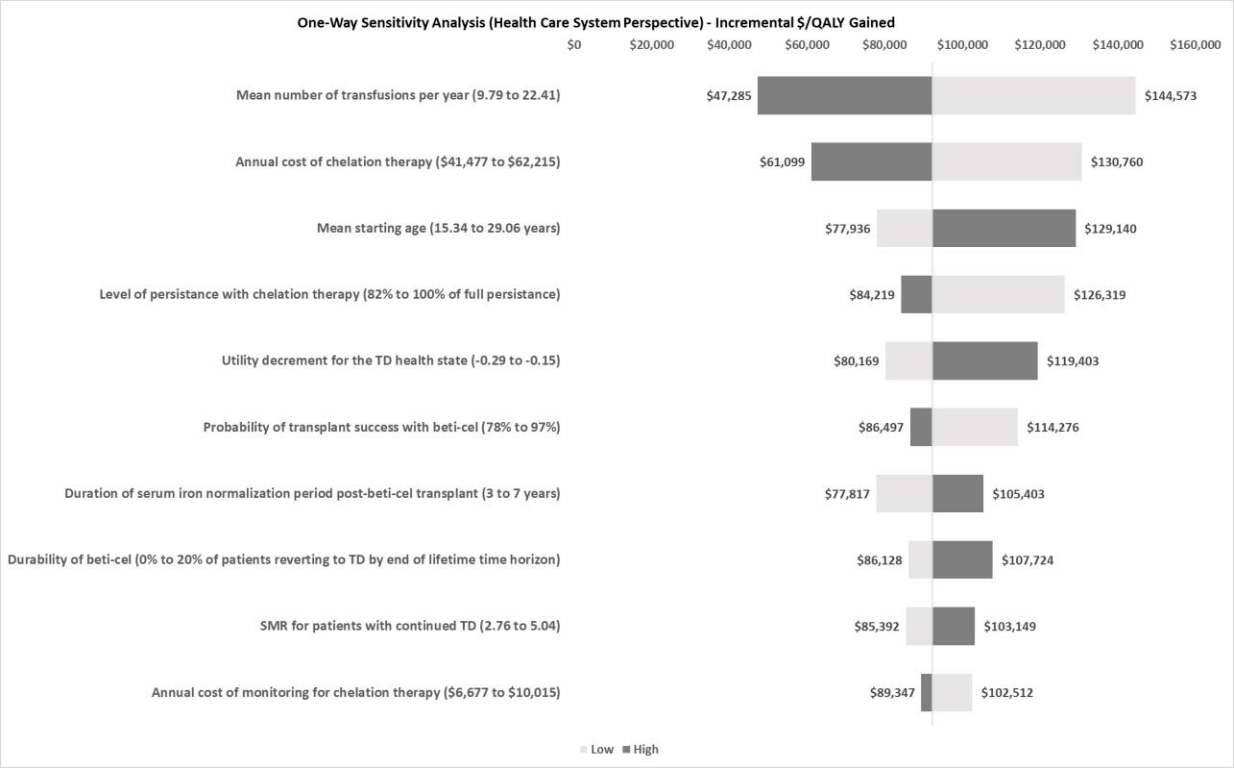
evLY: equal value life year, QALY: quality adjusted life years, SOC: standard of care, TD: transfusion dependent

Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors where available or reasonable ranges) to evaluate changes in findings.

We conducted one-way sensitivity analyses to vary one input parameter at a time across its plausible range for the health care system and the modified societal perspective. Figure 4.3 below presents this information graphically by way of a tornado diagram for the health care system perspective. Supplement E4.1 details the inputs and results for each input included in the tornado diagram. From the one-way sensitivity analyses, we found that results were most sensitive to the cost of transfusion and chelation therapy and mean starting age of the cohort. Other influential parameters included the duration of iron normalization period post-beti-cel transplant, characteristics of the TD health state (i.e., SMR, disutility), the durability of beti-cel, and the probability of success with beti-cel transplant. Supplement Figure E4.1 and Supplement Table E4.2, illustrate a tornado diagram and results for each input included in the tornado diagram, respectively, from the modified societal perspective.

Figure 4.3. Tornado Diagram (Health Care System Perspective)



SMR: standardized mortality ratio, TD: transfusion dependent, QALY: quality adjusted life year

A probabilistic sensitivity analysis was conducted to vary all inputs with noted uncertainty simultaneously. Tables 4.5 presents the percentage of iterations that were beneath thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY gained for both the health care system perspective and the modified societal perspective. Additional results from the PSA can be found in the Supplement Tables E4.3 and E4.4 and Figures E4.2 and E4.3. Supplement Table E4.5 presents the percentage of iterations that were beneath thresholds of $50,000, $100,000, $150,000, and $200,000 per evLY gained for both the health care system perspective and the modified societal perspective.

Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Beti-cel versus SOC

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Health Care System Perspective				
Beti-cel vs. SOC	19%	48%	81%	97%
Modified Societal Perspective				
Beti-cel vs. SOC	61%	89%	99%	100%

SOC: standard of care, QALY: quality adjusted life year

Scenario Analyses

We conducted numerous scenario analyses to assess the robustness of the results across alternative model assumptions and in accordance with the modifications to the ICER value framework for ultra-rare diseases and single and short-term therapies. We include the details and results of scenario analyses below, including: the optimistic and conservative benefit scenario, a 50/50 shared savings scenario, a cost-offset cap scenario, and under an up-front payment for beti-cel with no payback option for patients who do not achieve transfusion independence. Additional scenario analyses including an analysis based on Phase III trial baseline patient characteristics and for alternate time horizons (i.e., 5 year and 10 year) are presented in Supplement E5. Lower (i.e., more favorable) cost-effectiveness estimates were found when baseline patient characteristics were based on trial data. Higher (i.e., less favorable) cost-effectiveness estimates were found for the no payback option and for the shorter time horizons.

Scenario Analysis 1: Optimistic and Conservative Benefit Scenarios

Optimistic and conservative assumptions regarding the benefit of treatment with beti-cel were performed to reflect the uncertainty in the clinical data (e.g., deaths from infusion, percentage of patients achieving transfusion independence, and maintenance of transfusion independence). Details are provided in Table 4.6 below. Cost-effectiveness estimates for the conservative scenario were less favorable, increasing above $100,000 per additional QALY/evLY from a health care system perspective. Under the optimistic scenario results remained below $100,000 per additional

QALY/evLY. From the modified societal perspective, the conservative scenario resulted in costs per additional QALY/evLY of slightly above a $50,000 threshold, and under the optimistic scenario results were below a $50,000 per additional QALY/evLY threshold. Detailed results are presented in Table 4.7.

Table 4.6. Assumptions for Optimistic and Conservative Scenarios

	Base Case	Optimistic Scenario	Conservative Scenario
Deaths from beti-cel infusion, %	1.4%	0%	2.8%
Patients achieving transfusion independence, %	89.5%	90.2%	89.5%
Durability of treatment effect and % of patients reverting to TD	7 years, 0.271% per year	Lifetime, 0%	7 years, 0.581% per year
Number of transfusions per year for patients reverting to TD	7.5 (< 18 years) 8.0 (≥ 18 years)	NA	14.95 (< 18 years) 16.1 (≥ 18 years)

NA: not applicable, TD: transfusion dependence

Table 4.7. Scenario Analysis Results for the Optimistic and Conservative Benefit Scenarios

Scenario	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD year averted
Health Care System Perspective					
Base Case	SOC	$95,900	$90,800	$167,600	$24,700
Optimistic	SOC	$86,500	$82,100	$139,500	$23,800
Conservative	SOC	$125,500	$117,600	$236,300	$29,200
Modified Societal Perspective					
Base Case	SOC	$35,100	$33,300	$61,400	$9,100
Optimistic	SOC	$30,500	$28,900	$49,100	$8,400
Conservative	SOC	$59,500	$55,800	$112,200	$13,800

evLY: equal value life year, QALY: quality adjusted life year, SOC: standard of care, TD: transfusion dependent

Scenario Analysis 2: 50/50 Shared Savings Scenario

A 50/50 shared savings scenario analysis was undertaken in which 50% of lifetime health care and non-health care (for the modified societal perspective) cost offsets from beti-cel are assigned to the health care system instead of being assigned entirely to the treatment. The base case total cost offsets were $1,484,800 for the health system perspective and $1,784,000 for the modified societal perspective; 50% of these costs ($742,400 and $892,000, respectively) were assigned to the health care system instead of the treatment. Results are presented in Table 4.8.

Table 4.8. Scenario Analysis Results for the 50/50 Shared Savings Scenario

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD year averted
Health Care System Perspective					
Beti-cel	SOC	$246,400	$233,300	$430,600	$63,600
Modified Societal Perspective					
Beti-cel	SOC	$215,900	$204,400	$377,400	$55,700

evLY: equal value life year, QALY: quality adjusted life year, SOC: standard of care, TD: transfusion dependent

Scenario Analysis 3: Cost-offset Cap Scenario

A cost-offset cap scenario analysis was undertaken in which health care and non-health care (for the modified societal perspective) cost offsets generated by beti-cel are capped at $150,000 per year but are otherwise assigned entirely to the treatment. Cost offsets did not exceed $150,000 in any modeled year; therefore, results are aligned with the base-case findings.

Scenario Analysis 4: Full Upfront Payment for Beti-cel with no Payback for Failure Option

An alternate payment arrangement scenario analysis was undertaken in which the full cost of beti-cel was paid at the time of transplant (i.e., Year 1 in the model) with no payback for failure. Results are presented in Table 4.9.

Table 4.9. Scenario Analysis Results for Full Upfront Payment for Beti-cel with no Payback for Failure

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD year averted
Health Care System Perspective					
Beti-cel	SOC	$136,000	$128,800	$237,700	$35,100
Modified Societal Perspective					
Beti-cel	SOC	$75,200	$71,200	$131,500	$19,400

evLY: equal value life year, QALY: quality adjusted life year, SOC: standard of care, TD: transfusion dependent

Threshold Analyses

Threshold analyses were conducted to identify at what price beti-cel would meet certain cost-effectiveness thresholds. Table 4.10 presents the findings from these threshold analyses for the health care system perspective and modified societal perspective using outcomes of both the QALY and evLY. The prices presented in this table do not include costs for beti-cel workup and preparation, transplant, post-transplant monitoring or post-transplant normalization period costs and therefore represent threshold prices for beti-cel acquisition alone. Threshold analyses for a full upfront payment with no payback scenario and a 50:50 shared savings scenario is reported in Tables 4.11 and 4.12, respectively.

As is the case for all threshold analyses, a treatment's price that would meet a threshold is a factor of two main components: health gains and potential cost savings. When taking the health care system perspective and the evLY gained measure of changes in health, if we assigned $0 to the acquisition cost of beti-cel rather than $2.1 million, the resulting evLY gains remain as in the base case (5.21 evLY gained) while the potential cost savings are $1.43 million. At a threshold of $100,000 per evLY gained, the health care system perspective evLY-based threshold-based price of $2.15 million upfront (assuming a full upfront payment for beti-cel with guarantees of 80% payback for those who do not achieve/maintain transfusion independence) suggests that 27% of this threshold-based price is due to the health gains and the remaining 73% of the threshold-based price is due to potential cost savings mainly from reduced transfusions and chelation treatment.

Likewise, when taking the modified societal perspective and the evLY gained measure of changes in health, if we assigned $0 to the acquisition cost of beti-cel, the resulting evLY gains remain as in the base case (5. 21 evLY gained) while the potential cost savings are $1.73 million. At a threshold of $100,000 per evLY gained, the societal perspective evLY-based threshold-based price of $2.48 million (assuming the same full upfront payment for beti-cel with 80% payback option as in the health care system perspective) suggests that 23% of this threshold-based price is due to the health gains, and the remaining 77% of the threshold-based price is due to the potential cost savings.

Under a scenario where the full cost of beti-cel is paid up front and there is no payback option, threshold prices range from below the proposed beti-cel acquisition price at a $50,000 and $100,000 per QALY or evLY gained from a health system perspective to threshold prices greater than the proposed beti-cel acquisition cost at higher thresholds. Under a 50:50 shared savings scenario, the price of beti-cel to achieve a threshold of up to $200,000 per QALY or evLY gained, is below the proposed acquisition cost of beti-cel across all perspective and thresholds.

Table 4.10. QALY and evLY-Based Threshold Analysis Results for the Base Case Analysis (i.e., full upfront payment for beti-cel with 80% payback option)

	Anticipated Acquisition Cost*	Price* to Achieve $50,000 per QALY Gained	Price* to Achieve $100,000 per QALY Gained	Price* to Achieve $150,000 per QALY Gained	Price* to Achieve $200,000 per QALY Gained
Health Care System Perspective					
Beti-cel	$2,100,000	$1,840,000	$2,120,000	$2,390,000	$2,660,000
Modified Societal Perspective					
Beti-cel	$2,100,000	$2,180,000	$2,450,000	$2,720,000	$2,990,000
	Anticipated Acquisition Cost*	**Price* to Achieve $50,000 per evLY Gained**	**Price* to Achieve $100,000 per evLY Gained**	**Price* to Achieve $150,000 per evLY Gained**	**Price* to Achieve $200,000 per evLY Gained**
Health Care System Perspective					
Beti-cel	$2,100,000	$2,100,000	$1,860,000	$2,150,000	$2,440,000
Modified Societal Perspective					
Beti-cel	$2,100,000	$2,190,000	$2,480,000	$2,770,000	$3,050,000

*Excludes beti-cel workup and preparation, transplant, post-transplant monitoring or post-transplant normalization period costs. Acquisition cost and price represents the full upfront acquisition cost of beti-cel per patient. Based on the full upfront payment for beti-cel with 80% payback option proposed by the manufacturer, the expected value of beti-cel accounting for patients who do not achieve transfusion independence is $1.9 million (and therefore the full $2.1 million upfront cost of beti-cel is reduced on behalf of patients who did not achieve transfusion independence).

Table 4.11. QALY and evLY-Based Threshold Analysis Results for a Full Upfront Payment with no Payback Option Scenario

	Anticipated Acquisition Cost*	Price* to Achieve $50,000 per QALY Gained	Price* to Achieve $100,000 per QALY Gained	Price* to Achieve $150,000 per QALY Gained	Price* to Achieve $200,000 per QALY Gained
Health Care System Perspective					
Beti-cel	$2,100,000	$1,670,000	$1,920,000	$2,160,000	$2,410,000
Modified Societal Perspective					
Beti-cel	$2,100,000	$1,970,000	$2,220,000	$2,460,000	$2,710,000
	Anticipated Acquisition Cost*	**Price* to Achieve $50,000 per evLY Gained**	**Price* to Achieve $100,000 per evLY Gained**	**Price* to Achieve $150,000 per evLY Gained**	**Price* to Achieve $200,000 per evLY Gained**
Health Care System Perspective					
Beti-cel	$2,100,000	$1,680,000	$1,940,000	$2,210,000	$2,470,000
Modified Societal Perspective					
Beti-cel	$2,100,000	$1,980,000	$2,240,000	$2,510,000	$2,770,000

*Excludes beti-cel workup and preparation, transplant, post-transplant monitoring or post-transplant normalization period costs. Acquisition cost and price represents the full upfront acquisition cost of beti-cel per patient. Based on the full upfront payment for beti-cel with 80% payback option proposed by the manufacturer, the expected value of beti-cel accounting for patients who do not achieve transfusion independence is $1.9 million (and therefore the full $2.1 million upfront cost of beti-cel is reduced on behalf of patients who did not achieve transfusion independence).

Table 4.12. QALY and evLY-Based Threshold Analysis Results for a 50:50 Shared Savings Scenario

	Anticipated Acquisition Cost*	Price* to Achieve $50,000 per QALY Gained	Price* to Achieve $100,000 per QALY Gained	Price* to Achieve $150,000 per QALY Gained	Price* to Achieve $200,000 per QALY Gained
Health Care System Perspective					
Beti-cel	$2,100,000	$1,030,000	$1,300,000	$1,570,000	$1,840,000
Modified Societal Perspective					
Beti-cel	$2,100,000	$1,190,000	$1,460,000	$1,740,000	$2,010,000
	Anticipated Acquisition Cost*	**Price* to Achieve $50,000 per evLY Gained**	**Price* to Achieve $100,000 per evLY Gained**	**Price* to Achieve $150,000 per evLY Gained**	**Price* to Achieve $200,000 per evLY Gained**
Health Care System Perspective					
Beti-cel	$2,100,000	$1,040,000	$1,330,000	$1,620,000	$1,900,000
Modified Societal Perspective					
Beti-cel	$2,100,000	$1,210,000	$1,490,000	$1,780,000	$2,070,000

*Excludes beti-cel workup and preparation, transplant, post-transplant monitoring or post-transplant normalization period costs. Acquisition cost and price represents the full upfront acquisition cost of beti-cel per patient. Based on the full upfront payment for beti-cel with 80% payback option proposed by the manufacturer, the expected value of beti-cel accounting for patients who do not achieve transfusion independence is $1.9 million (and therefore the full $2.1 million upfront cost of beti-cel is reduced on behalf of patients who did not achieve transfusion independence).

Model Validation

We used several approaches to validate the model. First, we provided preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. We identified an error in the draft model code related to how disutility was estimated for health states. This error was resolved in subsequent versions of this report. As part of ICER's efforts in acknowledging modeling transparency, we also shared the model with the relevant manufacturers for external verification. Finally, we compared results to other cost-effectiveness models in this therapy area. In particular, we report our findings of a replication of Kansal et al.'s[34] patient-level simulation using our cohort-level model. These results are reported in Supplemental Material E7. The outputs from the model were validated against the trial/study data of the interventions and any relevant observational datasets.

