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2021025559

Datum 21 juli 2021
Betreft Pakketadvies sluisgeneesmiddel betibeglogene autotemcel (Zynteglo®)

Onze referentie
2021025559

Geachte mevrouw Van Ark,

Zorginstituut Nederland adviseert u over betibeglogene autotemcel (beti-cel; Zynteglo®) bij de behandeling van patiënten van 12 jaar en ouder met transfusie-afhankelijke bèta-thalassemie (TDT) die geen β0/β0-genotype hebben en voor wie transplantatie van hematopoëtische stamcellen (HSC) gepast is, maar geen humaan leukocytenantigeen (HLA)-compatibele gerelateerde HSC-donor beschikbaar is. De aanleiding voor dit advies is de plaatsing van beti-cel in de pakketsluis voor dure geneesmiddelen. Het Zorginstituut heeft de beoordeling binnen het 'Beneluxa Initiative' uitgevoerd en daarin samengewerkt met België.

Beti-cel is een innovatieve, veelbelovende en eenmalige behandeling die aangrijpt op de oorzaak van de ziekte en voldoet aan de stand van de wetenschap en praktijk. Er zijn echter onzekerheden over de effecten op langere termijn: of de transfusieonafhankelijkheid dan wel -reductie levenslang aanhoudt, hoe snel het gebruik van ijzerchelatoren kan worden gestopt en wat het effect is op bèta-thalassemie-gerelateerde complicaties. Verder is de kosteneffectiviteit op basis van de beschikbare data onzeker en vooralsnog ongunstig. Data die in de toekomst verzameld zullen worden door de beroepsgroep en de registratiehouder, zullen hierover meer informatie geven.

Het Zorginstituut adviseert u beti-cel op te nemen in het verzekerde pakket als voldaan is aan de volgende voorwaarden:
- Uitgaande van de genoemde onzekerheden mag het risico op een te hoge prijs niet uitsluitend bij de premiebetaler worden neergelegd. Er is een prijsreductie van 35% nodig om te kunnen spreken van een kosteneffectieve behandeling.
- Daarnaast adviseert het Zorginstituut een 'pay for performance'-afspraak met de registratiehouder te maken, waarbij de betaling afhangt van het al dan niet bereiken van relevante uitkomstmaten. De registratiehouder heeft 2 voorstellen gedaan voor een dergelijk arrangement. Onderstaande relevante uitkomstmaten kunnen deel uitmaken van deze afspraak:
  - transfusie(on)afhankelijkheid;
  - gebruik van ijzerchelatoren.

Zorginstituut Nederland
Zorg II

Datum
21 juli 2021

Onze referentie
2021025559

Het Zorginstituut adviseert u om de (prijs)onderhandeling aan te gaan binnen de al bestaande Beneluxa-samenwerking. Over 5 jaar zou het Zorginstituut een herbeoordeling kunnen doen om te zien hoe de kosteneffectiviteit zich op basis van de dan beschikbare data heeft ontwikkeld.

In deze brief licht ik onze bevindingen en eindconclusie toe.

Algemeen

Het Zorginstituut maakt op uw verzoek vanuit het oogpunt van het uit gezamenlijke premies betaalde basispakket de afweging of nieuwe zorg onderdeel zou moeten zijn van het verzekerde pakket. Om tot een advies te komen heeft het Zorginstituut beti-cel beoordeeld aan de hand van de vier pakketcriteria[1]: effectiviteit[2], kosteneffectiviteit[3], noodzakelijkheid en uitvoerbaarheid. We maken hierbij een weging, zowel in wetenschappelijke zin als vanuit maatschappelijk draagvlak, en we wegen aspecten van doelmatigheid en transparantie. Het Zorginstituut wordt bij zijn pakketbeoordelingen geadviseerd door twee onafhankelijke commissies:

- de Wetenschappelijke Adviesraad (WAR) voor de toetsing van de gegevens aan de stand van de wetenschap en praktijk en het bepalen van de kosteneffectiviteit; en
- de Adviescommissie Pakket (ACP) voor de maatschappelijke afweging.

Ook hebben wij belanghebbende partijen tijdens het proces over de beoordeling geconsulteerd.

Beti-cel (Zynteglo®)

Bèta-thalassemie is een vorm van erfelijke bloedarmoede; de aandoening is opgenomen in de hielprikscreening. Wanneer het om een ernstige vorm gaat, is een patiënt afhankelijk van regelmatige bloedtransfusies. Door de vele bloedtransfusies lopen patiënten een groot risico op ernstige ijzerstapeling. Deze ijzerstapeling kan de vitale organen aantasten en patiënten hebben dan ijzerchelatoren als basistherapie nodig.
De enige behandelingsoptie die mogelijk geneest door het onderliggende defect te corrigeren, is allogene hematopoëtische stamceltransplantatie (HSCT). De meerderheid van de patiënten met bèta-thalassemie komt hiervoor niet in aanmerking. Beti-cel kan worden gebruikt voor de behandeling van patiënten die geen β0/β0-genotype hebben en voor wie HSCT gepast is, maar geen humaan leukocytenantigeen (HLA)-compatibele gerelateerde HSC-donor beschikbaar is.

Integrale weging pakketcriteria

Gunstige en ongunstige effecten

Er zijn 4 gelijke single-arm studies uitgevoerd waar elke patiënt zijn eigen controle was; er is data beschikbaar van 2 jaar vóór en tot ruim 5 jaar ná de beti-cel behandeling. In totaal zijn er 33 patiënten behandeld met beti-cel. Transfusieonafhankelijkheid (gedurende ten minste 12 maanden) werd bereikt bij 27 van de 32 (84%) patiënten na een mediane follow-up van 35 maanden. Van de onderzochte patiënten zijn 7 patiënten al meer dan 60 maanden geleden behandeld met beti-cel, alle 7 patiënten (100%) waren in januari 2020 nog altijd transfusieonafhankelijk. Bij 5 van de 33 patiënten die geen

[1] Pakketbeheer in de praktijk 3 (2013). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[2] Beoordeling stand van de wetenschap en praktijk: geactualiseerde versie (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[3] Rapport kosteneffectiviteit (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

transfusieonafhankelijkheid bereikten, werd een vermindering in het aantal transfusies vastgesteld. Van de 33 patiënten waren 13 gedurende ten minste 6 maanden gestopt met het gebruik van ijzerchelatoren. Een afname van het gebruik van ijzerchelatoren en van de parameters voor ijzerovermaat moeten nog verder worden onderbouwd. Er is (nog) geen verschil waargenomen tussen de behandeling met beti-cel en de standaardbehandeling op de vermindering van bèta-thalassemiegerelateerde complicaties. Op de lange termijn zijn vergelijkingen met de standaardbehandeling nodig.
De veiligheid van HSCT zoals gerapporteerd in de literatuur is vergelijkbaar met de behandeling met beti-cel.

Stand van de wetenschap en praktijk
De Belgische Commissie Tegemoetkoming Geneesmiddelen (CTG) en Zorginstituut Nederland concluderen dat beti-cel bij patiënten van 12 jaar en ouder met transfusie-afhankelijke bèta-thalassemie (transfusion-dependent beta-thalassaemia; TDT) die geen β0/β0-genotype hebben, voor wie transplantatie van hematopoëtische stamcellen (HSC) gepast is, maar geen humaan leukocytenantigeen (HLA)-compatibele gerelateerde HSC-donor beschikbaar is, voldoet aan de stand van de wetenschap en praktijk. Na behandeling met beti-cel bereikt de meerderheid van de patiënten een zodanig hemoglobinegehalte dat zij niet meer afhankelijk zijn van bloedtransfusies.

Budgetimpact
De netto budgetimpact van beti-cel bedraagt in jaar 3 circa € 5 miljoen (als niet alle prevalente patiënten behandeld zullen gaan worden) tot € 8 miljoen (als alle prevalente patiënten behandeld zullen gaan worden) in Nederland.

Kosteneffectiviteit
De ICER wordt door de registratiehouder geschat op € 75.871 per QALY. Dit lijkt te optimistisch doordat een aantal aannames door het Zorginstituut niet realistisch worden geacht. Er is vooral veel onzekerheid over de langetermijneffectiviteit van beti-cel. Maar in het model van de registratiehouder wordt aangenomen dat patiënten na behandeling met beti-cel geen bloedtransfusies (en ijzerchelatietherapie) meer nodig hebben gedurende de rest van hun leven (behalve de 15% transfusiegereduceerde patiënten). Daaraan gerelateerd wordt ervan uitgegaan dat patiënten die behandeld zijn met beti-cel minder ijzerovermaatcomplicaties ontwikkelen en veel langer leven. Verder kan de duur van ijzernormalisatie na behandeling met beti-cel in de praktijk veel langer zijn dan de nu veronderstelde 2 jaar. Als we uitgaan van deze (te optimistische) ICER van de registratiehouder, dan moet de prijs van beti-cel met circa 20% dalen om onder de referentiewaarde van € 50.000 per QALY te vallen. Als een aantal aannames wordt aangepast (aantal jaar ijzernormalisatie, sterftekans bij TDT en alle transfusiegereduceerde patiënten worden transfusieafhankelijk na tien jaar), wordt de ICER circa € 90.000 per QALY en moet de prijs van beti-cel dalen met circa 35 % om kosteneffectief te zijn. Beti-cel is dus geen kosteneffectieve behandeling voor de behandeling van TDT- patiënten.

Weesgeneesmiddelenarrangement
Om de inzet van beti-cel te monitoren en te volgen, zal het Zorginstituut in samenwerking met de beroepsgroep een weesgeneesmiddelenarrangement opzetten. Hierin kunnen ook afspraken over een ander recent geregistreerd geneesmiddel voor een vergelijkbare indicatie (luspatercept; Reblozyl®) worden

opgenomen. Luspatercept is niet in de pakketsluis voor dure geneesmiddelen geplaatst en daarom zullen ook de zorgverzekeraars betrokken worden bij de afspraken.
De data die verzameld worden, zouden input moeten kunnen geven voor de geadviseerde voorwaarde 'pay for performance'.
De resultaten van het weesgeneesmiddelenarrangement zullen jaarlijks in de *Monitor weesgeneesmiddelen in de praktijk* worden gepubliceerd.
Daarnaast kunnen de data de mogelijkheid bieden om in de loop der tijd meer zekerheid te krijgen over de langetermijneffectiviteit van beti-cel.

Eindconclusie
Beti-cel is een innovatieve, veelbelovende en eenmalige behandeling die aangrijpt op de oorzaak van de ziekte en voldoet aan de stand van de wetenschap en praktijk. Er zijn echter onzekerheden over de effecten op langere termijn: of de transfusieonafhankelijkheid dan wel -reductie levenslang aanhoudt, hoe snel het gebruik van ijzerchelatoren kan worden gestopt en wat het effect is op bèta-thalassemie-gerelateerde complicaties. Verder is de kosteneffectiviteit op basis van de beschikbare data onzeker en vooralsnog ongunstig. Data die in de toekomst verzameld zullen worden door de beroepsgroep en de registratiehouder, zullen hierover meer informatie geven.

Het Zorginstituut adviseert u beti-cel op te nemen in het verzekerde pakket als voldaan is aan de volgende voorwaarden:
- Uitgaande van de genoemde onzekerheden mag het risico op een te hoge prijs niet uitsluitend bij de premiebetaler worden neergelegd. Er is een prijsreductie van 35% nodig om te kunnen spreken van een kosteneffectieve behandeling.
- Daarnaast adviseert het Zorginstituut een 'pay for performance'-afspraak met de registratiehouder te maken, waarbij de betaling afhangt van het al dan niet bereiken van relevante uitkomstmaten. De registratiehouder heeft 2 voorstellen gedaan voor een dergelijk arrangement. Onderstaande relevante uitkomstmaten kunnen deel uitmaken van deze afspraak:
  - transfusie(on)afhankelijkheid;
  - gebruik van ijzerchelatoren.

Het Zorginstituut adviseert u om de (prijs)onderhandeling aan te gaan binnen de al bestaande Beneluxa-samenwerking. Over 5 jaar zou het Zorginstituut een herbeoordeling kunnen doen om te zien hoe de kosteneffectiviteit zich op basis van de dan beschikbare data heeft ontwikkeld.

Hoogachtend,

Tiana van Grinsven
Plv. Voorzitter Raad van Bestuur

2021025164

ACP advies aan de Raad van Bestuur van het Zorginstituut over betibeglogene autotemcel (Zynteglo®) (verder beti-cel) bij de behandeling van patiënten in de leeftijd van 12 jaar en ouder met transfusie-afhankelijke β-thalassemie (TDT) die geen β0/β0-genotype hebben, voor wie transplantatie van hematopoëtische stamcellen (HSC) gepast is, maar geen humaan leukocytenantigeen (HLA)-compatibele gerelateerde HSC-donor beschikbaar is

De Adviescommissie Pakket (ACP) adviseert de Raad van Bestuur (RvB) van het Zorginstituut over voorgenomen pakketadviezen. Zij toetst deze adviezen aan de pakketcriteria en kijkt of de uitkomsten daarvan maatschappelijk wenselijk zijn. Daarbij kijkt zij zowel naar de belangen van de patiënten die in aanmerking komen voor vergoeding van een bepaalde interventie, als naar de belangen van patiënten met andere aandoeningen (die ook graag willen dat de behandeling van hun aandoening wordt vergoed) en van premiebetalers. Zij doet dit vanuit het principe dat de basisverzekering maximale gezondheidswinst dient op te leveren voor de gehele bevolking.
Om hier een uitspraak over te kunnen doen, hanteert de commissie zogenaamde referentiewaarden voor de kosteneffectiviteit. Deze referentiewaarden moeten worden opgevat als maximale bedragen die we als samenleving per gewonnen levensjaar willen investeren in een behandeling. Gaan we daarboven zitten, dan is er sprake van verdringing. Dat betekent dat voor hetzelfde bedrag meer gezondheidswinst kan worden verkregen door het aan andere behandelingen uit te geven. Er moeten dus hele goede redenen zijn om een kosteneffectiviteit gelijk aan de referentiewaarde of zelfs meer dan de referentiewaarde te accepteren.

De commissie heeft in haar vergadering van 25 juni 2021 (i.v.m. coronamaatregelen een videoconferentie) gesproken over de vraag of beti-cel bij de hierboven genoemde indicatie opgenomen dient te worden in de basisverzekering. Tijdens de vergadering hebben de patiëntenorganisatie, de beroepsgroep en de fabrikant gebruik gemaakt van de mogelijkheid tot inspreken. De patiëntenorganisatie bracht in dat dit middel uitkomst biedt voor patiënten waarvoor geen geschikte donor beschikbaar is. De patiëntenorganisatie en beroepsgroep benadrukken de impact van de bloedtransfusies, behandeling van ijzerstapeling en de complicaties (bijvoorbeeld orgaanschade). De beroepsgroep licht toe dat zij een document heeft opgesteld met daarin afspraken over welke centra de behandeling kunnen gaan toepassen en aan welke criteria een patiënt moet voldoen om in aanmerking te komen. Hierin is ook rekening gehouden met het recent beschikbaar gekomen middel luspatercept. Ook is op korte termijn een indicatie-uitbreiding te verwachten De fabrikant Bluebird bio heeft aangegeven patiënten langdurig te gaan volgen en zegt dat er geen aanwijzingen zijn dat het overtuigende effect op termijn zal gaan verdwijnen. Zij staat open voor een pay-for-performance afspraak. Alle partijen hopen dat het middel snel toegankelijk wordt voor patiënten.