Uncertainty and Controversies

The population of focus for the assessment is patients living with TDT, typically defined as eight or more transfusions per year. Although this population is considered broad, there is strong overlap between a narrower population that may consider beti-cel treatment, if approved, and those who would have considered allogenic HSCT but did not have a matched donor. Like beti-cel, HSCT requires high doses of conditioning chemotherapy and likely has a non-zero risk of short-term death. Additionally, and unlike beti-cel, HSCT places the recipient at risk for graft versus host disease. As we heard from patients living with TDT and their caregivers, some patients living with TDT may not opt for beti-cel, if available and covered under their health benefit, given their preferences and their own risk-benefit tradeoffs. In short, for some people living with TDT, the risks and time invested may not be worth the potential long-run health and other benefits. One major limitation in the cost-effectiveness model is that it assumes risk neutrality in estimating the expected lifetime health gains associated with beti-cel versus standard of care. Therefore, the expected lifetime health gains summarized in this section of the report may be best thought of conditioned on this narrower subpopulation of those who would have considered allogenic HSCT but did not have a matched donor (i.e., those that would consider the net health benefit of opting for beti-cel to be positive).

Estimating beti-cel's lifetime health outcomes and costs required assumptions and was conducted under conditions of evidence uncertainty. As shown in the one-way sensitivity analyses and supported by additional scenario analyses, the cost-effectiveness findings are sensitive to the type or mix of chelation treatment (and corresponding costs) and the mean starting age of the cohort. Other influential parameters included the normalization duration after beti-cel treatment (and corresponding risks of complications) and the durability of transfusion independence for which there is limited evidence available. Given beti-cel has yet to receive a final FDA decision, there is no known transaction price we can observe. Public statements made by the manufacturer prior to our updated Evidence Report suggested that beti-cel pricing would be consistent with a payment plan of five equal yearly payments adding to $2.1 million for those who achieve transfusion independence. Following comments on our draft Evidence Report, it was more likely that the payment model is expected to follow a full upfront payment of $2.1 million with a payback option of 80% for patients who did not achieve transfusion independence. In this model, the expected value of the $2.1 million payment with 80% payback option was $1.9 million per treated patient. We highlight that this payment plan lessens the impact that a non-zero acute death risk and that the estimate of treatment failure has on the incremental cost-effectiveness findings (given limited payment for those who die or do not achieve transfusion independence).

We note that given the annualized costs of chelation and transfusions that are a part of standard of care and given opportunities for fewer complications that are associated with an increased risk of death, the population's age will have impacts on the cost effectiveness of beti-cel (with all else equal, those of younger age are associated with a lower incremental cost-effectiveness ratio). Because policy making will remain at the population level, the base-case cost-effectiveness findings

and corresponding threshold-based prices presented in this report remain at the population level that average over the eligible population's age. Although we used a cohort-based model, we did account for known differences by age category in costs and outcomes. For example, we accounted for beti-cel workup costs, and transfusion and chelation costs that differ based on ages <18 and ≥18 years by assuming that 45% of the cohort would have a mean starting age of <18 years. We also accounted for differences in the likelihood of cardiac complications following the normalization period post-beti-cel transplant by assuming that there would be no risk of cardiac complications for patients who receive beti-cel between the ages of 2 and 11 years, and a low risk for patients who receive beti-cel when older than 11 years of age. Additionally, caregiver impacts (including disutility and productivity losses) were accounted for in the model for patients up to the age of 26 years old.

As observed in the threshold-based price findings, the potential cost savings (rather than health gains) are responsible for the majority of the threshold-based price justification. The potential cost savings being a driver was also demonstrated by the changes in cost-effectiveness findings to above commonly cited thresholds when assuming a 50/50 cost-savings scenario whereby only 50% of the cost savings were assigned when estimating beti-cel's cost effectiveness. A follow-on inquiry is whether the current standard of care achieves value for money. If standard of care does not achieve value for money (e.g., chelation therapy is overpriced for its conferred health benefits), then society may be perpetuating this lack of value for money if we were to reward a new intervention like beti-cel by attributing all the potential cost savings to its value and corresponding price. How society may break a perpetual chain of interventions that do not achieve value for money is controversial.

Finally, deliberations on the value of beti-cel may consider the closest alternative medical intervention, allogenic HSCT for those with a matched donor. Research suggests that the average cost of allogenic HSCT for those with myeloablative conditioning after 100 days was approximately $300,000 (2013 USD).[46] Beti-cel, if approved, is an opportunity for those who would have opted for allogenic HSCT but did not have a matched donor. Although beti-cel may therefore, expand those living with TDT chance's at living independent from transfusions, deliberators may find it helpful to consider whether beti-cel is considered high value care if the beti-cel acquisition cost for treating one person living with TDT approximates the costs of six or seven allogenic HSCT procedures.

4.4 Summary and Comment

Our report suggests that treating eligible patients living with TDT with beti-cel results in lifetime discounted health gains and added costs when compared to standard of care alone (e.g., transfusion and chelation therapy). After discounting future costs and outcomes at 3% per year, beti-cel has an incremental cost effectiveness that approaches $100,000 per QALY and evLY gained from the health care system perspective. Findings from the modified societal perspective that included estimates of productivity loss for patients and caregivers were below $50,000 per QALY

and evLY gained. Threshold pricing based on an anticipated payment plan consisting of a full up-front payment of $2.1 million with an outcomes-based agreement consisting of an 80% payback option suggests beti-cel would meet $100,000 to $150,000 per QALY and per evLYG thresholds. Under a 50:50 shared savings analysis where 50% of the cost-offsets from beti-cel were assigned to the health care system instead of the treatment, threshold prices were found to range between $1.30 million to $1.78 million US from the health care system and modified societal perspective, respectively. The cost-effectiveness findings were driven by the lifetime opportunity to reduce chelation and transfusion costs that may not be priced based on value (and reduce productivity costs in the modified societal perspective) while also demonstrating health gains that may be considered meaningful to those living (or caring for those living) with TDT.

5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the interventions in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	There is a moderate risk of morbidity/ disability from chronic iron overload.
Magnitude of the lifetime impact on individual patients of the condition being treated	Thalassemia is a lifelong chronic disease and as such, there is significant lifetime impact.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	If patients with Thalassemia were not dependent on transfusion, they would have more flexibility, time, and potential ability to achieve major life goals. A potential disadvantage of beti-cel compared to standard of care (e.g., transfusion, chelation) is the potential impact of myeloablative condition to impact future fertility.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Caregivers, particularly those of young children, would benefit from improved quality of life and also benefit from increased ability to achieve major life goals.
Patients' ability to manage and sustain treatment given the complexity of regimen	Standard of care places a high burden on patients and caregivers (e.g., frequent transfusions and health care monitoring visits, daily chelation). Conversely, treatment with beti-cel requires patients to be hospitalized and to receive myeloablative chemotherapy.
Society's goal of reducing health inequities	Minimal impact
Reduce burden on the health system's supply of red blood cells (RBC)	Under conditions of RBC supply shortages, patients who achieve transfusion independence with beti-cel will not draw on limited RBC resources.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for beti-cel's anticipated acquisition cost (excluding workup and preparation, transplant, post-transplant monitoring or post-transplant normalization period costs) based on a full upfront payment model with an 80% payback option for patients who do not achieve transfusion independence are presented in Table 6.1 and Table 6.2 below. Table 6.1 reports threshold prices for the base case analysis and Table 6.2 reports threshold prices for the 50:50 shared savings scenario analysis where 50% of lifetime health care and non-health care (for the modified societal perspective) cost offsets from beti-cel are returned to society rather than all being credited to the price of the treatment. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. While in the base case, no discount is needed from the anticipated price of $2.1 million to achieve typical HBPBs, assuming 50:50 shared savings, the HBPB range is $1.3 to $1.8 million.

Table 6.1. Cost-Effectiveness Threshold Prices for Beti-cel

	Anticipated Acquisition Cost*	Price at $100,000 Threshold	Price at $150,000 Threshold	Discount from Acquisition Cost* to Reach Threshold Prices
Health Care System Perspective				
QALYs Gained	$2,100,000	$2,120,000	$2,390,000	No discount needed
evLYs Gained	$2,100,000	$2,150,000	$2,440,000	No discount needed
Modified Societal Perspective				
QALYs Gained	$2,100,000	$2,450,000	$2,720,000	No discount needed
evLYs Gained	$2,100,000	$2,480,000	$2,770,000	No discount needed

evLY: equal value life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Excludes beti-cel workup and preparation, transplant, post-transplant monitoring or post-transplant normalization period costs. Unit price represents the full upfront acquisition cost of beti-cel per patient. Based on the full upfront payment for beti-cel with 80% payback option proposed by the manufacturer, the expected value of beti-cel accounting for patients who do not achieve transfusion independence is $1.9 million (and therefore the full $2.1 million upfront cost of beti-cel is reduced on behalf of patients who did not achieve transfusion independence).

Table 6.2. Cost-Effectiveness Threshold Prices for Beti-cel under a 50:50 Shared Savings Analysis

	Anticipated Acquisition Cost*	Price at $100,000 Threshold	Price at $150,000 Threshold	Discount from Anticipated Acquisition Cost* to Reach Threshold Prices
Health Care System Perspective				
QALYs Gained	$2,100,000	$1,300,000	$1,570,000	25% - 38%
evLYs Gained	$2,100,000	$1,330,000	$1,620,000	23% - 37%
Modified Societal Perspective				
QALYs Gained	$2,100,000	$1,460,000	$1,740,000	17% - 30%
evLYs Gained	$2,100,000	$1,490,000	$1,780,000	15% - 29%

evLY: equal value life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Excludes beti-cel workup and preparation, transplant, post-transplant monitoring or post-transplant normalization period costs. Unit price represents the full upfront acquisition cost of beti-cel per patient. Based on the full upfront payment for beti-cel with 80% payback option proposed by the manufacturer, the expected value of beti-cel accounting for patients who do not achieve transfusion independence is $1.9 million (and therefore the full $2.1 million upfront cost of beti-cel is reduced on behalf of patients who did not achieve transfusion independence).

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of beti-cel for patients with transfusion-dependent beta thalassemia. We used a proposed price of $2,100,000 per treated patient to be paid upfront (including an 80% payback option if patients do not achieve transfusion independence), the same as in the base case cost-effectiveness analysis, and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for beti-cel in our estimates of budget impact.

For this analysis, we assumed that all patients eligible for treatment with beti-cel were currently uncontrolled and therefore received treatment with standard of care. All costs were undiscounted and estimated over a five-year time horizon. This budget impact analysis included the estimated number of individuals ages 0 to 50 years with TDT in the US who would be eligible for treatment with beti-cel. Using this approach, we derived an estimate of 666 patients in the US eligible for treatment with beti-cel. Our estimate begins with prevalent cases of beta thalassemia in the US of roughly 2,100.[47] From there, we assumed that about 63% of patients could be classified as having TDT arriving at approximately 1,333 patients.[2] Of patients who are diagnosed with transfusion-dependent beta thalassemia, we assumed that 50% would be eligible for treatment with beti-cel, arriving at approximately 666 patients. Consistent with our budget impact methods, we further assumed that 20% of these 666 patients would initiate treatment in each of the five years, or approximately 133 patients per year. The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $734 million per year for new drugs. ICER's methods for estimating potential budget impact are described in detail in the Supplement Section F.

Results

Results showed that at the proposed price of $2.1 million per treatment course (to be paid upfront but including an 80% payback option if patients do not achieve transfusion independence), all eligible patients could be treated over the span of five years without crossing the ICER budget impact threshold of $734 million per year. Similarly, all eligible patients could be treated with beti-cel without reaching the potential budget impact threshold at the three threshold prices (approximately $1.84 million, $2.12 million, and $2.39 million per course of treatment). Given that

we did not observe any potential budget impact findings above our budget impact threshold, due to the small projected population size, we will not be presenting the above findings in graphical form.

The cumulative per patient budgetary impact findings assuming the proposed price for beti-cel are presented the Supplement Section F.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Severe Non-β0/β0 Genotypes: Includes $\beta 0/\beta^{+IVS\text{-}I\text{-}110}$ and $\beta^{+IVS\text{-}I\text{-}110}/\beta^{+IVS\text{-}I\text{-}110}$ genotypes.

Transfusion Independence: Defined as having an average hemoglobin level of 9 grams per deciliter without any red blood cell transfusions for 12 or more consecutive months after beti-cel infusion.[25]

Pediatric Quality of Life Inventory (PedsQL): Measures health-related quality of life (HRQoL) in children and adolescents over five domains of health: physical, emotional, psychosocial, social, and school functioning. Score range from 0-100 with higher scores indicating better HRQoL functioning.[48]

EuroQol-3 level visual analog scale (EQ-5D-3L VAS): Measures HRQoL in adults over five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Scores range from 0 (worst imaginable health) to 100 (best imaginable health).[49]

EuroQol-youth visual analog scale (EQ-5D-Y VAS): The child-friendly version of the EQ-5D measuring the same five dimensions of health. Scores range from 0 (worst imaginable health) to 100 (best imaginable health).[49]

Short Form-36 Health Survey (SF-36): Measures HRQoL in adults over eight domains of health: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health. Scores range from 0-100 with higher scores indicating better functioning.[50]

Functional Assessment of Cancer Therapy-General (FACT-G): Measures HRQoL in patients with cancer over four domains: physical, social, emotional, and functional well-being. Scores range from 0-108 with higher scores indicating better quality of life.[51]

Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT): Measures HRQoL in patients with bone marrow transplants over five domains: physical, social, emotional, and functional well-being, and an additional bone marrow transplant subscale. Scores range from 0-196 with higher scores indicating better quality of life.[51]

Normal Hemoglobin Levels: Range from 11.6-15 grams per deciliter for women and 13.2-16.6 grams per deciliter for men.[52]

Normal Liver Iron Concentration: Defined as <1.8 mg/g dry weight.[53]

Normal Ferritin Levels: Range from 11 to 307 micrograms per liter for women and 24 to 336 micrograms per liter for men.[54]

A2. Potential Cost-Saving Measures in Beta Thalassemia

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for beta thalassemia (e.g., reduction in transfusions), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of beta thalassemia beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with beta thalassemia that could be reduced, eliminated, or made more efficient. No suggestions were received.

Choosing Wisely recommendations from the American Society for Clinical Pathology recommend against repeat hemoglobin electrophoresis (or equivalent) in patients who have a prior result and who do not require therapeutic intervention or monitoring of hemoglobin variant levels.[55]

A3. Research, Development, and Manufacturing Costs

As described in ICER's modified framework for assessing value of treatments for ultra-rare diseases, ICER invited manufacturers to submit relevant information on research, development, and manufacturing costs that may impact pricing of a drug. For this report, no manufacturer submitted information on development or production costs that would be an important factor in justifying the price of their products.

B. Patient Perspectives: Supplemental Information

B1. Methods

During ICER's open input and public comment periods, we received public comment submissions from five stakeholders (two patient advocacy groups, two manufacturers, and one other organization) and participated in conversations with 20 key informants (three patient advocacy groups, six clinical experts, one manufacturer, one payer, one researcher, and eight individual patients). The feedback received from written input and scoping conversations helped us to discuss the impact on patients described in Chapter 2 of the evidence report.

C. Clinical Guidelines

Clinical practice guidelines for the treatment of TDT have been issued by several US-based and non-US-based organizations. The Thalassemia International Federation's (TIF) guidelines are the most comprehensive, recently updated in 2021, and referenced by many of the other organizations' guidelines, therefore a brief summary of key points of the TIF guidance is presented below.

Thalassaemia International Federation[53]

In 2021, the Thalassaemia International Federation published an update (4th edition) to their guidelines on the management of TDT.[53] These guidelines outline best practices on the screening, diagnosis, treatment, and monitoring of TDT. The guidelines emphasize standards for regular transfusions and the management of iron overload, the largest source of morbidity and mortality in patients with TDT. It is recommended that patients with TDT are transfused every 2-5 weeks, maintaining pre-transfusion hemoglobin above 9.0-10.5 g/dL or up to 11.0-12.0 g/dL for patients with cardiac complications. Maintaining higher hemoglobin prevents some consequences of Thalassemia (e.g., extramedullary hematopoiesis). Regarding chelation, the guidelines state that "Chelation therapy is an effective treatment modality in improving survival, decreasing the risk of heart failure and decreasing morbidities from transfusion induced iron overload." While this statement underscores the importance of chelation therapy, it is an oversimplified statement. In fact, chelation therapy is can be quite nuanced with the "optimal chelation regime tailored for the individual and their current clinical situation."

Regarding potential curative options, the guidelines conclude that HSTC is cost-effective compared to life-long supportive therapy and that HSTC should be offered to patients with thalassemia at a young age provided that they have sibling matched donor (or highly compatible unrelated match in certain circumstances). The TIF guidelines also review active gene therapy and gene editing trials, including the trials of beti-cel by bluebird bio. They state, "among the novel gene therapies, lentiviral vector gene therapy is the most mature intervention, shown to provide clinical efficacy and safety as a one-off life-changing treatment." However, they follow by highlighting that long term safety and sustainability must still be demonstrated. At the time the guidelines were published beti-cel (marketed under the brand name Zynteglo) had received approval in Europe and thus appears in the guideline as a recommended treatment for some patients (e.g., □⁺ genotype without a sibling match). While Zynteglo is no longer marketed in Europe, it stands to reason that approved gene therapy has a place in the guidelines for management of TDT.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review was patients living with TDT, typically defined as eight or more transfusions per year. While the historical categorization of beta thalassemia relied upon characterization of □-globin chain production and genotyping, more recently patients have been characterized according to their transfusion status (i.e., TDT or NTDT) as this is most closely aligned with clinical outcomes and quality of life. We considered both adult and pediatric patients with TDT without pre-specified age limits, however patients had to be clinically eligible to undergo bone marrow conditioning.

We assessed evidence on treatment for TDT for groups stratified by:

- Age
- Genotype (β0/β0 and non-β0/β0)

Interventions

The intervention of interest for this review is betibeglogene autotemcel ("beti-cel", bluebird bio) gene therapy.