De volgende punten vormen voor de commissie het vertrekpunt van de commissie:
- Het betreft een innovatieve en op korte termijn en op lange termijn veelbelovende gentherapie waarvoor de commissie haar waardering uitspreekt. Er is onzekerheid of de gevonden effecten levenslang aanhouden.
- Het betreft een eenmalige behandeling.
- Bij de huidige prijs is er geen sprake van een kosteneffectieve behandeling (ICER van €90.000 per QALY uitgaande van een referentiewaarde van €50.000 euro). Bij een prijsreductie van 35% komt de ICER onder de referentiewaarde van €50.000 euro per QALY te liggen.

Ook al acht de commissie het wenselijk dat deze behandeling spoedig beschikbaar komt voor de patiënt, vindt zij de prijs, bijna anderhalf miljoen per patiënt, te hoog. Het kosteneffectiviteitsmodel laat zien dat, uitgaande van de referentiewaarde van €50.000 euro per QALY, die van toepassing is bij de ziektelast van deze aandoening (0.53), beti-cel niet

kosteneffectief is (€90.000 per QALY). Er zou een prijsreductie van 35% nodig zijn om te kunnen spreken van een kosteneffectieve behandeling.

Gezien de onzekerheid over of het effect levenslang behouden blijft en omdat het een eenmalige behandeling betreft waarbij de kosten zich op één moment concentreren terwijl de baten nog onzeker zijn, adviseert de commissie om een pay-for-performance afspraak te maken en hierbij rekening te houden dat de claim is dat het levenslang werkt. De commissie is van mening dat het risico dat deze gentherapie niet levenslang werkt niet bij de maatschappij moet komen te liggen, maar bij de fabrikant. De commissie vindt het verder noodzakelijk dat deze afspraken openbaar worden gemaakt door het ministerie van VWS, zodat hiervan kan worden geleerd voor de toekomstige beoordelingen van gentherapieën en pay-for-performance afspraken.

Echter, naast de pay-for-performance afspraak acht de commissie, gezien de hoge prijs, ook een prijsreductie nodig. Hoewel de commissie veelbelovende innovatie wil belonen en stimuleren en daarom een zekere afwijking van de referentiewaarde soms acceptabel vindt, zijn er in dit geval ook argumenten die daartegen pleiten. Afhankelijk van bijvoorbeeld de duur van de pay-for-performance afspraak vraagt de grote mate van onzekerheid over de lange termijn effecten en kosteneffectiviteit om een prijsreductie. Verder leidt de huidige prijs die ver boven de referentiewaarde ligt tot verdringing van andere zorg. Tot slot is indicatie-uitbreiding te verwachten.[1]

Alle argumenten overwegende, komt de commissie tot de conclusie dat zij het belangrijk vindt dat het middel snel beschikbaar komt, mits er een goede pay-for-performance afspraak tot stand komt en de prijs van beti-cel met minimaal 35% is gereduceerd. De commissie adviseert om bij deze prijsonderhandeling daarnaast ook al rekening te houden met de te verwachten indicatie-uitbreiding.

De commissie acht dataverzameling noodzakelijk en adviseert om het systematisch verzamelen van kwaliteit van leven data hierin mee te nemen. Ook steunt de commissie het voorstel om een weesgeneesmiddelen-arrangement op te stellen waarin deze afspraken worden vastgelegd, maar ook rekening wordt gehouden met de inzet van luspatercept en de te verwachten indicatie-uitbreiding.

[1] Overbodig te zeggen dat de commissie geen inzicht heeft in de daadwerkelijke kosten die zijn gemaakt voor de ontwikkeling van dit middel. Met de hoge vraagprijzen van gentherapieën gaat dit steeds meer wringen. De commissie vraagt zich af of het juist is dat het consumentensurplus volledig naar de fabrikant gaat. Ook de maatschappij zou moeten kunnen profiteren van dit surplus.

RIJKSINSTITUUT VOOR ZIEKTE-EN INVALIDITEITSVERZEKERING

Openbare instelling opgericht bij de wet van 9 augustus 1963
Galileelaan 5 b1 - 1210 Brussel

Dienst Geneeskundige Verzorging

COMMISSIE TEGEMOETKOMING GENEESMIDDELEN

Nota CTG 20xx// 0154261501 /R90

BETREFT:
Dossier N°: 0154261501
Naam van de specialiteit :
ZYNTEGLO || 1,2-20 x 10 e6
1 doses suspensie voor infusie, 1 dosis
Document op agenda : Definitief beoordelingsrapport

PROCEDURE : Koninklijk Besluit 01.02.2018

OPDRACHT VAN DE COMMISSIE TEGEMOETKOMING GENEESMIDDELEN :

De Commissie wordt verzocht het beoordelingsrapport goed te keuren.

TREFWOORDEN
Geneeskundige verstrekkingen – Farmaceutisch product – Farmaceutische specialiteit

FARMACOTHERAPEUTIC REPORT

ZYNTEGLO 1,2-20 X 10 E6

1 DOSES SUSPENSIE VOOR INFUSIE, 1 DOSIS

1. SUBJECT OF THE SUBMISSION

The company Bluebird has submitted for reimbursement a dossier on the orphan medicinal product ZYNTEGLO beti-cel. ZYNTEGLO contains autologous CD34+ cell enriched hematopoietic stem cells, genetically modified via lentiviral vector mediated transduction encoding the $\beta^{A\text{-}T87Q}$ globin gene.

It is an Advanced Technology Medicinal Product, with a conditional marketing authorization received on May 29th 2019.

The therapeutic indication is: Treatment of patients 12 years old and older with transfusion-dependent β-thalassaemia who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen-matched related hematopoietic stem cell donor is not available.

The dossier is submitted within the Beneluxa Pharmaceutical Policy Initiative. For the HTA part, RIZIV-INAMI authors the pharmacotherapeutic part and ZIN the pharmaco-economic part and budget impact for the two countries.

2. SUMMARY

Patients with severe forms of **β-thalassaemia** need regular blood transfusions and iron chelators as basis therapy; they are transfusion-dependent for their survival. More than half of them die before the age of 50 years, even with optimal therapy. Only a minority of them has a suitable donor for allogeneic hematopoietic stem cell (HSC) transplantation; this is offered in early childhood (<14 years).

The need for **ZYNTEGLO beti-cel is** therefore 1° in patients < 14 years who do not have an HLA-matched donor and 2° patients older than 14 years for whom a HSC is not foreseen anymore but are nevertheless fit enough to undergo the entire procedure of an autologous HSC i.e. with stem cells from themselves. It is a once-in-a-lifetime treatment. ZYNTEGLO treatment consists of collection of patient's HSC, ex vivo transfer of the new gene, destruction of the bone marrow (myeloablation), keeping the patient in strict isolation and ZYNTEGLO infusion followed by HSC engraftment in order to produce sufficient red blood cells, white blood cells and platelets.

2.1. THERAPEUTIC VALUE

ZYNTEGLO contains autologous CD34+ enriched HSC transduced by a lentiviral vector encoding the β^{A-T87Q}-globin. The gene transfer leads to production in the renewed bone marrow of **functional hemoglobin**.

The EMA requested a **registry with 15-years of follow-up**. The evidence is based on similar **4 single-cohort studies** where each patient was his own control before (2 years' period) and after ZYNTEGLO. No spontaneous improvement in the disease occurs. The inclusion criteria for non β^0/β^0 genotype patients were the same in the cohort studies.