Comparators

We compared the intervention to standard clinical management, including blood transfusions and iron chelation. We also sought to compare the intervention to HSCT in transplant eligible patients.

Outcomes

- Patient-important outcomes
    - Transfusion independence
    - Reduction in transfusion burden
    - Manifestations of iron overload:
        - Cardiovascular events
        - Liver disease

- Splenomegaly and splenectomy
- Endocrine disease
  - Bone pain
  - Health-related quality of life
  - Other patient reported outcomes
  - Fertility
  - Mortality
  - Growth abnormalities
  - Burden of care for patients and caregivers (e.g., missed time from work)
  - Transplantation success/engraftment (e.g., neutrophil count)
  - Serious adverse effects (SAEs)
  - Treatment emergent adverse effects (TEAEs)
  - Adverse events (AEs) leading to discontinuation

- Other outcomes
  - Hemoglobin levels
  - Iron levels (including serum ferritin, liver iron concentration, and myocardial iron deposition)
  - Health care resource utilization

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration that meet the criteria set forth above and measure the outcomes of interest.

Settings

All relevant settings were considered, including inpatient, outpatient/clinic, office, and home settings.

Table D1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported in Section
TITLE			
Title	1	Identify the report as a systematic review.	3.1 Methods Overview
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Executive Summary
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1. Background
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > PICOTS
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > PICOTS
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Data Sources and Searches
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Data Sources and Searches > Table D2 and Table D3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Study Selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Data Extraction and Quality Assessment
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > PICOTS

	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2. Patient and Caregiver Perspectives D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > PICOTS/Data Extraction and Quality Assessment
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Assessment of Bias
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Data Synthesis and Statistical Analyses
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3. Comparative Clinical Effectiveness > 3.1 Methods Overview > Evidence Base D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Data Sources and Searches
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Data Extraction and Quality Assessment
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Data Extraction and Quality Assessment
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Data Extraction and Quality Assessment
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	3. Comparative Clinical Effectiveness > 3.2 Results > Subgroup Analyses and Heterogeneity
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A

Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Assessment of Bias
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	3. Comparative Clinical Effectiveness > 3.3 Summary and Comment
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Figure D1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	3. Comparative Clinical Effectiveness > 3.1 Methods Overview > Table 3.1 D. Comparative Clinical Effectiveness: Supplemental Information > D2. Evidence Tables
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	D. Comparative Clinical Effectiveness: Supplemental Information > D1. Detailed Methods > Assessment of Bias
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	D. Comparative Clinical Effectiveness: Supplemental Information > D2. Evidence Tables
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	3. Comparative Clinical Effectiveness > 3.2 Results
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A

Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	3. Comparative Clinical Effectiveness > 3.2 Results > Uncertainty and Controversies 3. Comparative Clinical Effectiveness > 3.3 Summary and Comment
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	3. Comparative Clinical Effectiveness > 3.2 Results
	23b	Discuss any limitations of the evidence included in the review.	3. Comparative Clinical Effectiveness > 3.2 Results > Uncertainty and Controversies
	23c	Discuss any limitations of the review processes used.	3. Comparative Clinical Effectiveness > 3.2 Results > Uncertainty and Controversies
	23d	Discuss implications of the results for practice, policy, and future research.	3. Comparative Clinical Effectiveness > 3.2 Results > Uncertainty and Controversies 8. Policy Recommendations (publication date: July 19, 2022)
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3. Comparative Clinical Effectiveness > 3.1 Methods Overview PROSPERO, David Rind, CRD42022300138
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Open Science Framework https://osf.io/9xwzb/
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	About ICER, page iii
Competing interests	26	Declare any competing interests of review authors.	About ICER, page iii
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	https://icer.org/beta-thalassemia-2022/

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on beti-cel for TDT followed established best research methods.[56,57] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[58] The PRISMA guidelines include a checklist of 27 items.

We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/).

Table D2. Search Strategy of Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and Cochrane Central Register of Controlled Trials

1	exp beta-Thalassemia/
2	exp Hemoglobins/ge
3	("beta thalass*emia" or "thalass*emia major" or ("transfusion dependent" and "thalass*emia") or ("TDT" and "thalass*emia") or "cooley* an*emia" or "mediterranean an*emia" or "homozygous beta thalass*emia" or "beta thalass*emia homozygous").ti,ab.
4	1 or 2 or 3
5	exp Gene Transfer Techniques/ or exp Gene Therapy/ or exp Genetic Vectors/ or exp Lentivirus/ge
6	"gene therapy".ti,ab.
7	5 or 6
8	4 and 7
9	("lentiglobin" or "zynteglo" or "bb305" or "bb 305" or "bb-305" or "betibeglogene autotemcel" or "beti-cel" or "beticel" or "beti cel" or "bb1111" or "bb 1111" or "bb-1111").ti,ab.
10	8 or 9
11	10 not ("address" or "autobiography" or "bibliography" or "biography" or "comment" or "congress" or "consensus development conference" or "duplicate publication" or "editorial" or "guideline" or "interview" or "lecture" or "legal case" or "legislation" or "letter" or "news" or "newspaper article" or "patient education handout" or "periodical index" or "personal narrative" or "portrait" or "practice guideline" or "review" or "video-audio media").pt.
12	11 not (animals not (humans and animals)).sh.
13	limit 12 to english language

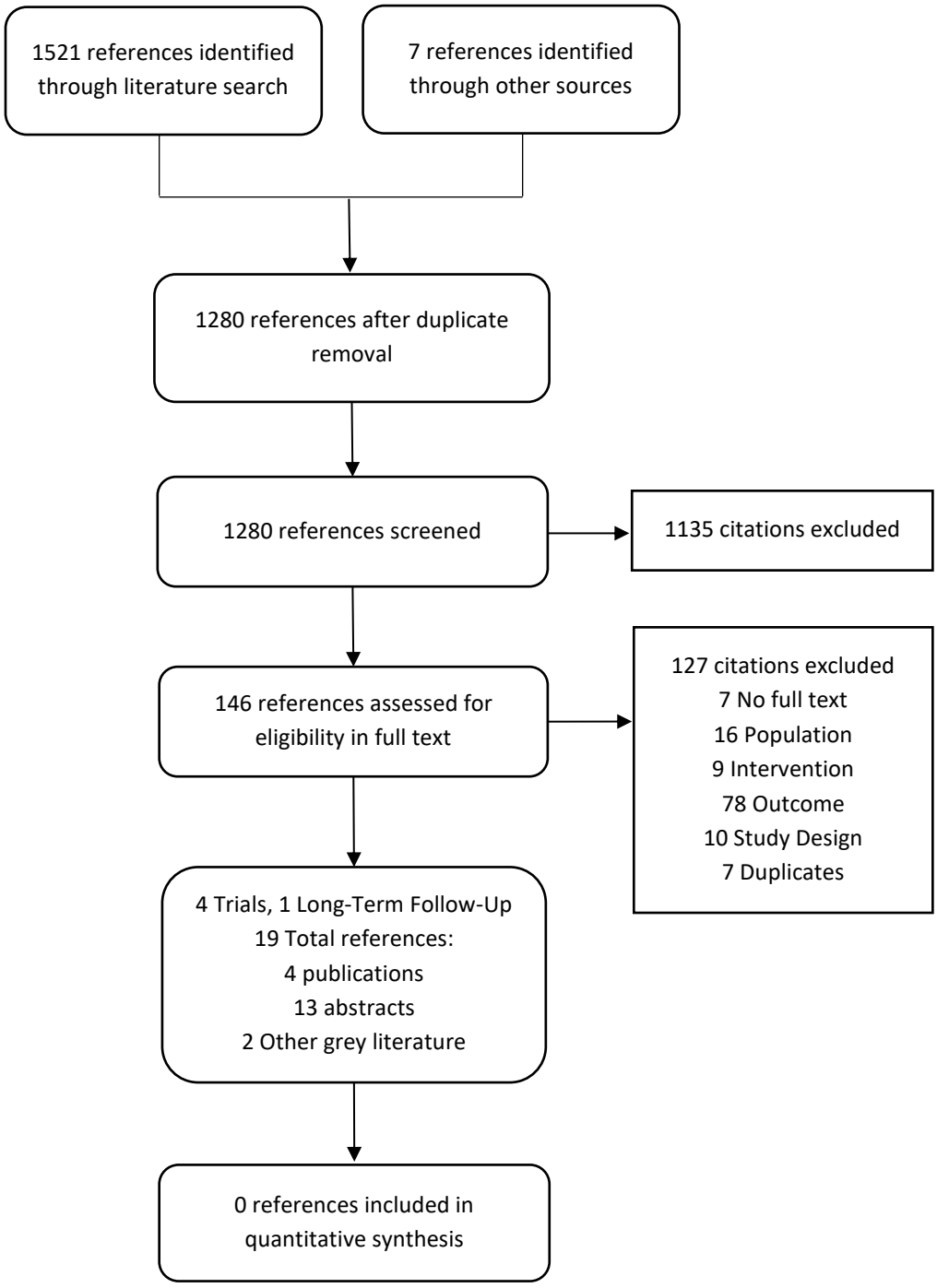
Search last ran on April 28, 2022

Table D3. Search Strategy of Embase

1	'beta thalassemia'/exp
2	‘hemoglobin’/exp
3	('beta thalass*emia' OR 'thalass*emia major' OR ('transfusion dependent' AND ‘thalass*emia') OR ('TDT' AND 'thalass*emia') OR 'cooley* an*emia' OR 'mediterranean an*emia' OR 'homozygous beta thalass*emia' OR 'beta thalass*emia homozygous'):ti,ab
4	#1 OR #2 OR #3
5	'gene transfer'/exp OR 'gene vector'/exp OR 'lentivirus vector'/exp OR 'gene therapy'/exp
6	'gene therapy':ti,ab
7	#5 OR #6
8	#4 AND #7
9	('lentiglobin' OR 'zynteglo' OR 'bb305' OR 'bb 305' OR 'bb-305' OR 'betibeglogene autotemcel' OR 'beti-cel' OR 'beticel' OR 'beti cel' OR 'bb1111' OR 'bb 1111’ OR 'bb-1111’):ti,ab
10	#8 OR #9
11	#10 NOT ('addresses' OR 'autobiography' OR 'bibliography' OR 'biography' OR 'comment' OR 'congresses' OR 'consensus development conference' OR 'duplicate publication' OR 'editorial' OR 'guideline' OR 'in vitro' OR 'interview' OR 'lecture' OR 'legal cases' OR 'legislation' OR 'letter' OR 'news' OR 'newspaper article' OR 'patient education handout' OR 'periodical index' OR 'personal narratives' OR 'portraits' OR 'practice guideline' OR 'review' OR 'video audio media')/it
12	#11 NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim OR mouse:ti OR murine:ti OR mice:ti)
13	#12 AND [english]/lim
14	#13 NOT [medline]/lim

Search last ran on April 28, 2022

Figure D1. PRISMA flow Chart Showing Results of Literature Search for Beti-Cel



Study Selection

We performed screening at both the abstract and full-text level. Three investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Three investigators reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction and Quality Assessment

Data were extracted into Excel tables (Microsoft Corporation, Redmond, Washington). The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of the patient population, sample size, duration of follow-up, study design features, interventions (agent, dosage, frequency, schedules), and outcome assessments for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.

2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Because studies were non-randomized and lacked a placebo or active control group, we did not assign any quality ratings to these trials. The limitations, uncertainties, and gaps in evidence of these trials are discussed in the Uncertainty and Controversies section.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[59,60]

Assessment of Bias

We evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include “betibeglogene autotemcel,” "LentiGlobin" and “transfusion dependent beta thalassemia”. We selected studies which would have met our inclusion criteria, and for which no findings have been published. We provided qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized qualitatively in the body of the review. Key differences between the studies in terms of the study design, patient characteristics, outcomes (including definitions and methods of assessments), and study quality were explored in the text of the report. The feasibility of conducting a quantitative synthesis was evaluated by looking at trial design, populations, analytic methods, and outcome assessments across outcomes of interest in the beti-cel trials. We were unable to conduct quantitative syntheses due to limitations in the available data (i.e., single-arm trials with small sample sizes). Nevertheless, pooled trial results from Phase I/II and Phase III trials of beti-cel have been published and we highlighted these data in our report.

D2. Evidence Tables

Table D4. Study Design

Trial	Study Design	Population	Inclusion & Exclusion Criteria	Key Outcomes [Timepoint]
NorthStar HGB-204[20] NCT01745120	Phase I/II, open label, multi-site, single-arm, non-randomized trial N = 19	B-thalassemia major	**Inclusions** - Age 12-35 years - Diagnosis of TDT - History of ≥100 mL/kg/year of pRBCs or ≥8 transfusions of pRBCs per year for the prior 2 years - Eligible for allogeneic bone marrow transplant **Exclusions** - Prior allogeneic transplant - Evidence of severe iron overload	- Transfusion independence (TI) [up to 24 months post-infusion] - Duration of TI [up to 24 months] - Time to achieving TI [up to 24 months] - Weighted average hemoglobin during TI [24 months]
HGB-205[21] NCT02151526	Phase I/II, open label, single-arm trial N = 7	Transfusion-dependent beta thalassemia (TDT) or severe sickle-cell disease (SCD)	**Inclusions** - Age 5-35 years - Severe SCD or TDT (≥100 mL/kg/year of pRBCs) - Eligible for HSCT, without matched related donor - Additional requirements for subjects with SCD **Exclusions** - Clinically significant infection - Prior/current malignancy, myeloproliferative, or immunodeficiency disorder - White blood cell count $<3\times10^9$/L and/or platelet count $<120\times10^9$/L - History of major organ damage	- Successful neutrophil and platelet engraftment [24 months post-infusion] - Transplant-related mortality [one-year post-transplant] - Overall survival [24 months] - Transfusion independence [24 months] - Weighted average hemoglobin during TI [24 months] - Duration of TI [24 months]
NorthStar 2 HGB-207[22] NCT02906202	Phase III, open label, multi-site, single-arm trial N = 23	TDT, without a β0 mutation at both alleles of the hemoglobin β gene (non-β0/β0 genotype)	**Inclusions** - Age ≤50 years (age <5 must weigh >6 kg and provide minimum cells for manufacturing process) - Diagnosis of TDT - History of ≥100 mL/kg/year of pRBCs, or ≥8 transfusions/year if age ≥12, for the prior 2 years - Eligible for HSCT **Exclusions** - β0/β0 genotype - Prior HSCT - Any known/available HLA-matched family donor	- Transfusion independence (TI) [12-24 months post-transplant] - Duration of TI [24 months] - Clinical adverse events [24 months]

Trial	Study Design	Population	Inclusion & Exclusion Criteria	Key Outcomes [Timepoint]
NorthStar 3 **HGB-212**[23] NCT03207009	Phase III, open label, multi-site, single-arm trial N = 18	TDT, who have a β0/β0, β0/IVS-I-110, or IVS-I-110/IVS-I-110 genotype (β0/β0 genotype)	**Inclusions** - Age ≤50 years (age <5 must weight >6 kg and provide minimum cells for manufacturing process) - Diagnosis of TDT - History of ≥100 mL/kg/year of pRBCs or ≥8 transfusions of pRBCs per year (subjects ≥12 years) for the prior 2 years - Eligible for HSCT **Exclusions** - Presence of a mutation other then β0 (e.g., β+, βE, βC) on at least one HBB allele - Prior HSCT - Any known/available HLA-matched family donor - Evidence of severe iron overload	- Transfusion independence (TI) [12-24 months post-transplant] - Duration of TI [12-24 months] - Weighted hemoglobin during TI [12-24 months] - Transfusion reduction [12-24 months]
NorthStar LTF-303[7,61] NCT02633943	Phase IV, multi-center, long-term follow-up study (LTF) N = 57 as of last follow-up*	β-thalassemia or severe sickle cell disease patients treated with bluebird bio gene therapy	**Inclusions** - Age ≤50 years - Treated with gene therapy for hemoglobinopathy in bluebird bio-sponsored clinical trial **Exclusions** - None	- Immune-related adverse events [15 years post-infusion] - Hematologic or neurologic disorders [15 years] - Malignancies [15 years] - Transfusion independence [15 years]
HGB-206[62] NCT02140554	Phase I/II, open label, multi-site, single arm trial N = 35‡	Severe sickle-cell disease	**Inclusions** - ≥12 and ≤50 years of age - Diagnosis of sickle cell disease with at least 4 vaso-occlusive events 24 months prior to consent **Exclusions** - Prior allogeneic transplant	- Adverse events† [24 months post-infusion]

HLA: human leukocyte antigens, HSCT: hematopoietic stem-cell transplantation, kg: kilogram, L: liter, mL: milliliter, N: total number, pRBCs: packed red blood cells, SCD: sickle cell disease, TDT: transfusion-dependent beta thalassemia, TI: transfusion independence

* At median follow-up of 41.5 months (maximum 87.5 months); projected enrollment N = 63

† Outcomes on interest for HGB-206 are adverse events only as the trial was conducted in patients with sickle cell disease

‡ 35 patients from "Group C" of HGB-206 who were treated using a manufacturing process enhanced from other groups in the trial

Table D5. Baseline Characteristics: Phase I/II Trials[19,20,29,63]

Trial		NorthStar HGB-204			HGB-205
Population		TDT (non-β0/β0)	TDT (β0/β0)	Overall	TDT
N		11	8	19	4
Study Disposition, n	Enrolled	NR	NR	23	4
	Mobilized	NR	NR	19	4
	Conditioned	NR	NR	18	4
	Infused	NR	NR	18	4
Age, years	Mean (SD)	22.7 (6.50)*	24.1 (7.62)*	23.3 (6.82)*	NR
	Median (range)	NR	NR	20 (12-35)	17.5 (16-19)*
Sex, n (%)	Female	7 (63.6)	6 (75.0)	13 (68.4)	2 (50)
	Male	4 (36.4)	2 (25.0)	6 (31.6)	2 (50)
Race, n (%)	Asian	8 (72.7)	6 (75.0)	14 (73.7)	2 (50)
	White	2 (18.2)	2 (25.0)	4 (21.1)	2 (50)
	Black	0	0	0	0
	Indigenous	0	0	0	0
	Other	1 (9.1)	0	1 (5.3)	0
Genotype, n (%)	β0/β0	0†	8†	8/18 (44)	0
	βE/β0	11†	0†	6/18 (33)	3 (75)
	β0/β+			4/18 (22)	0
	β+/β+				1 (25)
Age at first transfusion, years	Median (range)	NR	NR	3.5 (0-26.0)	1.8 (0-14.0)
Transfusion volume, ml/kg/year	Median (range)	NR	NR	164 (124-261)	182 (139-197)
Transfusions per year	Median (range)	NR	NR	Pooled: 13.0 (10.0-17.5)	
Liver iron concentration, mg/g	Median (range)	NR	NR	5.7 (0.4-26.4)	11.2 (3.9-14.0)
Cardiac T2*, msec	Median (range)	NR	NR	35 (10-54)	33 (29-46)
Previous splenectomy, n (%)		NR	NR	6/18 (33)	3 (75)
Fertility preservation, n (%)		NR	NR	9 (50)	4 (100)
Baseline characteristics not reported: Number of transfusions per year, serum ferritin level					

kg: kilogram, ml: milliliter, msec: millisecond, n: number, N: total number, NR: not reported, SD: standard deviation, TDT: transfusion-dependent beta thalassemia

* Age at consent

† Assumed from trial design

Table D6. Baseline Characteristics: Phase III Trials[6,24-26,29,41]

Trial		NorthStar 2 HGB-207	NorthStar 3 HGB-212	NorthStar 2 & 3 Pooled
Population		TDT (non-β0/β0)	TDT (β0/β0 & severe non-β0/β0)	Pooled
N		23	18	41
Study Disposition, n	Consented	32	19	NR
	Mobilized	24	19	43
	Conditioned	NR	NR	41
	Infused	23	18	41
Age, years	Mean (SD)	NR	NR	15.1 (7.9)
	Median (range)	15 (4-34)*	12.5 (4-33)	13 (4-34)
Sex, n (%)	Female	12 (52)	8 (44)	20 (48.8)
	Male	11 (48)	10 (56)	21 (51.2)
Race, n (%)	Asian	13 (57)	7 (10)	NR
	White	8 (35)	10 (56)	NR
	Black	0	NR	NR
	Indigenous	0	NR	NR
	Other	2 (9)	1 (6)	NR
Genotype, n (%)	β0/β0	0	12 (67)	12 (29)
	βE/β0	6 (26)	0	6 (15)
	β0/β+	12 (52)	3 (17)	15 (37)
	β+/β+	5 (22)	3 (17)	8 (20)
Age at first transfusion, years	Median (range)	1 (<1-7)	0.7 (0.3-11.0)	NR
Transfusion volume, ml/kg/year	Median (range)	207.9 (142.1-274.4)	194 (75-289)	199.6 (43.6)
Transfusions per year	Median (range)	16.0 (11.5-37.0)	17.5 (11.0-39.5)	Mean (SD): 17.9 (6.32)
Liver iron concentration, mg/g	Median (range)	5.3 (1-41)	3.6 (1-13)	Mean (SD): 6.9 (7.2)
Cardiac T2*, msec	Median (range)	36.7 (21.0-57.0)	37.0 (15-75)	NR
Serum ferritin level, ng/ml	Median (range)	1975.2 (349-10,021)	NR	Mean (SD): 4448 (3689)
Previous splenectomy, n (%)		4 (17)	3 (17)	7 (17.1)
Fertility preservation, n (%)		15 (65)	15 (83)	30 (73.2)

g: gram, kg: kilogram, mg: milligram, ml: milliliter, msec: millisecond, n: number, N: total number, ng: nanogram, NR: not reported, SD: standard deviation, TDT: transfusion-dependent beta thalassemia

* Age at consent

Table D7. Baseline Characteristics: Long-Term Follow-Up[7,29]

Trial		NorthStar LTF-303	
Phase		**Phase I/II**	**Phase III**
N		22	41
Age, years	**Median (range)**	20 (12-35)	13 (4-34)
Sex, n (%)	**Female**	15 (68.2)	20 (48.8)
	Male	7 (31.8)	21 (51.2)
Genotype	**β0/β0**	8 (36)	12 (29)
	non-β0/β0	14 (64)	29 (71)
Transfusion volume, ml/kg/year	**Median (range)**	171.2 (124.4-273.2)	192.9 (74.6-276.1)
Transfusions per year	**Median (range)**	13 (10-17.5)	17.5 (11-39.5)
Liver iron concentration, mg/g	**Median (range)**	7.1 (0.4-26.4)	4.9 (1.0-41.0)
Cardiac T2*, msec	**Median (range)**	34 (10-54)	37 (15-75)
Serum ferritin level, pmol/L	**Median (range)**	3146.8 (748-8629)	3671.9 (784-22517)
Previous splenectomy, n (%)		9 (41)	7 (17.1)
Fertility preservation, n (%)		13 (59.1)	30 (73.2)
Baseline characteristics not reported: Race, age at first transfusion			

g: gram, kg: kilogram, LTF: long-term follow-up, mg: milligram, ml: milliliter, msec: millisecond, n: number, N: total number, pmol: picomole, SD: standard deviation

Table D8. Efficacy: Phase I/II Trials[19,20,27,28,63]

Trial		NorthStar HGB-204			HGB-205
Population		TDT (non-β0/β0)	TDT (β0/β0)	Overall	TDT
N		10	8	18	4
Follow-up, Median months (Range)		40.7 (29.3-53.8)			49.6 (40.5-60.6)
Successful Neutrophil Engraftment	Incidence, n (%)	10 (100)	8 (100)	18 (100)	4 (100)
	Time to Event, median days (range)	18.5 (14-27)	19.5 (15-30)	18.5 (14-30)	16.5 (14-29)
Successful Platelet Engraftment	Incidence, n (%)	10 (100)	8 (100)	18 (100)	4 (100)
	Time to Event, median days (range)	50.5 (19-191)	36 (31-55)	39.5 (19-191)	23 (20-26)
Duration of Hospitalization*	Median days (range)	NR	NR	40 (27-69)	NR
Transfusion Independence	Incidence, n (%)	8 (80.0)	3 (37.5)	11 (61.1)	3/4 (75)
	Duration, median months (range)	38.0 (21.2-45.3)	16.4 (16.1-20.8)	NR	21.7 (21.2-21.8)‡
	Time to Event, median days (range)	17.12 (15.0-20.9)	17.5 (17.5-17.5)	17.51 (15.0-20.9)	14.9 (14.9-15.6)‡
Transfusion Volume Reduction in patients without TI	Median % (range)	Patient 1: 73 Patient 2: 43	53 (10-72)	NR	NR
Hemoglobin level during TI, g/dl	Mean (SD)	10.44 (1.28)	10.11 (NC)	10.41 (1.20)	NR
	Median (range)	10.3 (9.1-13.2)	9.9 (9.5-10.1)	NR	11.3 (10.6-13.1)‡
Liver iron concentration, % reduction	Median (range)	NR	NR	56 (38-83)†	NR
Cardiac T2*, msec	Median (range)	NR	NR	NR (31.4 - 57.6)	NR
Serum ferritin level, % reduction	Median (range)	NR	NR	55 (16-78)†	NR
Iron chelation post-infusion in patients with TI	Restarted and stopped, n (%)	NR	NR	NR	4 (100)
Efficacy outcomes not reported: N restarting and continuing or never restarting iron chelation post-infusion					

dl: deciliter, g: gram, kg: kilogram, mg: milligram, ml: milliliter, msec: millisecond, n: number, N: total number, NC: not calculated, ng: nanogram, Pt: patient, SD: standard deviation, TI: transfusion independent/independence

* Hospitalization from conditioning to discharge

† From screening to month 48 (N=4)

‡ Data as of March 2020, all other HGB-205 data as of June 2019

Table D9. Efficacy: Phase III Trials[6,24-26,29]

Trial		NorthStar 2 HGB-207	NorthStar 3 HGB-212	NorthStar 2 & 3 Pooled
Population		TDT (non-β0/β0)	TDT (β0/β0 & severe non- β0/β0)	Pooled
N		23	18	41
Follow-up, Median months (Range)		29.5 (13.0-48.2)	23.0 (4.1-26.8)	24.3 (0.9-42.2)
Successful Neutrophil Engraftment	Incidence, n (%)	23 (100)	18 (100)	41/41 (100)
	Time to Event, median days (range)	23 (13-32)	26 (14-39)	25.5 (13-39)
Successful Platelet Engraftment	Incidence, n (%)	23 (100)	18 (100)	41/41 (100)
	Time to Event, median days (range)	46 (20-94)	49.5 (21-26)	46 (13-94)
Duration of Hospitalization*	Median days (range)	45 (30-92)	42.5 (29-68)	44 (29-92)
Transfusion Independence	Incidence, n (%)	20/22 (91)	12/14 (86)	34/38 (89.5)
	Duration, median months (range)	20.4 (15.7-21.6)	13.6 (12.2-21.2)	31.6 (13.3-49.1)
Transfusion Volume Reduction in patients without TI	Median %	Patient 2: 67.4 Patient 20: 22.7	Patient 4: 80 Patient 8: 31	NR
Hemoglobin level during TI, g/dl	Median (range)	11.7 (9.5-12.8)	11.5 (9.5-13.5)	11.3 (9.5-13.7)
Liver iron concentration, mg/g	Median (range)	4.9 (1.4-20.3)	NR	NR
Cardiac T2*, msec	Median (range)	35.1 (15–47)	NR	NR
Serum ferritin level, ng/ml	Median (range)	862 (94-8443)	NR	NR
Iron chelation post-infusion in patients with TI	Restarted and stopped, n (%)	4/20 (20)	NR	NR
	Restarted and continued, n (%)	7/20 (35)	NR	NR
	Never restarted, n (%)	9/20 (45)	NR	NR
Efficacy outcomes not reported: Time to TI, mean hemoglobin level during TI				

dl: deciliter, g: gram, kg: kilogram, mg: milligram, ml: milliliter, msec: millisecond, n: number, N: total number, ng: nanogram, SD: standard deviation, TI: transfusion independent/independence

* Hospitalization from conditioning to discharge

Table D10. Efficacy: Long-Term Follow-Up[7,29]

Trial		NorthStar LTF-303	
Population		**Phase I/II**	**Phase III**
N		22	41
Follow-up, Median months (Range)		67.6 (59.2-86.5)	27.2 (4.1-48.2)
Successful Neutrophil Engraftment	**Incidence, n (%)**	22 (100)	41 (100)
	Time to Event, median days (range)	18 (14-30)	26 (13-39)
Successful Platelet Engraftment	**Incidence, n (%)**	22 (100)	41 (100)
	Time to Event, median days (range)	36 (19-191)	46 (20-94)
Duration of Hospitalization*	**Median days (range)**	40 (27-69)	44 (29-92)
Transfusion Independence	**Incidence, n (%)**	15 (68)	34/38 (89.5)
	Duration, median months (range)	65.9 (19.8-84.5)	31.6 (13.3-49.1)
Weighted Average Hemoglobin level during TI, g/dl	**Median (range)**	10.3 (9.1-13.2)	11.3 (9.5-13.7)
Liver iron concentration, mg/g	**Median (range)**	n=15; 4.5 (0.9-11.2)	n=24; 4.5 (1.4-20.3)
	Median reduction from baseline in patients achieving TI, %	n=15, 36†	NR
Cardiac T2*, msec	**Median (range)**	n=15; 40 (30-65)	n=23; 34 (23-47)
Serum ferritin level, pmol/L	**Median (range)**	n=15; 1267 (209-8613)	n=25; 1389 (351-15378)
Iron chelation post-infusion in patients with TI	**Restarted and stopped, n (%)**	21/49 (43)	
	Restarted and continued, n (%)	16/49 (33)	
	Never restarted, n (%)	12/49 (24)	
Efficacy outcomes not reported: Duration of hospitalization from conditioning to discharge, time to TI, transfusion infusion reduction in patients without TI			

dl: deciliter, g: gram, kg: kilogram, LTF: long-term follow-up, mg: milligram, ml: milliliter, msec: millisecond, n: number, N: total number, pmol: picomole, TI: transfusion independent/independence

* Hospitalization from conditioning to discharge

† At Month 48

Table D11. Safety: Phase I/II Trials[20,63,64]

Trial		NorthStar HGB-204			HGB-205	HGB-206
Population		TDT (non-β0/β0)	TDT (β0/β0)	TDT	TDT	SCD*
N		11	8	19	4	35
Adverse Events, n (%)	Overall	10 (90.9)	8 (100)	18 (94.7)	4 (100)	35 (100)
	Serious	6 (54.5)	4 (50.0)	10 (52.6)	2 (50)	12 (34)
	Grade 3/4	NR	NR	NR	NR	34 (97)
Treatment-related Adverse Events, n (%)	Overall	NR	NR	NR	NR	3 (9)†
	Serious	NR	NR	NR	0	NR
Mortality, n (%)	Overall	0	0	0	0	1
	AE-related	0	0	0	0	0
	Transplant-related	0	0	0	0	0
Adverse Events of Special Interest, n (%)						
Stomatitis	Overall	8 (72.7)	5 (62.5)	13 (68.4)	NR	NR
	Grade ≥3	NR	NR	NR (≥25)	4 (100)	24 (69)
Anemia	Overall	9 (81.8)	8 (100)	17 (89.5)	NR	NR
	Grade ≥3	NR	NR	NR	NR	13 (37)
Neutropenia	Overall	6 (54.6)	4 (50)	10 (52.6)	NR	NR
	Grade ≥3	NR	NR	NR	NR	19 (54)
Febrile Neutropenia	Overall	7 (63.6)	4 (50.0)	11 (57.9)	NR	NR
	Grade ≥3	NR	NR	NR (≥25)	NR	15 (43)
Thrombocytopenia	Overall	10 (90.9)	8 (100)	18 (94.7)	NR	NR
	Grade ≥3	NR	NR	NR	NR	23 (66)
Leukopenia	Overall	5 (45.5)	1 (12.5)	6 (31.6)	NR	NR
	Grade ≥3	NR	NR	NR	NR	11 (31)
Lymphopenia	Grade ≥3	NR	NR	NR	NR	2 (6)
Veno occlusive liver disease	Serious	1 (9.1)	1 (12.5)	2 (10.5)	NR	0
	Grade ≥3	NR	NR	NR	NR	0
Splenomegaly	Overall	0	1 (12.5)	1 (5.3)	NR	NR
Bone Pain	Overall	2 (18.2)	1 (12.5)	3 (15.8)	NR	NR
Infection	Overall	0 (0)	4 (50.00)	4 (21.05)	NR	NR
Pharyngeal inflammation	Grade ≥3	NR	NR	NR (≥25)	NR	2 (6)
Decreased Appetite	Grade ≥3	NR	NR	NR	NR	3 (9)
Nausea	Grade ≥3	NR	NR	NR	NR	4 (11)

Increase in alanine aminotransferase	**Grade ≥3**	NR	NR	NR	2 (50)	3 (9)
Increased blood bilirubin level	**Grade ≥3**	NR	NR	NR	NR	2 (6)
Acute myeloid leukemia		NR	NR	No reported "oncogenesis"	NR	NR
Safety outcomes not reported: Pyrexia, congestive cardiac failure, epistaxis, hypoxia, neutropenic sepsis, mucosal inflammation, myelodysplastic syndrome, infertility						

AEs: adverse events, n: number , N: total number, NR: not reported, SCD: sickle cell disease, TDT: transfusion-dependent beta thalassemia

* 35 patients from "Group C" of HGB-206 who were treated using a manufacturing process enhanced from other groups in the trial

† All events resolved one week following their onset

Table D12. Safety: Phase III Trials[6,24,25]

Trial		NorthStar 2 HGB-207	NorthStar 3 HGB-212	NorthStar 2 & 3 Pooled
Population		TDT (non-β0/β0)	TDT (β0/β0 & severe non- β0/β0)	TDT
N		23	15	41
Adverse Events, n (%)	Overall	23 (100)	NR	NR
	Serious	NR	3 (20)	NR
Treatment-related* Adverse Events, n (%)	Overall	Thrombocytopenia: 2 (9)	Number of events: 5	Abdominal pain: 3 (7) Thrombocytopenia: 3 (7)
	Serious	1 (4)	0	Thrombocytopenia: 1 (2)
Mortality, n (%)	Overall	0	0	0
Adverse Events of Special Interest, n (%)				
Stomatitis	Serious	NR	1 (7)	2 (5)
	Grade ≥3	14 (61)	5 (33)	17/34 (50)
Anemia	Serious	NR	NR	NR
	Grade ≥3	14 (61)	NR	NR
Neutropenia	Serious	NR	1 (7)	2 (5)
	Grade ≥3	18 (78)	NR	NR
Febrile Neutropenia	Serious	NR	1 (7)	2 (5)
	Grade ≥3	8 (35)	9 (60)	20 (49)
Thrombocytopenia	Serious	2 (9)	1 (7)	3 (7)
	Grade ≥3	22 (96)	NR	NR
Leukopenia	Grade ≥3	13 (57)	NR	NR
Lymphopenia	Grade ≥3	2 (9)	NR	NR
Neutropenic sepsis	Grade ≥3	2 (9)	NR	NR
Veno occlusive liver disease	Serious	NR	0 (0)	3 (7)
	Grade ≥3	Grade 4: 3 (13)	NR	3 (7)
Mucosal inflammation	Grade ≥3	NR	3 (20)	NR
Congestive cardiac failure	Serious	NR	1 (7)	NR
Pyrexia	Serious	2 (9)	2 (13)	4 (10)
	Grade ≥3	4 (17)	NR	5 (12)
Pharyngeal inflammation	Grade ≥3	2 (9)	2 (13)	NR
Epistaxis	Grade ≥3	5 (22)	NR	8 (20)
Hypoxia	Grade ≥3	2 (9)	NR	NR
Decreased Appetite	Grade ≥3	3 (13)	3 (20)	6 (15)