The data lock in the present report was January 2020. Of note is that the data lock at the EMA was February 2018 with addendum December 2018.

2.1.1. Efficacy / Efficiency in practice

Primary outcome

Transfusion-independence was defined as presenting a hemoglobin concentration of ≥ 9 g/dL without packed red blood cell (RBC) transfusions for at least 12 months; this timeframe started at the latest 6 months after ZYNTEGLO beti-cel, as patients needed RBC on intensive care and sometimes beyond. Transfusion-independence was 84% (27/32) with 95% CI 67%-95% with a median follow-up of 35 months (range 1-72 months) at data lock. Transfusion-independence at month 60 was 100% (7/7) with 95% CI 59%-100%.

Selected secondary outcomes

- The time to reach transfusion-independence was on average 16 months after ZYNTEGLO, with range 15-21 months.
- For 5 out of 33 patients who did not reach transfusion-independence, transfusion reduction was noted. This varied from 100% to 46% as compared to before ZYNTEGLO infusion; a reduction of 50% or more is considered clinically relevant (in 3/5).
- Discontinuation of iron chelators. 13/33 patients had stopped taking iron chelators for at least 6 months. Some of them received phlebotomy to remove iron excess, which makes the interpretation of the data less obvious.
- Data on reduced iron excess levels were not conclusive.

Selected exploratory outcomes
The few data on quality of life were exploratory and lack input from the first 6 months after ZYNTEGLO infusion.

2.1.2. Adverse effects

Most frequent adverse events were thrombocytopenia, anaemia, stomatitis, alopecia, nausea, vomitus and neutropenia.
Of these frequent adverse events, the following were reported as grade 3 or 4 of severity : thrombocytopenia, anaemia and vomitus.
Serious adverse events were reported such as e.g. infection and thrombosis ; one third occured before ZYNTEGLO and two third occurred after ZYNTEGLO infusion.
Adverse events of importance according to the SmPC are bleeding, hepatic veno-occlusive disases and infusion-related reactions to ZYNTEGLO.
No patient left the study. No patient died in the studies.

In comparison with safety issues related to HSC transplantation reported in the literature, the CHMP noted that for ZYNTEGLO it was in the same line (EPAR). Nevertheless, a delayed platelet engraftment was observed with ZYNTEGLO : median 41 days for engraftment versus 30 days in the literature. A delayed platelet engraftment is an *important identified* risk, the only one, in the Risk Management Plan. The engraftment of neutrophils was within values reported in the literature.

2.1.3. Applicability

Contra-indications are those of any HSC transplantation.
Special precautions and vaccine therapy are the same as done in any HSC transplantation. The patient is life-long infertile. Because of the invasive nature of myeloablation, cryopreservation of spermatocytes or ovocytes is to be organised.

2.1.4. Practical use

In the early phase of the procedure, HSC are to be collected. As an adjunct for HSC mobilization, plerixafor MOZOBIL was systematically used in the studies. This use is off-label ; the CHMP considered its use safe in a ZYNTEGLO procedure.

The practical issues are those of any HSC transplantation. The shipment from the autologous from the aferesis-centre and back (lenti-virus treated HSC) to the intensive care unit are to be organised. Afterwards, the patient carries a Patient Alert Card, stating that he/she is not to donate tissue or cells life-long.

2.2. ADDED VALUE VERSUS ALTERNATIVES
MORTALITY – MORBIDITY – QUALITY OF LIFE

► Mortality
All patients treated with beti-cel were alive. No reduction in mortality was observed as compared to polytransfusions and iron chelation therapy (standard of care).

► Morbidity
- Less to no transfusions
As compared to the period before ZYNTEGLO (within-patient comparison) and as compared to standard of care polytransfusions and iron chelator therapy (indirect comparison), the long-term presence of sufficient haemoglobin levels without transfusions (27/32) is a relevant improvement. Cutting the transfusions by more than half (3/5) is also a relevant improvement.
- Reduction of iron burden
A decrease in use of iron chelators and in iron excess parameters is to be substiantated.
- Reduction in beta-thalassaemia-related complications
No difference has been observed (yet) between ZYNTEGLO treatment and standard of care.

► Quality of life
- No formal comparison has been made between standard of care and ZYNTEGLO in terms of efficiency in practice, adverse events, applicability nor ease of use.
- The quality of life in the first 6 months, myeloablation and HSC transplantation is not reported, but can be expected to be worse due to their invasive nature. On the long term run, comparisons with standard of care are needed.

Therefore, ZYNTEGLO beti-cel treatment is considered a *Therapeutische meerwaarde* (BE) / *Stand van wetenschap en praktijk* (NL) because of a obtaining haemoglobin levels as expected in this disease, but obtained without blood transfusions anymore, and this in a majority of treated patients.

2.3. UNCERTAINTIES AND PROBLEMS

Criteria	**Uncertainties** **(= expected to be resolved at the end of the Managed Entry Agreement)**	**Problems** **(= not being resolved at the end of the Managed Entry Agreement)**
Clinical evaluation	Duration of expression of the gene transfer for the duration of the MEA Longer follow-up of patients who are already treated	EMA registry with follow-up up to 15 years after ZYNTEGLO Comparison on quality of life with ZYNTEGLO versus without ZYNTEGLO
Place and role in medical practice	No uncertainties	No problems
Budget impact	Number of treated patients	Future label expansion to patients younger than 12 years Future label expansion to patients with the the β^0/β^0 genotype
Cost-effectiveness	Less utilisation of iron chelator therapy Less iron excess levels	See Clinical evaluation

3. HEALTH TECHNOLOGY ASSESSMENT

The label of ZYNTEGLO beti-cel states :

'Treatment of patients 12 years and older with transfusion-dependent β-thalassaemia who do not have a β°/β° genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen-matched related donor is not available.'

PICO-table

P	Patients 12 years and older with transfusion-dependent β-thalassaemia who do not have a β°/β° genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen-matched related donor is not available
I	Autologous CD34-cells encoding $\beta^{A\text{-}T87Q}$ – globin gene i.e. ZYNTEGLO beti-cel, once in a lifetime infusion
C	-In-patient comparison, namely the 2-year period before ZYNTEGLO beti-cel infusion versus the period after infusion for at least 18 months.[1] -Indirect comparison: continuation of repeated red blood cell transfusions and iron chelation therapy, lifelong
O	-*Red Blood cells (RBC) aspect* Transfusion-independency[2] [crucial], defined as a weighted average Hb concentration of ≥ 9 g/dL without any packed RBC transfusions for a continuous period of ≥ 12 months at any time after ZYNTEGLO beti-cel infusion. Outcome defined in the clinical development program. It was the most important clinical outcome because the natural evolution of the disease does not consist of transfusion-free periods. -Discontinuation of iron chelators for at least 6 months [crucial] -*White blood cells aspect* Recuperation of neutrophil production by the bone marrow after ZYNTEGLO beti-cel infusion [important]. Outcome valid in any hematopoietic stem cell transplantation. -*Thrombocytes aspect* Recuperation of platelet production by the bone marrow after ZYNTEGLO beti-cel infusion [important]. Outcome valid in any hematopoietic stem cell transplantation. -QoL [crucial] -Serious adverse events [crucial] -Proportion of patients stopping the study [crucial]
Relevant follow-up period	Based on the primary outcome, transfusion-independency (≥ 12 months transfusion-free) and the start of this period in the first months after beti-cel infusion, at the latest 6 months, 18 months follow-up is a minimal follow-up period and should be *at least* 18 months.
Study design	The in-patient comparison and thus a single-cohort study is acceptable because the natural history does not consist of transfusion-free periods. An indirect comparison would also be preferred in order to compare the QoL between untreated and treated patients. However, this comparison is lacking.