Increase in alanine aminotransferase	**Grade ≥3**	2 (9)	3 (20)	5 (12)
Increased blood bilirubin level	**Grade ≥3**	2 (9)	NR	NR
Acute myeloid leukemia		0	No reported "oncogenesis"	0
Safety outcomes not reported: Grade 3/4 AEs, treatment-related AEs, splenomegaly, bone pain, infection, myelodysplastic syndrome, infertility				

n: number , N: total number, NR: not reported, TDT: transfusion-dependent beta thalassemia

* Related or possibly related to beti-cel as determined by investigators

Table D13. Safety: Long-Term Follow-Up[7,29,65]

Trial		NorthStar LTF LTF-303
Population		**TDT**
Follow-Up Time		41.5 months (range: 23-87.5)
N		63
Adverse Events, n (%)	**Overall**	0
	Serious	8/57 (15.7)
Treatment-related Adverse Events, n (%)	**Between infusion and engraftment**	7 (11)
	Between engraftment and 2 years post-infusion	4 (6)
	>2 years post-infusion	0
Mortality, n (%)	**Overall**	0
Adverse Events of Special Interest, n (%)		
Veno-occlusive Disease	**Overall**	7 (11)
	Serious	5 (8)
Pyrexia	**Serious**	5 (8)
Neutropenia	**Serious**	3 (5)
Thrombocytopenia	**Serious**	3 (5)
Sepsis	**Serious**	3 (5)
Appendicitis	**Serious**	2 (3)
Febrile neutropenia	**Serious**	2 (3)
Major depression	**Serious**	2 (3)
Stomatitis	**Serious**	2 (3)
Acute myeloid leukemia		No reported malignancies
Safety outcomes not reported: Grade 3/4 adverse events, stomatitis, anemia, neutropenia, febrile neutropenia, lymphopenia, neutropenic sepsis, veno occlusive liver disease, splenomegaly, bone pain, infection, mucosal inflammation, congestive cardiac failure, pyrexia, pharyngeal inflammation, epistaxis, hypoxia, decreased appetite, nausea, increase in alanine aminotransferase, increased blood bilirubin level, myelodysplastic syndrome, infertility		

n: number , N: total number, NR: not reported, TDT: transfusion-dependent beta thalassemia

* Occurring at median 15.7 months (range: 0.5-60.6) of follow-up, N = 51; not occurring two years after LTF-303.

Table D14. Health-Related Quality of Life: Pooled Phase III Trials (NorthStar 2 & 3)[26]

HRQoL Instrument	Population	Timepoint	N assessed	Mean Score (SE)
EQ-5D-Y VAS Score range: 0-100	11-17 years	Baseline	12	81.4 (SD: 19.2)
		Month 12	NR	91.6 (SD: 4.9)
		Month 24	NR	92.4 (SD: 6.0)
EQ-5D-3L VAS Score range: 0-100	> 18 years	Baseline	12	85.2 (SD: 10.5)
		Month 12	NR	90.9 (SD: 4.5)
		Month 24	NR	94.2 (SD: 4.8)
EQ-5D-3L Index Score range: 0-1	> 18 years	Baseline	12	0.92 (0.04)
		Month 12	12	0.96 (0.02)
		Month 24	12	0.96 (0.02)
PedsQL* Score range: 0-100, MCID = 4.36	< 18 years	Baseline	18	77.4 (3.4)
		Month 12	18	85.3 (1.9)
		Month 24	18	86.4 (1.7)
SF-36 PCS† Score range: 0-100, MCID = 2	> 18 years	Baseline	12	53.8 (1.4)
		Month 12	12	55.4 (1.2)
		Month 24	12	55.4 (1.3)
SF-36 MCS† Score range: 0-100, MCID = 2	> 18 years	Baseline	12	51.0 (1.7)
		Month 12	12	52.7 (2.0)
		Month 24	12	53.5 (2.1)
FACT-BMT Score range: 0-196	> 18 years	Baseline	11	125.8 (3.4)
		Month 12	11	128.4 (3.3)
		Month 24	11	128.9 (3.0)
FACT-G Score range: 0-108	> 18 years	Baseline	11	94.2 (2.6)
		Month 12	11	96.1 (2.5)
		Month 24	11	95.8 (2.1)
Quality of life data not reported for: HGB-204, HGB-205, LTF-303				

Higher scores indicate better HRQoL

EQ-5D-3L VAS: EuroQol visual analog scale, EQ-5D-Y VAS: EuroQol visual analog scale-youth, FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow, FACT-G: Functional Assessment of Cancer Therapy-General, HRQoL: health-related quality of life, MCID: minimal clinically important difference, NR: not reported, PedsQL: Pediatric Quality of Life Inventory, SD: standard deviation, SE: standard error, SF-36 MCS: Short Form-36 Health Survey Mental Component Summary, SF-36 PCS: Short Form-36 Health Survey Physical Component Summary

* Global population norm = 81

† General population norm = 50

Table D15. Additional Subgroups: Pooled Phase III Trials[33]

Trial		NorthStar 2 & 3 Pooled		
Age Subgroups, years		**<12**	**≥12, <18**	**>18**
N		16	11	14
Follow-up, median months (range)		25.5 (4.1-41.5)		
Baseline Characteristics				
Age, years	**Median (range)**	8 (4-11)	15 (12-17)	22.5 (18-34)
Liver iron concentration, mg/g	**Median (range)**	3.0 (1.2-12.7)	5.6 (1.0-13.2)	
Cardiac T2*, msec	**Median (range)**	37 (15-57)	39 (25-75)	53)
Splenectomy	**n (%)**	1 (6.3)	0	
Efficacy Outcomes				
Time to Neutrophil Engraftment	**Median days (range)**	26 (17-39)	26 (16-38)	21 (13-27)
Time to Platelet Engraftment	**Median days (range)**	51 (20-94)	50 (25-84)	43 (21-58)
Transfusion Independence	**Incidence, n (%)** max. 35.5 months follow-up	9/11 (81.2)*	10/10 (100)*	11/13 (84.6)*
	Incidence, n (%) max. 41.5 months follow-up	20/22 (90.9)		NR
	Duration, median months (range)	19.5 (12.3-32.0)*		NR
Hemoglobin level during TI, g/dl	**Median (range)**	10.0 (9.5-11.4)*	11.5 (9.6-13.0)*	12.6 (9.9-13.6)*
Safety Outcomes				
Treatment-Related Adverse Events, n (%)		2 (12.5)	2 (18.2)	NR
Veno-occlusive liver disease, n (%)	**Grade 2**	1 (6.3)	0	
	Grade 4	0	2 (18.2)	
Serious AEs, n (%)	**Pyrexia**	4 (14.8)		
	Stomatitis	2 (7.4)		
	Veno-occlusive disease	2 (7.4)		
	Neutropenia	2 (7.4)		
	Thrombocytopenia	2 (7.4)		
	Febrile neutropenia	2 (7.4)		
Grade ≥3 Adverse Events†, n (%)	**Stomatitis**	15 (55.6)		
	Febrile Neutropenia	15 (55.6)		
	Epistaxis	6 (22.2)		
	Decreased appetite	5 (18.5)		
	Hypoxia	3 (11.1)		

Trial		NorthStar 2 & 3 Pooled		
Age Subgroups, years		<12	≥12, <18	>18
	Pyrexia	3 (11.1)		
	Increased alanine aminotransferase	3 (11.1)		
	Pharyngeal inflammation	3 (11.1)		

dl: deciliter, g: gram, max: maximum, n: number, N: total number, NR: not reported, TI: transfusion independence
* Data as of November 2020, median 23 months of follow-up (range: 0.9-35.5)
† in ≥3 patients

Table D16. Real-World Experience of Beti-cel[66]

		Patient 1	Patient 2
Baseline	Age at infusion, years	14	28
	Genotype	$B0/B^{+IVS-I-110}$	$B+/B^{+IVS-I-110}$
	Liver iron content, mg/g	2.0	0.7
	Serum ferritin, µg/L	1059	295
	Transfusion volume, mL/kg/year	158	173
Efficacy	Time to Neutrophil Engraftment, days	27	21
	Time to Platelet Engraftment, days	55	20
	Duration of Hospitalization*, days	27	34
	Duration without transfusions	Up to 6 months	Up to 6 months
	Weighted Average Hemoglobin level, g/dl (Month 1)	10.5	NR
	Weighted Average Hemoglobin level, g/dl (Month 6)	12.9	NR
Safety	Adverse events	Febrile neutropenia, elevated C-reactive protein, pruritus, gingivitis, mild mucositis, vertigo	Febrile neutropenia, mucositis (Grade 3)
	Veno-occlusive disease	none	none

dl: deciliter, g: gram, kg: kilogram, mg: milligram, mL: milliliter, NR: not reported, µg: microgram
* from infusion to discharge from inpatient treatment

D3. Ongoing Studies

Table D17. Ongoing Studies*

Title / Trial Sponsor	Study Design & Intervention	Patient Population	Key Outcomes	Estimated Completion
A Study Evaluating the Efficacy and Safety of the LentiGlobin® BB305 Drug Product in Subjects with Transfusion-Dependent β-Thalassemia, who do Not Have a β0/β0 Genotype (NorthStar-2) bluebird bio NCT02906202	Single-arm, multi-site, single-dose, Phase III study **Actual enrollment**: N = 23 **Intervention**: IV infusion of beti-cel following myeloablative conditioning with busulfan	**Inclusions** - Age ≤50 years (age <5 years must weigh >6 kg and provide minimum cells for manufacturing process) - Diagnosis of TDT - History of ≥100 mL/kg/year of pRBCs, or guideline-driven management of ≥8 transfusions/year if age ≥12, for the prior 2 years - Eligible for HSCT **Exclusions** - β0/β0 genotype - Prior HSCT - Any known/available HLA-matched family donor	**Primary** - Transfusion independence [12-24 months post-transplant] **Secondary** - Engraftment - Insertional oncogenesis - Adverse events	February 2022
A Study Evaluating the Efficacy and Safety of the LentiGlobin® BB305 Drug Product in Participants with Transfusion-Dependent β-Thalassemia (NorhtStar-3) bluebird bio NCT03207009	Single-arm, multi-site, single-dose, Phase III study **Actual enrollment**: N = 18 **Intervention**: IV infusion of beti-cel following myeloablative conditioning with busulfan	**Inclusions** - Age ≤50 years (age <5 years must weight >6 kg and provide minimum cells for manufacturing process) - Diagnosis of TDT - History of ≥100 mL/kg/year of pRBCs or ≥8 transfusions of pRBCs per year (subjects ≥12 years) for the prior 2 years - Eligible for HSCT **Exclusions** - Presence of a mutation other then β0 (e.g., β+, βE, βC) on at least one HBB allele. - Prior HSCT - Any known/available HLA-matched family donor - Evidence of severe iron overload	**Primary** - Transfusion independence [12-24 months post-transplant] **Secondary** - Duration of transfusion independence - Average weighted hemoglobin during transfusion independence	November 2022

Source: www.ClinicalTrials.gov

HLA: human leukocyte antigen, HSCT: hematopoietic stem-cell transplantation, kg: kilogram, mL: milliliter, N: total number, pRBC: packed red blood cells, TDT: transfusion-dependent beta thalassemia

* Ongoing studies of beti-cel are also included in this review

D4. Previous Systematic Reviews and Technology Assessments

We identified one health technology assessment that was initiated by NICE. We identified completed assessments from France and Germany.

National Institute for Health and Care Excellence (NICE, England)

Betibeglogene autotemcel for treating transfusion-dependent beta thalassaemia

NICE began an appraisal of the clinical and cost effectiveness of betibeglogene autotemcel for the treatment of transfusion-dependent beta-thalassemia. The review was officially suspended in December 2021 due to a decision from the company sponsor to withdraw its marketing application from the Medicines and Healthcare products Regulatory Agency.

Haute Autorité de Santé (HAS, France)

Zynteglo (betibeglogene autotemcel) for β-thalassemia

France's HAS judged the clinical benefit of betibeglogene autotemcel to be substantial and recommended its reimbursement in the treatment of patients ages 12 – 35 years with transfusion-dependent beta-thalassemia who do not have a β0/β0 genotype, for whom HSCT is appropriate, but an HLA-matched related donor is not available. In this population, the clinical added value was judged to be moderate (CAV III).

The assessment determined there was insufficient evidence of clinical benefit to support funding by the French national insurance system in patients over 35 years.

Federal Joint Committee (G-BA, Germany)

Benefit Assessment of betibeglogene autotemcel (β-thalassemia)

The German Federal Joint Committee's (G-BA's) benefit assessment focused on betibeglogene autotemcel for the treatment of patients ages >12 years with transfusion dependent beta thalassemia and a non- β0/β0 genotype. The G-BA concluded that the data did not permit quantification of clinical benefit due to the lack of comparative data. Although they acknowledged that the data on transfusion independence demonstrated a clear benefit with regard to preventing anemia, the extent to which transfusion independence resolves complications from routine transfusions remained uncertain. The G-BA was also uncertain about whether iron chelation therapy remained necessary in patients who achieved transfusion independence.

Systematic Literature Review

Badawy S.M., et al., (2021). "A systematic review of quality of life in sickle cell disease and thalassemia after stem cell transplant or gene therapy"[67]

Investigators conducted a systematic review of recent evidence for the effectiveness of HSCT and gene therapy on health-related quality of life (HRQOL) in patients with sickle cell disease (SCD) and thalassemia. Sixteen studies were included in the review, ten of which included patients with thalassemia. The thalassemia studies evaluated HRQOL with a variety of HRQOL instruments, including the Pediatric Quality of Life, Short Form 36, European Quality of Life 5D, and Functional Assessment of Cancer Therapy-Bone Marrow Transplant survey.

Overall, studies reported significant improvement in HRQOL following HSCT in thalassemia patients. Worse HRQOL scores were generally associated with graft versus host disease. Studies identified for HRQOL outcomes following gene therapy in thalassemia have shown promising improvements in outcomes. Those who achieved transfusion independence following gene therapy in the thalassemia population had greater improvement in HRQOL.

E. Long-Term Cost Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	Includes caregiver impacts for modified societal perspective
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	X	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	X	
	Unpaid caregiver-time costs	NA	X	
	Transportation costs	NA	¨	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	X	
Consumption	Future consumption unrelated to health	NA	¨	
Social services	Cost of social services as part of intervention	NA	¨	
Legal/Criminal Justice	Number of crimes related to intervention	NA	¨	
	Cost of crimes related to intervention	NA	¨	
Education	Impact of intervention on educational achievement of population	NA	¨	
Housing	Cost of home improvements, remediation	NA	¨	
Environment	Production of toxic waste pollution by intervention	NA	¨	
Other	Other impacts (if relevant)	NA	¨	

NA: not applicable

Adapted from Sanders et al.[68]

Treatment Strategies

The intervention of interest was betibeglogene autotemcel (beti-cel), and the comparator of interest for this intervention was standard of care (RBC transfusions and iron chelation).

Target Population

The population of focus for the economic evaluation included patients with TDT and a mean age of 22.2 years (45.0% between 2 and 17 years old with an average age of nine years old in this subset) in the base-case analysis. The mean age for patients in the <18-year-old subset was specified in order to account for differences in costs within the Markov traces for beti-cel and SOC. We applied age-specific costs (i.e., <18 years and ≥18 years) for the percentage of patients in the cohort that were assumed to be <18 years (45%). These cost differences were applied for 9 years based on an assumed mean starting age of 9 years for this subset. Cost differences were applied for pre-transplant costs, cost of beti-cel transplant, annual acquisition cost of chelation therapy, transfusion costs, and the number of transfusions assumed per year. Other age-specific parameter inputs were applied for the disutility associated with the transfusion dependence health state (i.e., age <16 years or ≥16 years), and the disutility associated with caregiving (assumed to end when the patient reached the age of 26 years). Lastly, the probability of cardiac complications post-beti-cel transplant was also dependent on age. For patients who received beti-cel treatment prior to the age of 12, it was assumed that these patients would have no risk of cardiac complications; otherwise, for patients who receive beti-cel transplant at age 12 years or above, a low risk of cardiac complications was assumed.

The patient characteristics that informed the model's base-case cohort were primarily informed by the Thalassemia Longitudinal Cohort (TLC) study (Table E1.2). We supplemented data from the TLC with other sources, where data gaps existed – e.g., age distribution, mean number of transfusions per year, and mean weight of the cohort. To explore the impact of alternate baseline population characteristics, we conducted a scenario analysis using data from Phase III beti-cel trials.