[1] Period for at least 16 months after beti-cel was the median duration between the moment of beti-cel infusion and time to reach transfusion-independency. Of note is that packed red blood cells are still given after beti-cel infusion (when the patient is in intensive care), up to 6 months at the latest. As the definition transfusion-free relates to 12 months minimally, the proposed 18 months covers it entirely: transfusions up to 6 months + 12 months transfusion-free.

[2] Transfusion-independency was considered by CHMP, Dutch and Belgian key opinion leaders consulted by the company, as a clinically meaningful endpoint. It provided the CHMP consistency for analyses of data across the beti-cel clinical development program. Transfusion-independency was agreed upon with the EMA through prior scientific advice procedures, in advance of initiation of the phase 3 clinical development program.

3.1. CLINICAL DOMAIN

The clinical domain is therefore β-thalassaemia, one of the haemoglobinopathies. The label of ZYNTEGLO mentions the following characteristics of the target patient population :

- Not the β°/β° genotype, being the genotype with homozygous null mutations in both the allels of the β-globin gene of haemoglobin. This means that the ZYNTEGLO label includes at least the following genotypes : β^+/β° ; β^+/β^E ; β^+/β^+ ; β^E/β° ; IVS-1-10/IVS-1-10 ; IVS-1-10/ β° and any unidentified mutation.
- Transfusion dependency. This pertains to the necessary regular transfusions of red blood packed cells usually every 2 to 5 weeks. The label does not use the terms *thalassaemia major* and *thalassaemia intermedia* given the variation of transfusion frequency in the latter.
- Appropriate for a hematopoietic stem cell transplantation, meaning that the patient is fit enough to undergo a stem cell transplantation (HSCT).
- No human leukocyte-antigen-matched donor in his/her family.
- Aged 12 years or older. Almost all allogeneic (with a donor) HSCT for β-thalassaemia take place in childhood and almost never beyond 18 years. See below.

3.1.1. Disease description[1,3,4]

β-thalassaemia is a genetic blood disease caused by a defect of the β-globin gene in chromosome 11. It is characterised by a decreased synthesis (β^+ or β^E) or absent synthesis (β°) of the β-globin chains. β-globin chains form together with the ὰ-chains and haem, the physiological haemoglobin molecule : HbA. The IVS-1-10 mutant (see further study HGB-12) has phenotypic characteristics of both β^+ and β° ; it is a common β-globin variant in the Mediterranean population.

There are more than 260 known mutations in the β-globin gene locus that cause a reduced or zero synthesis of β-globin chains. Every year, about 2 new mutations are discovered. All mutations are documented in the global databases HbVar and ITHANET.

A defective β-globin synthesis leads to a relative excess of ὰ-chains, hence an ineffective HbA-production and an ineffective erythropoiesis, as HbA is the main form of haemoglobin after birth. This defect stimulates production of other haemoglobin forms like HbF (fœtal hemoglobin), even up to adulthood in patients. In situations of important deficiency of β-globin synthesis, more than 90% of circulating Hb-levels is composed of HbF.

In a healthy person, the sequence of production during fœtal life and beyond of ὰ-globin, β-globin, δ-globin and ϒ-globin is given hereunder in the scheme.

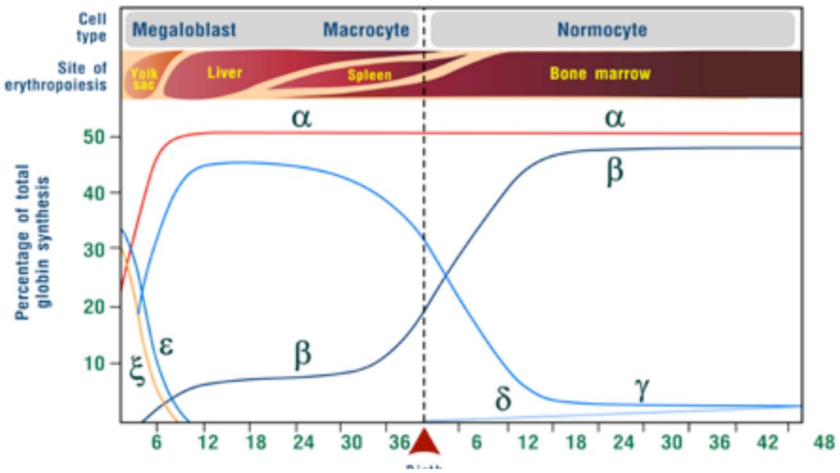
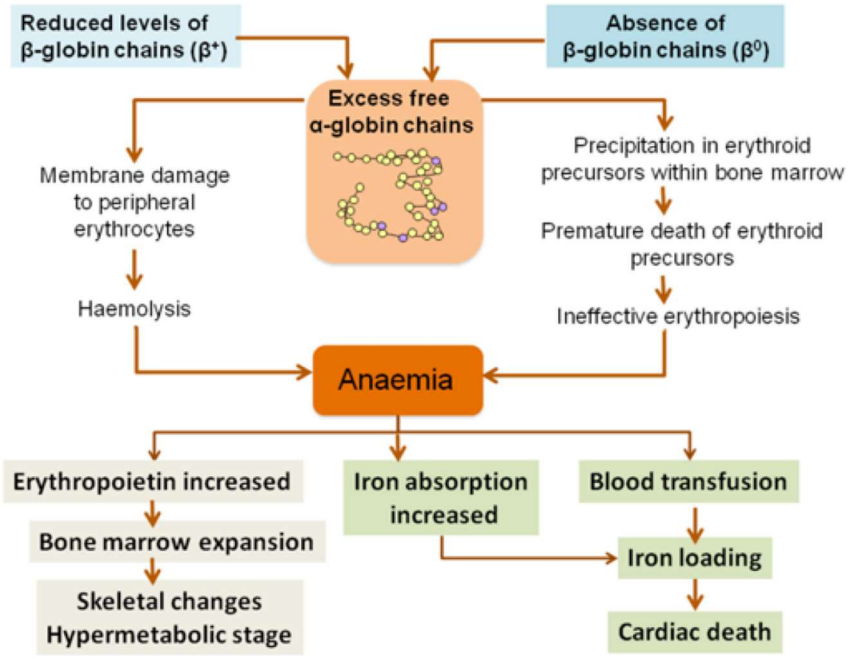


Figure 1. Globin synthesis at various stages of embryonic, foetal and adult erythroid development.

 ref[2]

Therefore, symptoms of β-thalassemia presents clinically from early childhood on. The bone marrow expands and extra-medullary hematopoiesis occurs. Anaemia is the typical presentation of a child with β-thalassaemia. The iron absorption is increased, which, together with regular blood transfusions, leads to iron overload. Increased production of erythropoietin-hormone leads to the bone marrow expansion and skeletal changes, as well to a hypermetabolic stage. These abnormal mechanisms are given schematically below.



igure 3. Effects of excess production of free α-globin chains in β-thalassaemia.

 Cappellini 2014

The diagnosis of β-thalassemia can be suspected based on family history, physical examination e.g. enlarged spleen and characteristics of circulating red blood cells such as low mean corpuscular volume. The diagnosis is confirmed by hemoglobin electrophoresis or high-performance liquid chromatography. In order to identify molecularly the β-thalassaemia e.g. β^E, DNA analysis is carried out to specify the genotype.[3]

For newborns born in the Netherlands, screening for β-thalassemia is foreseen in heelprick testing. This is not done in Belgium. For people not subject to heelprik screening, the diagnosis is made, or at least suspected, at a later age of the child, usually during the first year of life.

The clinical symptoms, the complications of the syndrome at term and therapeutic problems in the child with β-thalassaemia are given in the scheme below:[4]

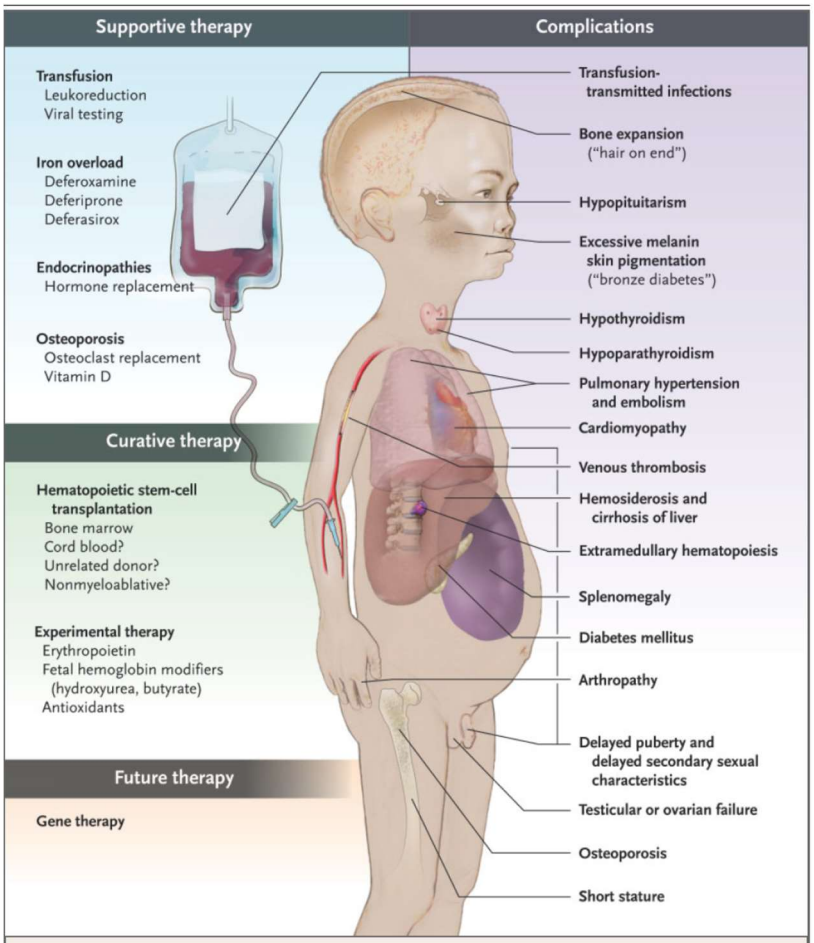


Figure 1. Management of Thalassemia and Treatment-Related Complications.

The anemia that is associated with thalassemia may be severe and is accompanied by ineffective erythropoiesis, with bone expansion and extramedullary hematopoiesis in the liver, spleen, and other sites, such as paravertebral masses. Transfusion therapy, which is the mainstay of treatment, allows for normal growth and development and suppresses ineffective erythropoiesis. Transfusion-transmitted infections (primarily hepatitis B and C) are an important cause of death in countries where proper testing is not available. Iron overload results both from transfusional hemosiderosis and excess gastrointestinal iron absorption. Iron deposition in the heart, liver, and multiple endocrine glands results in severe damage to these organs, with variable endocrine organ failure. The endocrinopathies can be treated with hormone replacement. However, the most serious result of iron overload is life-threatening cardiotoxicity, for which chelation therapy is required. Thalassemia can be cured by bone marrow transplantation. Experimental therapies to ameliorate the anemia that have been or are currently under investigation include fetal hemoglobin modifiers and antioxidants. In the future, gene therapy or other molecular methods may be feasible.

β-thalassaemia can be divided into two main groups : non-transfusion dependent and transfusion-dependent. This division is based on the patient's needs for blood tranfusions. Patients with the transfusion-dependent form require regular blood transfusions to survive. The Thalassaemia International Federation guidelines do not provide a definition or number when a patient is categorized as regular transfusions required. However, the guidelines do provide guidance on the Hb-levels to maintain. Red blood cells are to be given every 2 to 5 weeks to maintain a pre-transfusion Hb level of 9 to 10,5 g/dL and hence achieve a post-transfusion Hb level of 14-15 g/dL. The treatments with repeated transfusion and iron chelation are life-long.

Patients who are not adequately treated with transfusions and iron chelation therapy, develop serious complications like cardiomyopathy, pulmonary hypertension, osteoporosis, skeletal deformities, arthropathy, hepato-splenomegaly, endocrinopathies, diabetes, delayed puberty and gonadal dysfunction. Without adequate transfusion support, patients would suffer from several complications and have a short life span. Untreated, patients will die before the age of 3 years.[5]

Risks from regular blood transfusions are immune-mediated adverse reactions, transfusional iron overload. Poor adherence to iron chelator therapy was associated with increased rate of hospitalisations and emergency visits as shown with American patients with β-thalassaemie.[6]

The only treatment option that potentially cures by correcting the underlying β-globin synthesis defect, is allogeneic HSCT. Unfortunately, the majority of patients do not qualify for allogeneic HSCT. The reasons are advanced age, absence of an available matched stem cell donor or co-morbidity/complications of β-thalassaemia that increase the risk of transplant complications. An international expert panel observed that 25% to 30% of patients undergo an allogeneic HSCT ; all the others not.[7] Above the age of 18 years, an allogeneic HSCT is almost never done for reasons evoked : too advanced complications of iron overload.

In the submission file, the applicant stresses the serious risks of allogeneic HSCT. It carries the risk of graft failure, severe infections, graft-versus-host-disease (all forms) and increased mortality. It is important to mention that ZYNTEGLO always implies a HSCT, be it autologous from origin. Graft-versus-host-disease is therefore never seen in patients with ZYNTEGLO-infusion.[8]

Some numbers on mortality, morbidity, quality of life.

- Mortality. Patients with transfusion-dependent β-thalassaemia have a shorter life span, even with optimal treatments. More than half of them die before the age of 50, as was observed in WHO data for Europe.[9] Common causes of death are cardiac and liver-related complications due to iron overload, as observed in 70% of Greek patients.[10]

- Morbidity. The burden of complications increases with age. In the age group ≤ 25 years, 16% of the patients experienced three or more comorbidities at the same time ; in the age group 26-40 years, this increased to 51%, and increased further in the age group ≥40 years to 86%.[11] A majority of patients report pain : 64% of 252 American patients reported experiencing pain with with Brief Pain Inventory and 69% of 265 with the SF-36.[12,13] The degree of pain was at least moderate in 28% to 63% of patients.

- Quality of life. As compared with the general population norms, patients with transfusion-dependent β-thalassaemia have low health-related quality-of-life scores. The low scores are due to fatigue, pain, lower school function and school attendance (due to the polytransfusional program), social functioning, emotional functioning and

psychosocial functioning. The scores vary between European registries and retrospective cohorts.[14,15] There exists clinical heterogeneity in this syndrome but also variation according to the country, namely how patients in one country score the psychosocial subscale in contrast to another country.[16] In routine healthcare in 9 UK centres, EQ-5D-3L utility scores were observed as follows, expressed as mean±SD : by carers 0,88±0,15 (n=34) ; patients 4-7 years by proxy 0,73±0,27 (n=9) and patients ≥16 years themselves 0,69±0,33 (n=94), which is to be compared with UK reference of 0,91 (unpublished UK study).[17]

3.1.2. Epidemiology

Transfusion-dependent β-thalassemia (TDT) is a rare genetic disease. For discussion on Dutch and Belgian numbers, see section Budget Impact ZIN. Hereunder follows the summary.