Table E1.2. Model Cohort Characteristics

	Betibeglogene Autotemcel	
	Base Case	**Scenario Analysis**
Mean Age, years	22.2 (12.5)	15.1 (7.95)
Age distribution, %	-	-
2 to 11 years	31.6*	NA
12 to 17 years	13.4*	NA
18 to 23 years	11.1*	NA
24 to 29 years	11.1*	NA
30 to 34 years	8.2*	NA
35 to 39 years	8.2*	NA
40 to 44 years	8.2*	NA
45 to 50 years	8.2*	NA
Age < 18 years, %	45.0*	65.9[33]
Weight, kg	-	NA
< 18 years	34.4*	NA
≥ 18 years	72.4*	NA
Female, %	52.3	48.8
Mean number of transfusions per year	-	17.9 (6.3)
< 18 years	14.95*	NA
≥ 18 years	16.1*	NA
Type of iron chelation therapy, %	-	-
Deferasirox (oral)	54.0*	NA
Deferiprone (oral)	16.0*	NA
Deferasirox + Deferiprone (oral)	4.0*	NA
Deferoxamine mesylate (SC)	7.0*	NA
Oral + Deferoxamine mesylate (SC)	19.0*	NA
Serum ferritin, low / moderate / high, %**	41.0 / 40.0 / 19.0	NA
LIC, low / moderate / high, %§	45.0 / 32.0 / 23.0	NA
Myocardial T2*, low / moderate / high, %#	71.0 / 29.0 / 0.0	NA
Primary Data Source	Thalassemia Longitudinal Cohort (Kwiatkowski et al., 2012, 2006)	Phase III Trial Data (Northstar-2 and -3)
Additional data sources	Kwiatkowski et al., 2012[69]; NERI, 2018[42]; Kansal 2021[34]; *Market Scan data reported in Kansal 2021[70]	Bluebird bio data on file[41]; Kulozik et al., 2021[33]

LIC: liver iron concentration, NA: not available, SC: subcutaneous

* Value not available in primary data source

† Median (range)

‡ Median (IQR)

§ low iron, <7 mg/g; moderate iron, 7–15 mg/g; high iron, ≥15 mg/g

Myocardial T2*: low iron, >20 ms; moderate iron, 10–20 ms; high iron, <10 ms

¤ patients up to 19 years of age

** low iron, ≤1,000 ng/mL; moderate iron, 1,000–2,500 ng/mL; high iron, >2,500 ng/mL

E2. Model Inputs and Assumptions

Model Inputs

Our model includes several assumptions stated in Table E2.

Table E2.1. Key Model Inputs

Assumption	Rationale
Real world cohort study sources were used to characterize the model cohort.	Larger sample sizes were available from cohort studies and experts suggested wider possible age bands will consider beti-cel therapy, if available.
The baseline distribution of iron overload risk categories was consistent between beti-cel and SOC arms. Patients entering the model in the transfusion dependent health state retained this distribution of iron overload for the duration of the model. Patients entering the model in the transfusion independent health state progressed through an iron normalization period of five years for cardiac iron, liver iron, and serum ferritin where a disutility aligned with the TD state was applied. At the end of the iron normalization period, patients aged 2 to 11 years of age were considered at no risk of complications and patients ≥12 years were considered at "low risk" of complications.	Manufacturer submitted data and longitudinal cohort studies suggest no strong evidence of increases in the proportion of iron overload severity over time. A five-year iron normalization period was deemed reasonable based on data suggesting that the median time to achieve target ferritin levels (<300ng/mL or <500ng/mL) for individuals with baseline ferritin levels of ≥2500ng/mL was 64 months and 65 months, respectively.[37] Finally, after a normalization period, evidence suggests serum ferritin may remain above the reference range. This risk is likely to vary by age, and thus, we assigned "low risk" of complications rather than zero risk for patients aged ≥12 years.[25,38]
Complications modeled included cardiac, liver, diabetes, and hypogonadism. Annualized risks were derived from real world evidence and contingent upon baseline iron levels.	Cardiac, liver and endocrine complications are primary comorbidities resulting from high iron associated with beta thalassemia.[14,25]
The base-case risk of death from beti-cel infusion was 1.4% and was tested in sensitivity and scenario analyses.	Experts suggested that mortality seen with autologous HSCT would be the best proxy for what may be expected with beti-cel in clinical practice. Literature-based estimates for acute risk of death from autologous HSCT was found to be 2.8%;[39] however, this estimate was derived from a population with a more severe disease. Input from clinical experts suggested that acute risk of death from beti-cel for TDT is likely to be 1 to 2%. Consequently, an estimate of 1.4% was deemed a reasonable estimate based on the available evidence and clinical expert opinion. We explored alternate assumptions in sensitivity and scenario analyses.
At year seven 0.271% of patients reverted to the TD health state (with half the baseline frequency of transfusions per year) and continued at a rate of 0.271% per year. This rate of reversion resulted in approximately 10% of patients reverting to TD by the end of the lifetime time horizon.	The long-term durability of beti-cel treatment effect is unknown. Trial data suggest that all patients who have achieved TI from beti-cel have remained TI; however, these data are based on a limited number of patients (n=32 in Phase III trials) and limited duration of time (7 years of data for 3 patients receiving beti-cel).[7] We heard from an expert in gene therapy that it

Assumption	Rationale
	would be theoretically possible for patients to revert to TD if the population of infused stem cells that were not genetically modified became clonally dominant; it was estimated that over a lifetime post-treatment, approximately 10% of patients would revert to TD. Other expert opinion suggested assuming 0% reversion and this was explored in a scenario analysis.
Percentage of patients adherent to chelation therapy was dependent on the type of chelator used and did impact the cost of treatment. No impact on treatment effectiveness or patient utility was anticipated for patients who are not 100% adherent but remain within a range of good adherence (e.g., 95%). Adherence less than 100% is meant to represent the duration of time where the chelation prescription is not filled by the patient.	Evidence suggested that adherence to chelation therapy varies by type of chelator (3% for patients taking combination therapy to 23% for patients taking deferasirox).[40] Lack of 100% adherence to chelation therapy was expected to be intermittent and not substantially affect patient outcomes given the assumption (above) that iron overload status remains constant for TD patients.
Patients in beti-cel trials who start the process of pre-transplant assessments and preparation but do not proceed with treatment are included in the model.	Preparation for beti-cel transplant (e.g., assessments, tests, visits) incur additional costs that should be accounted for in the model.
The treatment effect of beti-cel determined the proportion of patients entering the transfusion independent and dependent health states of the Markov model.	The primary endpoint of the trial was achievement of transfusion independence, which is defined, in part, as having not received RBC transfusions for 12 months or longer.[25]
Mortality was modeled using age and sex specific background mortality rates modified by an increased risk of death due to transfusion dependence (standardized mortality ratio [SMR] 3.9), transfusion independence (SMR 1.25) and cardiac complications (13% risk of death). The transfusion dependent SMR of 3.9 was assumed to account for increased risk of death due to liver and endocrine complications.	Risks associated with ongoing transfusions and chelation therapy, myeloablative conditioning for patients receiving beti-cel, and comorbidities associated with high iron resulted in increased risk of mortality compared to the general population.
The cycle length of the model is one year.	Given the chronic nature of beta thalassemia, a cycle length of one year was expected to appropriately capture health outcomes and costs and allow for sufficient flexibility to explore our planned sensitivity and scenario analyses.
For model inputs with no evidence-based specified uncertainty range we used a range of +/- 20%.	Inclusion of parameter uncertainty within one-way and probabilistic analysis allowed for a reasonable characterization of uncertainty.

HSCT: hematopoietic stem cell transplant, QoL: quality of life, RBC: red blood cell, SMR: standardized mortality ratio, SOC: standard of care, TDT: transfusion-dependent β-thalassemia

Model Inputs

Key model inputs included clinical probabilities, utility values, and health care costs as outlined in Tables E2.2 to E2.7 below.

Clinical Inputs

The primary measure of clinical efficacy was consistent with the beti-cel phase III trial endpoint of the proportion of the intention-to-treat (ITT) cohort that achieved transfusion independence (Table E2.2.). Transfusion independence was achieved by 34/38 (89.5%) of the patient population.

Table E2.2. Details of Primary Clinical Efficacy Endpoint

Treatment Phase	Total (Phase III Trial Data)
N (meeting inclusion criteria)	43
n (%) Underwent Apheresis	43 (100.0)
Did not continue, n (%)	2 (4.7)
n (%) Underwent Conditioning	41 (95.3)
Beti-cel infusion, n (%)	41
Number of "***unevaluable***" patients	3
Transfusion Independence, n/N (%)	34/38 (89.5)*
Source	Data on file[41]

N: total number, n: number

* Evaluable patients (i.e., patients with at least 12 months of transfusion independence were considered evaluable)

Iron Complications

The baseline characteristics of the model cohort describe the proportion of a natural history cohort within three levels of iron overload risk related to serum ferritin, liver iron concentration, and myocardial T2.[42] Manufacturer submitted data and longitudinal cohort studies suggest no strong evidence of increases in the proportion of iron overload severity over time. Therefore, we assumed that the cohort will not change in their distribution of iron overload risk categories for those remaining in the TD state. The annualized risk of liver complications, cardiac complications, diabetes, and hypogonadism was based on the three risk levels and were generated from natural history (real world) evidence sources for risk of cardiac complications,[42] liver complications,[70] and risk of diabetes and hypogonadism (Table E2.3.).[43]

For those who achieved transfusion independence, a transition period was assumed after which time, individuals shifted to the lowest level of iron overload risk for serum ferritin, liver iron concentration, and myocardial T2. The model incorporated a five-year period of cardiac iron, liver iron, and serum ferritin normalization following successful transplantation. Given the limited data available for optimal normalization periods post-beti-cel infusion, a five-year time period was assumed based on data from patients who underwent an allogeneic HSCT.[37] In this study, patients with baseline ferritin levels of ≥ 2500ng/mL achieved target ferritin levels (<300ng/mL or <500ng/mL) after 64 months and 65 months, respectively.[37]

Table E2.3. Annualized Risk of Complications

Severity of Overload and Complication Risk	Value	Source
Low Cardiac Complications*	0.0023	NERI[42] and Kansal et al., 2021[34]
Moderate Cardiac Complications*	0.0177	NERI[42] and Kansal et al., 2021[34]
High Cardiac Complications*	NA	NA
Low Liver Complications†	0	Marketscan and Kansal et al., 2021[34]
Moderate Liver Complications†	0	Marketscan and Kansal et al., 2021[34]
High Liver Complications†	0.0198	Marketscan[70] and Kansal et al.[34]
Relative risk for increased age (year) for diabetes	1	Assumption
Relative risk for diabetes given moderate or high Myocardial T2*	19.3	Ang et al.[43]
Relative risk for diabetes given high serum ferritin‡	14.8	Ang et al.[43]
Relative risk for increased age (year) for hypogonadism	1	Assumption
Relative risk for hypogonadism given moderate or high Myocardial T2*	3.9	Ang et al.[43]
Relative risk for hypogonadism given high serum ferritin‡	2.9	Ang et al.[43]

NA: Not applicable

* Low iron, >20 ms; moderate iron, 10–20 ms; high iron, <10 ms

† Low iron, <7 mg/g; moderate iron, 7–15 mg/g; high iron, ≥15 mg/g

‡ Low iron, ≤1,000 ng/mL; moderate iron, 1,000–2,500 ng/mL; high iron, >2,500 ng/mL

Discontinuation

Discontinuation for a one-time gene therapy was not a consideration beyond the intention-to-treat model analysis and assumptions around the durability of beti-cel.

Mortality

During stakeholder correspondences, experts suggested that mortality seen with autologous stem cell transplant would be the best proxy for what may be expected with beti-cel in clinical practice. Although some experts suggested that this mortality risk after transplant may be as high as 5%, due to no observed deaths in the beti-cel beta thalassemia trials, the base-case risk of death was 1.4% (0% to 5% range for use in sensitivity analyses).[39] Beyond the short-run potential harms associated with procedures similar to beti-cel, the long-run risk of mortality was also an important model input. The long-run mortality approach followed the general framework outlined in Kansal et al.[34] First, we estimated all-cause background annual risk of death that is age and sex specific from the Centers for Disease Control and Prevention.[71] Then, we applied a standardized mortality ratio to this background annualized mortality risk based on those who are not experiencing cardiac complications and who are in the TD health state (standardized mortality ratio [SMR] = 3.9) or who are in the TI health state (SMR = 1.25). Note that the SMR of 3.9 was based on prior cost-effectiveness analyses in beta thalassemia[72] whereas the SMR for TI was consistent with the Kansal

et al. assumption of a 25% increased risk over that of the general population to account for potential long-term effects of undergoing myeloablative conditioning.[34] For those experiencing cardiac complications, we assumed an annualized probability of death of 0.13. The cardiac death risk was an assumption consistent with Kansal et al., that may overestimate death in those of younger ages with cardiac complications but may underestimate death in those of older age. Finally, note that we assumed the annualized SMR of 3.9 includes the risk of death for non-cardiac complications (liver complications and endocrine complications). The SMR model input sensitivity was explored through uncertainty analyses.

Adverse Events

Adverse events (AEs) associated with beti-cel infusion or preparation for infusion included potential infertility from myeloablative conditioning (31% in males; 57% in females based on gonadal function measures taken after bone marrow transplantation for sickle cell disease)[34,73] and engraftment failure. The model base case assumed no engraftment failures based on the clinical trial data. All other AEs associated with pre-infusion, infusion, and immediate post-infusion monitoring were expected to be managed in hospital and were accounted for in the costs and disutilities associated with beti-cel transfusion.

No AEs were included for AEs associated with RBC transfusion and chelation therapy as they were assumed to be accounted for within TD health state disutilities and monitoring costs.

Health State Utilities

Health state utilities were derived from publicly available literature and/or manufacturer submitted data and we used consistent health state utility values across treatments (i.e., for beti-cel and SOC) evaluated in the model. Age and sex specific utilities[74] were used over the lifetime of the model with disutilities applied to account for level of transfusion dependence. Health state disutilities were based on a UK study of individuals with TDT.[40] Disutilities were calculated based on the difference between the utility score reported for the UK general population (0.91) and the utility scores for TDT estimated from 165 patients with a median age of 24.1 years (25% <12 years of age) and a median duration of TDT of 9.5 years.[40] The EQ-5D-3L and EQ-5D-Y for adult and pediatric patients, respectively, were used to derive utility estimates using the UK-based value set.[40] Research has found that patients receiving subcutaneous chelation (deferoxamine) experience greater decreases in quality of life compared to oral chelation. Given that 14% of individuals in Shah 2021[40] were receiving subcutaneous deferoxamine, we assumed that the overall disutility for the transfusion dependent health state, on average, accounts for the additional disutility associated with subcutaneous chelation therapy. It is expected that oral chelation will the preferred option moving forward; therefore, the assumed disutility may slightly overestimate the disutility associated with chelation therapy. We used utility data reported in Matza 2021[44] – a vignette-based study using time trade off methods from a UK sample with a mean age of 43.2 years – for intervention-

related disutilities; however, for the transfusion dependent health state disutility (as described above), we deemed EQ-5D data collected from patients with TDT to be a preferred source.[40] Health-related quality of life (HRQoL) data collected in the Northstar-2 and -3 trials were limited by small sample sizes.[26] No additional disutilities will be included for transfusion and chelation impacts or AEs as they are assumed to be accounted for within health state disutilities.

We also included disutilities for potential infertility from myeloablative conditioning, and disutilities for complications resulting from high iron (i.e., cardiac, liver, and endocrine complications). Disutility for infertility was accounted for in the disutility associated with the transfusion independent health state and transfusion dependent health state (for individuals that do not achieve transfusion independence from beti-cel) and was assumed to apply over the lifetime of the model. Disutilities for cardiac, liver, and endocrine complications were based on a study assessing HRQoL in patients with beta thalassemia in Iran.[45] This study used the EQ-5D-3L and a US time trade off value set to obtain mean health utility scores from 512 patients with a mean age of 22 years according to the presence or absence of cardiac, liver, and endocrine complications.[45]

Caregiver disutility (-0.03) (for one care giver per patient ≤26 years of age in the transfusion dependent health state and during the normalization period post-infusion) was included in the societal perspective analysis. The disutility value was based on the same source as used for the derivation of disutilities for the transfusion dependent health state.[40]

Disutility values are reported in Table E2.4.

Table E2.4. Disutility Values

	Disutility	Source
Health State		
Transfusion dependent (oral and subcutaneous chelation)	-0.22 (age ≥16 years) -0.18 (<16 years)	Shah et al., 2021 [40] (Age ≥16 years; n=94) (Age 4 to 7 years; n=9) Assumption (Ages 8 to 15 years; -0.18)
Transfusion independent	-0.02	Kansal et al., 2021 (Assumption)[34]
Intervention (Beti-cel)		
Beti-cel infusion (one year)	-0.31	Matza et al., 2021[34]
Complications from Iron Overload		
Cardiac	-0.03	Seyedifar et al., 2015[45]
Liver	-0.03	Seyedifar et al., 2015[45]
Diabetes	-0.04	Seyedifar et al., 2015[45]
Hypogonadism	-0.04	Seyedifar et al., 2015[45]

IV: intravenous

*Potential complications of myeloablative conditioning

Economic Inputs

The model included direct medical costs, including treatment acquisition and administration costs, treatment and condition related monitoring costs, and costs due to complications from iron overload (cardiac, liver, and endocrine complications). Future unrelated health care costs were also included based on age-adjusted health care costs over the lifetime of the model.[75] Costs associated with patient and caregiver productivity loss were included in a separate analysis. Where applicable, all costs used in the model were updated to 2021 US dollars.

Drug Acquisition Costs

Beti-cel is currently under regulatory review in the US and therefore does not have a published price. The anticipated acquisition cost of beti-cel was based on a published press release estimate shared by the manufacturer of beti-cel ($2.1 million US).[9] This cost is based on a single intravenous infusion of at least 5.0 × 106 CD34+ cells/kg.[41] Beti-cel acquisition cost was modeled in the base case using an 80% payback option if patients do not achieve transfusion independence. To maintain all intervention costs in present value and to avoid potential confusion over discounting, we assumed that all beti-cel payments and paybacks occur at the start of the model horizon. For example, if 80% were assumed to achieve transfusion independence by Year 5 whereas 20% were assumed to fail after the beti-cel infusion (up to Year 5), the expected value base-case payment per person who received beti-cel = ($2,100,000) * 0.80 + ($2,100,000 * 0.2) * 0.20 = $1,764,000. Subsequent threshold-based prices and eventual Health Benefit Price Benchmarks will be based on the expected value payment per person who undergo beti-cel transplant.

We also included costs of preparation for beti-cel infusion which includes pre-procedure visits and tests, a period of hyper transfusion, apheresis, and myeloablative conditioning. We assumed that

22% of patients require two cycles of mobilization and apheresis to obtain sufficient cells.[25] Post-infusion monitoring requirements and frequency followed the approach used in Kansal 2021.[34] Resource use and costs associated with beti-cel are reported in Tables E2.5.-E2.7.

Table E2.5. Resource Use Associated with Intervention

	Duration	Frequency	Dose	Notes/Source
Pre-procedure visits and tests*	NA	1 time	NA	FINOSE 2019[76], NICE 2021[77,78]
Pre-transplant hyper transfusion	90 days	1 x every 2 weeks	NA	Kansal et al., 2021[34]
Filgrastim for mobilization	5 days	1 x per day	10 mcg/kg	Kansal et al., 2021[34]
Filgrastim home administration	5 days	1 visit per day	NA	Kansal et al., 2021[34]
Plerixafor for mobilization	2 days	1 x per day	0.24 mg/kg	Kansal et al., 2021[34]
Apheresis procedure	1 day	1 time	NA	Kansal et al., 2021[34]
Hospitalization for apheresis procedure	1 day	1 time	NA	Kansal et al., 2021[34]
Prophylaxis for veno-occlusive disease (Ursodeoxycholic acid)	90 days	2 x per day	300 mg	Kansal et al., 2021[34]
Prophylaxis for seizures (levetiracetam)	6 days	2 x per day	500 mg	Locatelli et al., 2021;[25] Assumption – during and 1 day prior and 1 day after busulfan
Fertility preservation	NA	1 time	NA	Assumption
Myeloablative conditioning with busulfan (≥18 years)	4 days	1 x per day (3-hour IV infusion)	3.2 mg/kg/day	Bluebird bio, data on file[41]
Myeloablative conditioning with busulfan (<18 years)	4 days	4 x per day (2-hour infusion)	0.8 mg/kg/day	Bluebird bio, data on file[41]
Hospitalization for conditioning	At least 6 days	1 time	NA	EMA summary[79]
Hospitalization for infusion/post-infusion	3 to 6 weeks	1 time	NA	EMA summary[79]
Post-infusion monitoring†	Years 1-6	Variable	NA	Kansal et al., 2021[34]

mg: milligrams, NA: not applicable

*Pre-procedure tests include: one outpatient visit, one blood test, one genotyping test, one liver biopsy, and one bone marrow analysis.

†Based on the post-transplant monitoring frequency reported in Kansal 2021.[34]

Table E2.6. Unit Costs of Resource Use Associated with Intervention

Resource	Cost	Notes	Source
Outpatient visit	$224.25	HCPCS 99205 (Comprehensive outpatient office visit)	Centers for Medicare and Medicaid Services - Physician Fee Schedule[80]
Blood test	$10.56	HCPCS 80053 (Blood test, comprehensive group of blood chemicals)	Centers for Medicare and Medicaid Services – Clinical Laboratory Fee Schedule (22CLABQ1)[81]
Genotyping test	$324.58	HCPCS 81364 (Gene analysis [hemoglobin, subunit beta] full sequence analysis.)	
Liver Biopsy	$2,250	US-based	Allen et al., 2018[82] (Assumption)
Bone marrow analysis	$143.57	HCPCS 88237 (tissue culture for tumor disorders of bone marrow and blood cells)	Centers for Medicare and Medicaid Services – Clinical Laboratory Fee Schedule (22CLABQ1)[81]
Home administration of filgrastim	$646.20	Based on 2020 Physician's Fee and Coding Guide	Kansal et al., 2021[34]
Apheresis procedure	$254.16	Based on 2020 Physician's Fee and Coding Guide	Kansal et al., 2021[34]
Hospitalization for apheresis procedure	$3,935.83	Based on estimates from the HCUP NIS	Kansal et al., 2021[34]
Fertility preservation	$10,000	Medically assisted procreation cost of $10,000 utilized by 60% of patients*	Kansal et al., 2021[34]
Hospitalization for transplant (<18 years)	$128,298	Based on estimates from the HCUP NIS	Kansal et al., 2021[34]
Hospitalization for transplant (≥18 years)	$71,443		
Post-transplant monitoring (Year 1)	$8,883	Includes visit with HCP, laboratory tests and imaging studies	Kansal et al., 2021 [34]
Post-transplant monitoring (Year 2)	$8,772		
Post-transplant monitoring (Years 3-6)	$7,734		

HCPCS: Healthcare Common Procedures Coding System

*57% of females and 31% of males assumed infertile due to myeloablative conditioning.[34]

Ongoing Treatment Costs

Ongoing treatment costs for transfusion dependence included the costs of transfusions, iron chelation therapy, annual monitoring costs for chelation therapy, and any relevant complication costs (cardiac, liver, diabetes, and hypogonadism). We assumed that patients <18 years have an average of 14.95 transfusions per year, and patients ≥18 years have an average of 16.1 transfusions per year which is based on Market Scan data reported in Kansal 2021.[70] The percentage of patients receiving each type of chelation agent and their costs also followed Market Scan data reported in

Kansal 2021 and inflated to 2021 US dollars.[70] Annual acquisition cost of chelation for patients aged < 18 years ranged from $22,550 for deferasirox to $37,191 for deferiprone and for patients aged ≥18 years ranged from $45,100 for deferasirox to $74,382 for deferiprone. Combination deferasirox and deferiprone was the costliest, estimated to be $82,291 annually for patients aged <18 years and $168,340 annually for patients aged ≥18 years. Deferoxamine mesylate was the least costly, estimated to be $1,970 annually for patients aged <18 years, and $5,253 annually for patients aged ≥18 years with an annual administration cost of $6,389.

Patients in the TI health state incurred costs during the iron normalization period, (Year 1 to 5) post-transplant monitoring costs (Years 1 to 6 and limited annual monitoring costs Year 7+ - e.g., blood tests), and any relevant complication costs (cardiac, liver, diabetes, and hypogonadism).

Complication Costs

Occurrence of cardiac, liver, or endocrine complications were assumed to incur costs for the lifetime of the model. Annual costs followed the estimates provided in Kansal 2021[34] which include cardiac, liver, and other costs for Year 1 and Year 2 onwards. Costs were inflated to 2021 US dollars and are reported in Table E2.8.

Table E2.7. Complication Costs

Complication, year	Cost	Notes	Source
Cardiac Complications, Year 1	$7,980.74	US MarketScan data and Karnon 2012 (UK based study)	Kansal 2021[34]
Cardiac Complications, Year 2+	$6,346.73		
Liver Complications, Year 1	$1,944.77	US MarketScan data and NHS 2015-2016	
Liver Complications, Year 2+	$3,001.52		
Endocrine Complications, Year 1	$1,059.85	US MarketScan data and Karnon 2012 (UK based study)	
Endocrine Complications, Year 2+	$1,636.07		

Productivity Costs and Other Indirect Costs

We included costs associated with lost productivity due to illness for both patients and caregivers in a modified societal perspective. We assumed one caregiver per patient up to the age of 26 years and our estimates for lost time from work was applied for all patients regardless of age to capture potential impacts to educational attainment and non-market productivity (i.e., lost productivity was included for school-age children and individuals in retirement age). Estimates for lost productivity were derived from a prospective study assessing patient and caregiver reported burden for TDT.[83] This study captured the mean number of daily hours that patients (23% US) spend on managing their illness. This study found that patients spend a total of 688 hours managing illness per year (including for example, time spent on transfusions, traveling to infusions, preparing and taking chelators, making appointments, organization insurance payments, etc.).[83] Using a mean hourly wage of $27.07/hour[84] (based on a mean of all US occupations), this would equate to approximately $18,624 lost annually for both patient and caregiver. This finding aligns well with findings from a UK-based cross-sectional survey of patients and caregivers that reported on absenteeism, presenteeism, and overall productivity loss associated with TDT,[40] and reflects our consultation with patients and patient groups which suggest that time spent managing their illness is essentially a "part time job."

Model Outcomes

Model outcomes included total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained, transfusion dependent years averted, and total costs for each intervention over a lifetime time horizon. Costs, LYs, QALYs, and evLYs were also reported by the health state to understand the contribution of different costs elements. Total costs, LYs, QALYs, and evLYs were reported as discounted values, using a discount rate of 3% per annum.

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[85]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

E3. Results

Base-Case Results

Table E3.1. Undiscounted Results for Beti-cel Compared to SOC

Treatment	Treatment cost*	Transfusion and Chelation Costs†	Total Cost	TD Years	QALYs	Life Years	evLYs
Health Care System Perspective							
Beti-cel	$1,900,000	$420,000	$3,310,000	5.77	37.11	49.10	38.16
SOC		$3,250,000	$4,060,000	38.36	23.14	38.36	23.14
Modified Societal Perspective							
Beti-cel	$1,900,000	$420,000	$3,540,000	5.77	37.00	49.10	38.04
SOC		$3,250,000	$4,850,000	38.36	23.02	38.36	23.02

evLY: equal value life year, QALY: quality adjusted life years, SOC: standard of care, TD: transfusion dependent

* Only includes beti-cel acquisition cost (i.e., excludes workup, preparation, transplant, post-transplant monitoring and normalization period costs).

† Only includes transfusion costs and chelation acquisition costs (i.e., excludes chelation administration and monitoring costs).

Table E3.2. Disaggregated Beti-cel and SOC Intervention-related Costs (Base case, discounted)

Treatment	Beti-cel workup	Beti-cel transplant	Beti-cel acquisition	Post-beti-cel monitoring	Post-beti-cel iron normalization	Transfusion	Chelation acquisition	Chelation administration and monitoring
Beti-cel	$24,000	$97,000	$1,902,000	$43,000	$165,000	$91,000	$127,000	$26,000
SOC	$-	$-	$-	$-	$-	$757,000	$1,060,000	$221,000
Incremental*	$24,000	$97,000	$1,902,00	$43,000	$165,000	$(666,000)	$(933,000)	$(195,000)

evLY: equal value life year, QALY: quality adjusted life years, SOC: standard of care, TD: transfusion dependent

*Note: Incremental may not total beti-cel minus SOC costs due to rounding.

Table E3.3. Disaggregated Non-intervention-related Costs (Base case, discounted)

Treatment	Cardiac Complication Costs	Liver Complication Costs	Endocrine Complication Costs	Unrelated Medical Costs	Patient and Caregiver Productivity Costs
Beti-cel	$3,100	$2,000	$18,200	$232,900	$182,300
SOC	$5,900	$4,500	$19,800	$190,900	$482,200
Incremental*	$(2,800)	$(2,500)	$(1,600)	$42,000	$(299,900)

evLY: equal value life year, QALY: quality adjusted life years, SOC: standard of care, TD: transfusion dependent

*Note: Incremental may not total beti-cel minus SOC costs due to rounding.

E4. Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. The key inputs and results from the one-way sensitivity analyses can be found in Tables E4.1-E4.5. Figures E4.1-E4.3 present this information graphically by way of a tornado diagram.

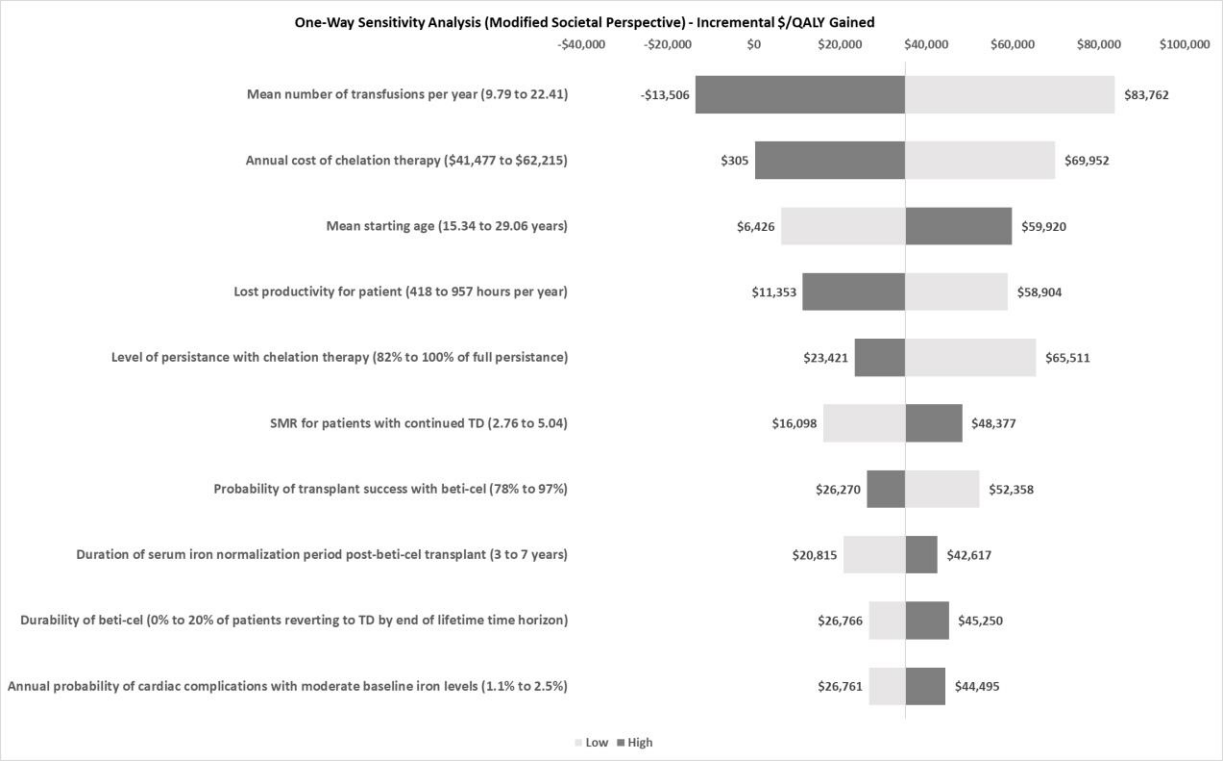
Table E4.1. Tornado Diagram Inputs and Results for Beti-cel versus SOC (Health Care Sector Perspective)

	Lower Input Incremental CE Ratio	Upper Input Incremental CE Ratio	Lower Input*	Upper Input*
Mean number of transfusions per year	$144,573	$47,285	9.79	22.41
Annual cost of chelation therapy	$130,760	$61,099	$41,477	$62,215
Mean starting age	$77,936	$129,140	15.34	29.06
Level of persistence with chelation therapy	$126,319	$84,219	82%	100%
Utility decrement for the TD health state	$80,169	$119,403	-0.29	-0.15
Probability of transplant success with beti-cel	$114,276	$86,497	78%	97%
Duration of serum iron normalization period post-beti-cel transplant	$77,817	$105,403	3	7
Durability of beti-cel (0% to 20% of patients reverting by the end of the lifetime time horizon)	$86,128	$107,724	0%	20%
SMR for patients with continued TD	$85,392	$103,149	2.76	5.04
Annual cost of monitoring for chelation therapy	$102,512	$89,347	$6,677	$10,015

CE: cost-effectiveness, SMR: standardized mortality ratio, TD: transfusion dependent

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Figure E4.1. Tornado Diagram (Modified Societal Perspective)



SMR: standardized mortality ratio, TD: transfusion dependent, TI: transfusion independence, QALY: quality adjusted life year

Table E4.2. Tornado Diagram Inputs and Results for Beti-cel versus SOC (Modified Societal Perspective)

	Lower Input Incremental CE Ratio	Upper Input Incremental CE Ratio	Lower Input*	Upper Input*
Mean number of transfusions per year	$83,762	($13,506)	9.79	22.41
Annual cost of chelation therapy	$69,952	$305	$41,477	$62,215
Mean starting age	$6,426	$59,920	15.34	29.06
Lost productivity for patient	$58,904	$11,353	418	958
Level of persistence with chelation therapy	$65,511	$23,421	82%	100%
SMR for patients with continued TD	$16,098	$48,377	2.76	5.04
Percentage of patients achieving TI from Beti-cel	$52,358	$26,270	78%	97%
Duration of serum iron normalization period post-beti-cel transplant	$20,815	$42,617	3	7
Durability of beti-cel (0% to 20% of patients reverting by the end of the lifetime time horizon)	$26,766	$45,250	0%	20%
Annual probability of cardiac complications with moderate baseline iron levels	$26,761	$44,495	1.1%	2.5%

CE: cost-effectiveness, SMR: standardized mortality ratio, TD: transfusion dependent

*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Results are presented in Table E4.3 and Table E4.4.