There were about 7-8 TDT cases per 1,000,000 persons in Belgium in 2020. This corresponds to *87 patients* diagnosed with TDT in Belgium. The annual incidence of thalassemia was assumed to be *about 2-3 new TDT* diagnoses per year. From the BIA it can be concluded that of these patients a total of 6 adolescent and 8 adult patients are potentially eligible for beti-cel per the licensed indication (see ref 3 in the BIA).[18] Thus, *14 patients in total.* It is assumed there are 2.5 new patients per year, of which *0.94 patient* (2,5*75%*50%) is eligible for treatment with beti-cel.

For the Netherlands it is assumed that the prevalence of β-thalassaemia in 2020 was between 150 and 200 patients.[19,20] Dutch key opinion leaders indicate that of those patients, approximately one-third of the adult patients are transfusion-dependent.[19,20] Each year 3-5 patients are diagnosed with β-thalassaemia in The Netherlands. Of the prevalent patients 14,17 patients would be eligible to receive beti-cel and a maximum of 0.44 *newly diagnosed TDT patient* is eligible for beti-cel per year (see ref 1 and 2 in the BIA).

3.1.3. Therapeutic options and therapeutic and social needs

Dutch and Belgian expertise centres in thalassaemia don't have formal proper treatment guidelines but refer to the international Guidelines for the management of transfusion-dependent thalassaemia.[2] Treatment options consist of two pathways : either repeated transfusions of red blood cells (RBC) and iron chelators, either allogeneic HSCT and subsequently iron chelators for the existing pre-transplant iron overload, if required. The next graph shows the therapeutic pathway.

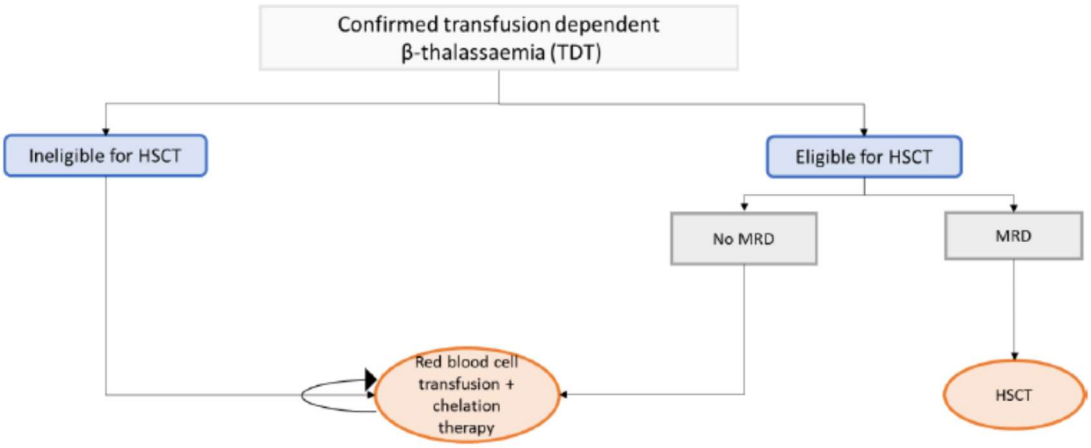


Figure 12 Pathway of care for the treatment of TDT

Abbreviations: HSCT, haematopoietic stem cell transplantation; MRD, matched related donor; TDT, transfusion-dependent β-thalassaemia
Source: TIF guidelines[1, 74]

■ Allogeneic hematopoietic stem cell transplantation (HSCT)

Currently, in the Netherlands and Belgium, none of the transfusion-dependent thalassaemia patients 12 years or older, are eligible to receive transplantation. Research has shown that outcomes are best in children aged below 14 years who lack iron-related comobordities and have an HLA-matched sibling donor.[7] Transplantation is the only treatment option that potentially cures the genetic cause of the disease. Therefore, allogenenic HSCT is offered at the earliest stage possible.[21] In a long-term follow-up of more than 170 HSCT, the following complications were observed : impaired renal function (20%) and hypogonadotropic hypogonadism (37%) ; the latter was due to iron overload and busulfan gonodotoxicity. 27% had developed acute graft-versus-host-disease (within the first year after HSCT) and <1% developed chronic graft-versus-host-disease.[22]

As requested by ZIN, the company performed a database research on historical data of allo-geneic HSCT in Leiden since 2006, in the national pediatric transplant centre for this disease (LUMC). The average is approximately 5 HSCT per year. All were paediatric patients, before the age of 14 years in the last years.

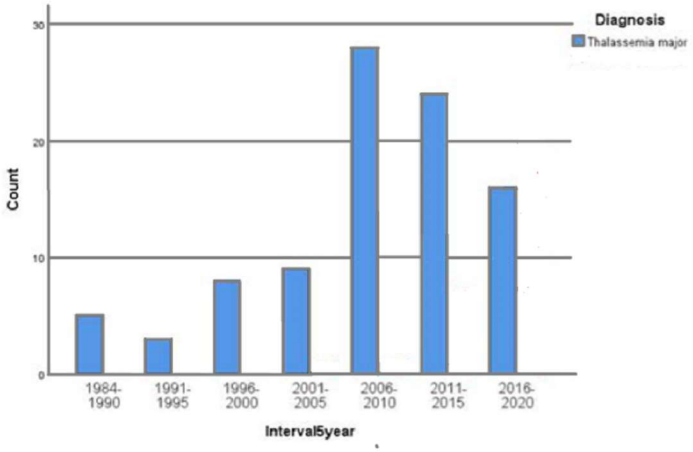


Figure 13 Number of allo-HSCTs performed for TDT patients from 1984-2020 in the LUMC (Netherlands)[77] *Edited from original*

In the pretransplant work-up, evaluation of iron levels, including in cardiac and liver tissue, is carried out. Endocrine dysfunction has no relevance on HSCT outcomes, it should nevertheless be checked to allow accurate post-transplant follow-up. Iron chelators should be withheld before the moment of allo-HSCT; preferably, the iron should be removed as much as possible.

In the post-transplant follow-up, monitoring of haematological and engraftment parameters, infectious complications and graft-versus-host-disease in the first year, is needed. Appropriate immunisation during the second year is done if there is no graft-versus-host-disease. Removal of excess iron by iron chelators or/and phlebotomy (especially immediately post-transplant) with standardised protocols is essential. It should be started only after graft stabilisation and discontinuation of immunosuppressants.

■ Blood transfusions

Life-long repeated packed red blood cell transfusions are carried out according to the international guidelines mentioned before. Extended red blood cell typing is essential before the first transfusion. All patients are transfused with ABO, Rhesus and Kell antigen compatible red blood cells in order to avoid alloimmunisation against these antigens. The transfusion regimen promotes normal growth, allows for regular physical activities, suppresses bone marrow activity and especially extramedullary hematopoiesis.

Usually patients are transfused every 2 to 5 weeks to maintain a pre-transfusion haemoglobin level of 9-10,5 g/dL and achieve a post-transfusion haemoglobin level of 14-15 g/dL. Concretely in the Netherlands, specialists indicated to the company that on average patients have 15-20 transfusion episodes a year, in order to follow the international standards. Belgian experts indicated approximately 13 transfusion episodes per year, usually every 4 weeks, and for some patients 17 times per year (being every 3 weeks).

Currently in the Netherlands, all patients aged ≥ 12 years of age (n=66) receive repeated transfusions and iron chelators. In Belgium, this number is 54 patients.

■ Iron chelators

Iron chelation therapy aims at reducing the serum ferritin level between 500-1.000 µg/L. Liver and heart iron concentration is regularly monitored by magnetic resonance imaging. For myocardial iron, the measured parameter CMRI T2* should be above 20 ms. Patients with values below 6 ms are at high risk for symptomatic heart failure, irrespective of the liver iron content.[23]

Iron chelation therapy is to be monitored on the following aspects : adherence, side-effects of iron chelators and sometimes negative iron balance.