Table E4.3. Results of Probabilistic Sensitivity Analysis for Beti-cel versus SOC (Health Care System Perspective)

	Beti-cel Mean	SOC Mean	Incremental
Costs	$2,728,000	$2,234,000	$494,000
QALYs	18.68 (16.95 to 20.29)	13.76 (11.69 to 15.72)	4.92 (3.67 to 6.21)
evLYs	18.95 (17.24 to 20.54)	13.76 (11.69 to 15.72)	5.19 (3.90 to 6.49)
Incremental CE Ratio ($/QALY)			$100,000
Incremental CE Ratio ($/evLY)			$95,000

CE: cost-effectiveness, evLY: equal value life year, QALY: quality adjusted life years, SOC: standard of care

Table E4.4. Results of Probabilistic Sensitivity Analysis for Beti-cel versus SOC (Modified Societal Perspective)

	Beti-cel Mean	SOC Mean	Incremental
Costs	$2,907,000	$2,744,000	$163,000
QALYs	18.60 (16.97 to 20.16)	13.68 (11.61 to 15.70)	4.92 (3.64 to 6.16)
evLYs	18.87 (17.26 to 20.38)	13.68 (11.61 to 15.70)	5.19 (3.87 to 6.46)
Incremental CE Ratio ($/QALY)			$33,000
Incremental CE Ratio ($/evLY)			$31,000

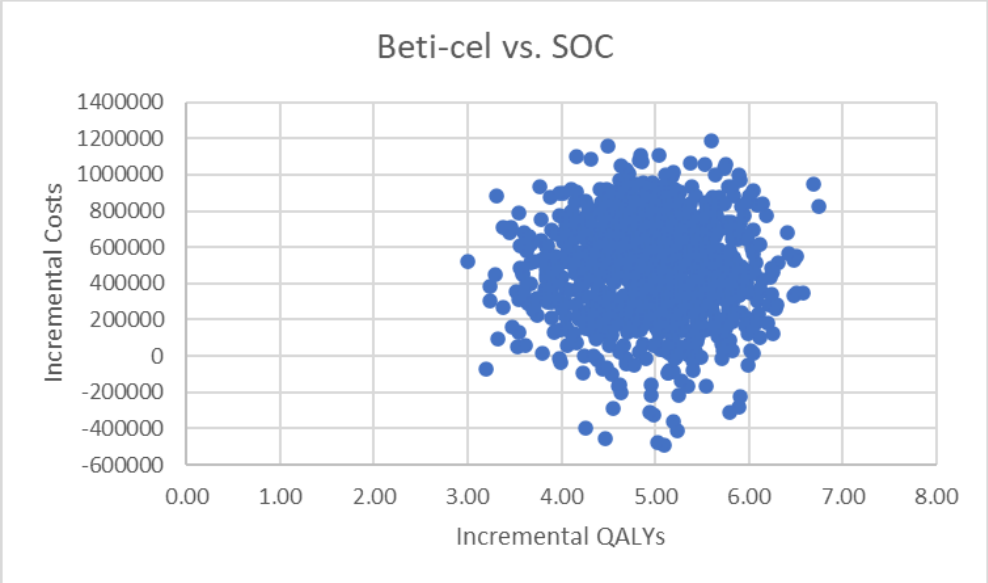
CE: cost-effectiveness, evLY: equal value life year, QALY: quality adjusted life years, SOC: standard of care

Table E4.5. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Beti-cel Versus SOC

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Health Care System Perspective				
Beti-cel vs. SOC	21%	52%	85%	98%
Modified Societal Perspective				
Beti-cel vs. SOC	63%	91%	99%	100%

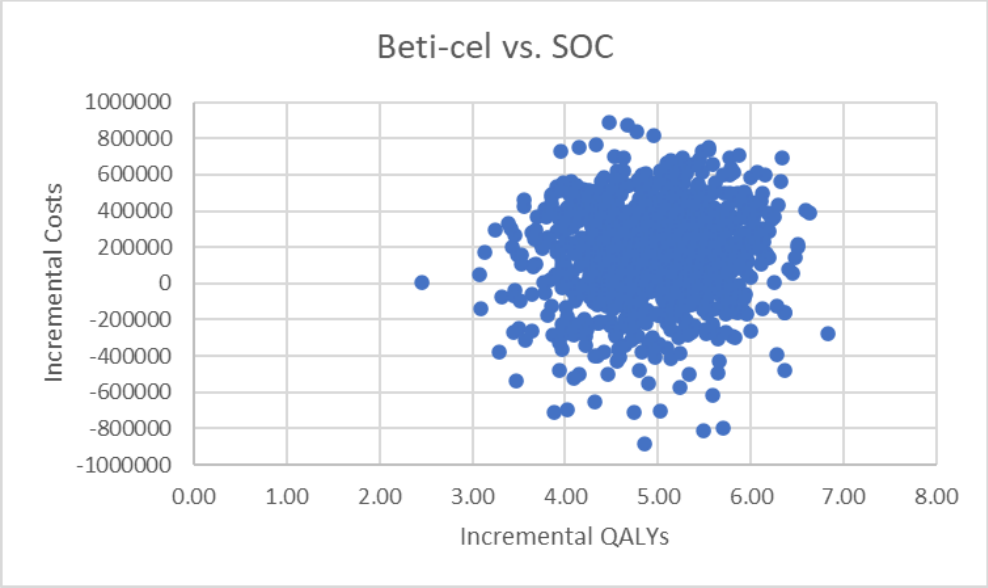
evLY: equal value life year, QALY: quality adjusted life years, SOC: standard of care

Figure E4.2. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud, Health Care System Perspective



QALY: quality adjusted life year, SOC: standard of care

Figure E4.3. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud, Modified Societal Perspective



QALY: quality adjusted life year, SOC: standard of care

E5. Scenario Analyses

Scenario Analysis 3: Cost-offset Cap Scenario

Table E5.1. Scenario Analysis Results for the Cost-offset Cap Scenario (aligned with base-case results)

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD year averted
Health Care System Perspective					
Beti-cel	SOC	$95,900	$90,800	$167,600	$24,700
Modified Societal Perspective					
Beti-cel	SOC	$35,100	$33,300	$61,400	$9,100

evLY: equal value life year, QALY: quality adjusted life year, SOC: standard of care, TD: transfusion dependent

Scenario Analysis 5: Phase III Baseline Patient Characteristics

We conducted a scenario analysis based on a baseline cohort of patients that have characteristics consistent with the Phase III trial data for beti-cel (e.g., mean age, percentage female, and level of transfusion dependence). Results are presented in Table E5.2.

Table E5.2. Scenario Analysis Results using Phase III Baseline Patient Characteristics

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD year averted
Health Care System Perspective					
Beti-cel	SOC	$68,100	$64,800	$129,400	$17,100
Modified Societal Perspective					
Beti-cel	SOC	Less costly, more effective	Less costly, more effective	Less costly, more effective	Less costly, more effective

evLY: equal value life year, QALY: quality adjusted life year, SOC: standard of care, TD: transfusion dependent

Scenario Analysis 6 – 5- and 10-year Time Horizons

We conducted a scenario analysis based on alternative model time horizons (5 years and 10 years). Results are presented in Table E5.3 and Table E5.4.

Table E5.3. Scenario Analysis Results Based on a 5-Year Time Horizon

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD year averted
Health Care System Perspective					
Beti-cel	SOC	More costly, less effective	More costly, less effective	More costly, less effective	$369,300
Modified Societal Perspective					
Beti-cel	SOC	More costly, less effective	More costly, less effective	More costly, less effective	$363,200

evLY: equal value life year, QALY: quality adjusted life year, SOC: standard of care, TD: transfusion dependent

Table E5.4. Scenario Analysis Results Based on a 10-Year Time Horizon

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained	Cost per TD year averted
Health Care System Perspective					
Beti-cel	SOC	$4,567,100	$4,567,200	More costly, less effective	$183,100
Modified Societal Perspective					
Beti-cel	SOC	$4,275,200	$4,275,300	More costly, less effective	$171,900

evLY: equal value life year, QALY: quality adjusted life year, SOC: standard of care, TD: transfusion dependent

E6. Heterogeneity and Subgroups

Due to small sample sizes in the beti-cel studies, we did not propose any pre-specified subgroup analyses. However, we note that certain model cohort characteristics, such as age, transfusion frequency, and iron overload severity and chelation utilization, may influence the cost-effectiveness findings. We programmed the model to accommodate age subgroups as specified in Table E1.2. We further explored the impact of model cohort characteristics on the cost-effectiveness findings through one-way sensitivity analyses and scenario analyses (see below for scenario list).

E7. Model Validation

Presented in Table E7.1 are the ICER-derived replication findings of the patient-level microsimulation developed by Kansal et al. 2021. Using our cohort-level model, and the assumptions and data inputs reported in Kansal et al. 2021, our model predicted an incremental cost-effectiveness ratio within 5% of Kansal et al.'s 2021 findings.

Table E7.1. ICER Replication Findings versus Kansal et al. 2021 (Discounted)

	ICER Replication		Kansal et al., 2021		% Difference in incremental (Beti-cel vs. SOC) Findings*
	Beti-cel	SOC	Beti-cel	SOC	
Effectiveness					
LYs	26.14	22.26	25.64	21.82	1.6%
QALYs	21.54	14.55	19.96	13.11	1.9%
Costs					
Beti-cel	$1,746,169	--	$1,704,985	--	2.4%
Pre/post beti-cel†	$252,666	--	$241,567	--	4.6%
Transfusion/Chelation	$305,348	$2,063,162	$308,718	$2,005,549	3.6%
Chelation AEs ‡	$238.00	$1,557	$238.00	$1,557	--
Infertility	$2,437	--	$2,532	--	3.7%
Complications	$20,412	$29,732	$18,981	$31,277	-24.2%
Total costs	$2,327,270	$2,094,451	$2,277,093	$2,038,384	-2.5%
ICER (/QALY gained) Beti-cel vs. SOC	--	$33,352	--	$34,848	-4.3%

*ICER replication vs. Kansal 2021.

† Includes pre-transplant, transplant, post-transplant monitoring, and iron chelation during normalization costs.

‡ Chelation AEs not included in the ICER cohort model. Assumed the same costs as Kansal et al., 2021 for the purposes of calculating total costs.

Prior Economic Models

To our knowledge there was only one other peer-reviewed cost-effectiveness analysis journal publication, conducted by Kansal et al.,[34] that assessed the cost effectiveness of beti-cel for the treatment of TDT. In addition, we identified a NICE appraisal[78] and an assessment by the Nordic collaboration of Finland, Norway and Sweden in Health Technology Assessment (FINOSE)[76] for beti-cel that are relevant for this current ICER review.

All evaluations took a health care system perspective and assessed total cost and outcomes over a lifetime time-horizon. The main focus of all identified reviews of beti-cel was transfusion independence, as well as iron overload as a driver for future cardiac, liver, and endocrine complications, which highlights the impact these complications have on morbidity and mortality in patients with beta thalassemia. As in any one-time gene therapy that is potentially curative, other themes across the above assessments suggest that cost-effectiveness results are sensitive to estimates of annual transfusion dependent utility and transfusion dependent costs (transfusion and chelation cost).

Kansal et al. evaluated beti-cel compared to SOC (including RBC transfusions and chelation therapy) by means of a microsimulation model that tracked patients with TDT.[34] Health states were defined by transfusion requirements (transfusion independence and transfusion dependence), and cardiac, liver, and serum iron levels, which can lead to iron-related complications and death. Transfusion

independence (defined as a weighted average total hemoglobin of at least 9 g/dL for at least 12 continuous months after transplantation) was a key effectiveness input in the model. In the base case, patients who achieved transfusion independence were assumed to no longer require chelation therapy after a normalization period, thus minimizing the risk of further iron-related complications. Results suggested that over a lifetime, treatment with beti-cel adds 6.9 QALYs when compared to SOC and an ICER of $34,833 per QALY gained. Total cost and outcomes were discounted at 3% per annum. Kansal et al., 2021 was a helpful starting point for building our de novo cohort-level model. Key differences between our base-case model and Kansal et al. include:

- we used a small but non-zero likelihood of acute death due to beti-cel (Kansal et al. assumed no added acute death risk beyond a lifetime SMR of 1.25 for patients who achieved TI);
- we used a very small but non-zero likelihood of patients who achieved TI to revert back to requiring transfusions (Kansal et al. assumed no reversion in their base case but did provide estimates in a scenario analysis);
- we used a 5-year duration for normalization for those who achieved TI (Kansal et al. assumed a 1-year duration for cardiac iron normalization and a 3-year duration for serum ferritin and liver iron);
- after the normalization period, we assumed that those older than 12 would remain at a low risk of iron-related complications (Kansal et al. assumed no risk after normalization across all ages).

The NICE assessment evaluated the cost effectiveness of beti-cel from an NHS perspective using a discrete event simulation approach. In contrast to our review and the assessment conducted by Kansal and colleagues, NICE included a third post-transplant health state, transfusion reduction, in addition to transfusion independence and transfusion dependence. Base-case results from the Evidence Review Group's (ERG) reanalysis suggested that over a lifetime, treatment with beti-cel adds 3.05 QALYs when compared to SOC. Results for the ICERs (£/QALY gained) were redacted. Total cost and outcomes were discounted at a rate of 3.5% in the ERGs reanalysis whereas the manufacturer used a 1.5% discount rate. A key difference between the ERG's reanalysis and our base-case incremental QALY finding of approximately 5.2 was in the disutility values assigned to the health states and NICE's inclusion of a transfusion reduction health state. In our analysis, the difference between TI and TD states in terms of utility was approximately 0.18 (0.18 higher in TI vs. TD) whereas the difference between TI and TD for the ERG's reanalysis was difficult to identify but based on one-way sensitivity analysis ranges appeared to be much smaller than 0.18. The larger this difference in utility is, the larger the modeled incremental QALYs over a lifetime will be. Further, the ERG's assignment of a proportion of treated patients to the transfusion reduction state (versus transfusion independence state) would further reduce the lifetime modeled health gains.

The FINOSE assessment was based on the manufacturer's dossier submission.[76] The base-case results from the manufacturer submitted model yielded 8.17 QALYs gained when compared to lifelong SOC. FINOSE raised concerns about whether transfusion independence would be sustained over a life-time time horizon. It was also noted that it would have been preferrable if HRQoL data were collected from the patients in the trials, rather than using a vignette study. Two scenario analyses were conducted by FINOSE, with and without survival gains (Scenario 1 and Scenario 2, respectively), for which three assumptions were adjusted. First, the manufacturer had estimated 20 RBC transfusions per year for patients with TDT, FINOSE found this to be an over-estimation as per international and Nordic treatment guidelines and reduced it to 15 RBC transfusions per year. Second, FINOSE assumed no difference in utility between oral and SC iron chelation therapy. Third, the percentage of patients on oral and SC iron chelation was assumed to be equal (50% each), as opposed to 70% SC and 30% oral treatment assumed by the manufacturer). Scenario 1 resulted in fewer QALYs gained (6.88) at a higher cost compared to the manufacturer's base case. Similarly, scenario 2 resulted in fewer QALYs gained (4.88) at a higher cost. FINOSE concluded that the results of the cost-effectiveness analysis for beti-cel were highly sensitive to the treatment success rate, its durability, as well as mortality and HRQoL inputs.

Admittedly, all modeling approaches may have similar goals of using the best-available evidence, but also require assumptions. Compared to the NICE ERG's reassessment, our approach assigns more lifetime health benefits to beti-cel (3.05 vs. 5.2 QALYs gained) whereas compared to Kansal et al., our approach assigns fewer lifetime health benefits to beti-cel (5.2 vs. 6.9 QALYs gained). Finally, we acknowledge that it is more difficult to compare cost savings across analyses given challenges in transferability and in changes to unit costs over time. We stress that potential cost savings are a key component of value in this assessment and therefore should be included in value assessment deliberations and policy making.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we applied incidence estimates for beta thalassemia (1 in 100,000 individuals; 0.001%)[47] to the 2022-2027 projected US population ages 2 to 50 years, followed by an estimate for the prevalence of transfusion-dependent beta thalassemia (63.0%).[2] Lastly, we assumed that only 50% of transfusion-dependent beta thalassemia patients would be eligible to receive beti-cel, due to age or various comorbidities. Applying these sources results in estimates of 666 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 133 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[86,87] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that beti-cel would displace current treatment with standard of care within the eligible patient population.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/), this threshold is based on an underlying assumption that health care

costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

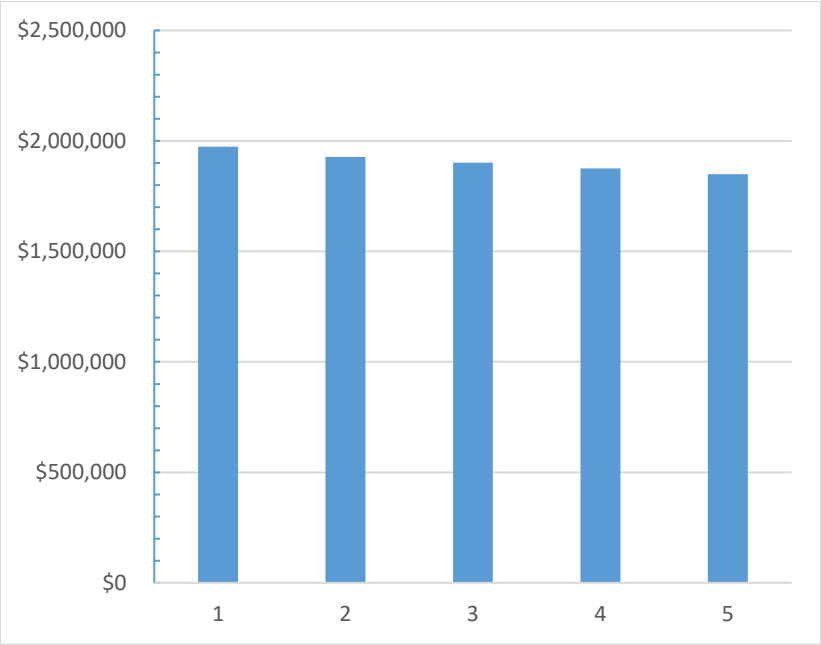
For 2021-2026, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $734 million per year for new drugs.

Results

Figure F1 illustrates the cumulative per-patient budget impact calculations for beti-cel compared to standard of care based on the proposed price of $2.1 million to be paid upfront but including an 80% payback option if transfusion independence is not achieved. Note that the cumulative budget impact per patient over five years decreases over time. This is due to beti-cel being a one-time treatment with high upfront treatment cost, but subsequent cost savings in years beyond the first year after treatment.

Treatment with beti-cel would result in an average potential budgetary impact of approximately $882,000 per patient per year when assuming our standard uptake of 20% per year. Note that this estimate is not smoothed to approximate 1/5th of the beti-cel acquisition cost less cost savings given the 20% per year uptake assumption does not allow for cost offsets to occur for those who started beti-cel in year five of the model.

Figure F1. Cumulative Annual Per Patient Treated with Beti-cel at the Anticipated Price of $2.1 Million*



*including an 80% payback option if transfusion independence is not achieved