Three chelation therapies are available and recommended : deferoxamine or desferrioxamine, deferiprone and deferasirox. Deferoxamine is given subcutaneously, intramuscularly or intravenously. The two others orally. For optimal treatment results, patients should be monitored every 3 months according to the international guidelines.

■ Complications of β-thalassaemia

The clinical management of patients with transfusion-dependent thalassaemia is more than the control of haemoglobin levels and iron burder alone. In the international recommendations, management of all the complications are dealt with such as e.g. osteoporosis, (in)fertility, infectious risks and liver cirrhosis.

■ ZYNTEGLO and unmet medical need

Within the therapeutic armamentarium for the treatment of β-thalassaemia, additional treatment options are warranted, such as addressing the underlying genetic defect of the disease and reducing/eliminating supportive treatments, in particular the blood transfusions and iron chelators. Allogeneic HSCT is typically reserved for fit paediatric patients, < 14 years, for whom a HLA-matched related sibling is present. Only 25-30 % of patients have this donor.

Therefore the therapeutic and social needs that ZYNTEGLO beti-cel (label : ≥ 12 years) is to address, are as follows:

- Young patients < 14 years who do not have an HLA-matched related donor. The Belgian expert consulted by the company stated that ZYNTEGLO is to be given as early as possible, and preferentially (in the future) below the age of 12 years.
- Patients older than 14 years for whom a HSCT is not foreseen anymore, but are nevertheless fit enough to undergo the entire procedure of an autologous stem cell transplantation.

The proposed position of ZYNTEGLO within the pathway of are is as follows, indicated in green :

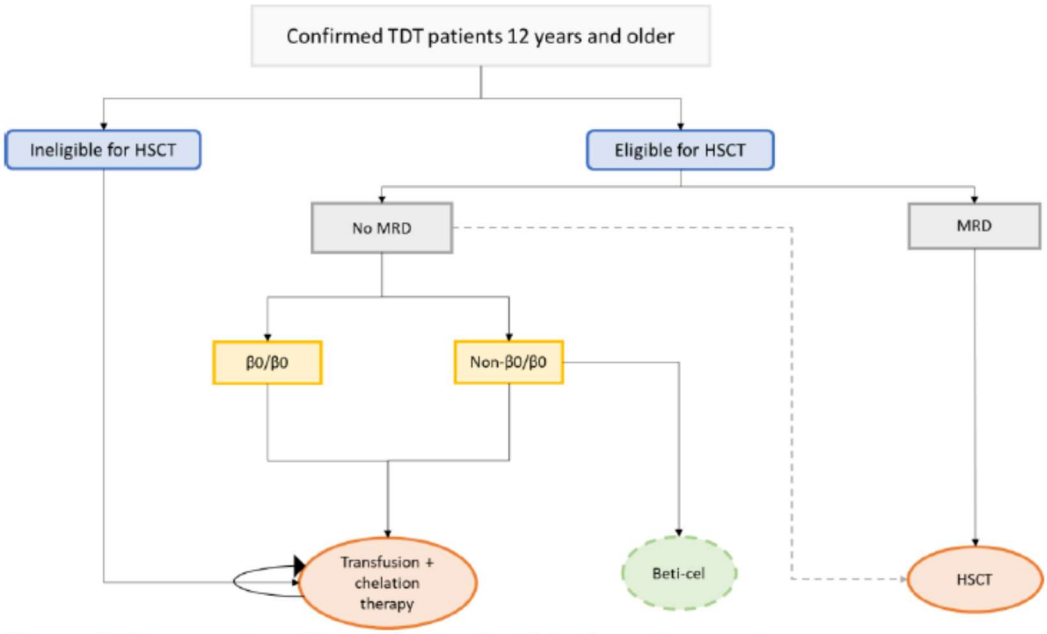


Figure 14 Proposed position of beti-cel within the pathway of care

Abbreviations: HSCT, haematopoietic stem cell transplantation; MRD, matched related donor; TDT, transfusion-dependent β-thalassaemia. Please note that the dotted arrow between No MRD and HSCT is only relevant for specific adolescent patients.

Source: TIF guidelines[1, 74] plus input from Dutch KOLs[58, 59]

■ REBLOZYL luspatercept ?

On July 8th 2020, the European Commission licensed REBLOZYL luspatercept in 2 indications, myelodysplastic syndrome and thalassaemia. The latter indication is in full 'Treatment of adult patients with transfusion-dependent anaemia associated with β-thalassaemia.' This treatment is not available in the Netherlands and Belgium.

3.2. MOLECULAR PHARMACOTHERAPY

International non-proprietary name : Autologous CD34-cells encoding $\beta^{A\text{-}T87Q}$ – globin gene
Other names : betibeglogene autotemcel, or short beti-cel
ZYNTEGLO ; the former name was LentiGlobin.

Construction of the lentiviral vector

The type of vector applied to produce functional copies of the $\beta^{A\text{-}T87Q}$ – globin gene is BB305-LVV. It is a replication-defective, self-inactivating, third-generation human immunodeficiency virus type-1 (HIV-1) based lentivirus. The vector is pseudotyped with an envelope protein of the vesicular stomatitis virus carrying the human β-globin gene. The gene has a single modification at codon 87 under the transcriptional control of the erythroid human β-globin promoter and erythroid specific enhancer elements of the β-globin locus control region. The lentiviral vector contains proteins responsible for forming the lentiviral virions that are encoded by plasmids used to transfect human embryonic kidney (HEK297T) cells during the production phase.

Dispersion for infusion

ZYNTEGLO contains autologous, i.e. from the patient, CD34+ enriched HSC transduced by a lentiviral vector encoding the $\beta^{A\text{-}T87Q}$-globin. The product is available in a 20 mL cryoperservation bag or multiple bags according to higher body weight. The minimum recommended dose is 5 million CD34+ cells/kg. After single intravenous infusion, the HSC engrafts in the bone marrow area and differentiates into erythrocytes, leukocytes and platelets. In the erythroid cell series, the modified β-globin $\beta^{A\text{-}T87Q}$ transgene comes to expression as a protein addressing the underlying genetic defect of the disease.

3.2.1. Mechanism of action

Biologically active β-globin

The erythrocytes express biologically active $\beta^{A\text{-}T87Q}$-globin, which is a modified β-globin of haemoglobin. $\beta^{A\text{-}T87Q}$-globin combines with ὰ-globin and haem to form haemoglobin. This haemoglobin is called HbA^{T87Q}. The $\beta^{A\text{-}T87Q}$-globin expression was designed to correct the β/ὰ globin imbalance in erythroid cells of patients with transfusion-dependent β-thalassemia. The $\beta^{A\text{-}T87Q}$-globin contains a single amino acid modification that was chosen because of its presence in the ϒ-globin and δ-globin chains. The $\beta^{A\text{-}T87Q}$-globin can be quantified relative to other globin species in peripheral blood using a high-performance liquid chromatography technique.

Following successful engraftment and achievent of the transfusion independence, the effects of ZYNTEGLO beti-cel are expected to be life-long (SPC). In pharmacodynamic studies studying the presence of HbA^{T87Q} in haemoglobin electrophoresis, median HbA^{T87Q} levels increased from month 1 through approximately month 6 to month 9, after which time they stabilized (EPAR).

3.2.2. Pharmacotherapeutic group

Gene transfer therapy ; ATC code not yet assigned.

Beti-cel is an ATMP and further classified as a gene therapy medicinal product.

For the EMA, beti-cel addresses an unmet medical need and was therefore part of the EMA-Adaptive Pathways Pilot and was granted PRIME designation. On March 28th 2019, the CHMP adopted a positive opinion. On May 29th 2019, EMA granted a conditional marketing autorisation for ZYNTEGLO beti-cel. Extension of indications are in the pipeline for β°/β° genotype and for patients under the age of 12 years.[24]

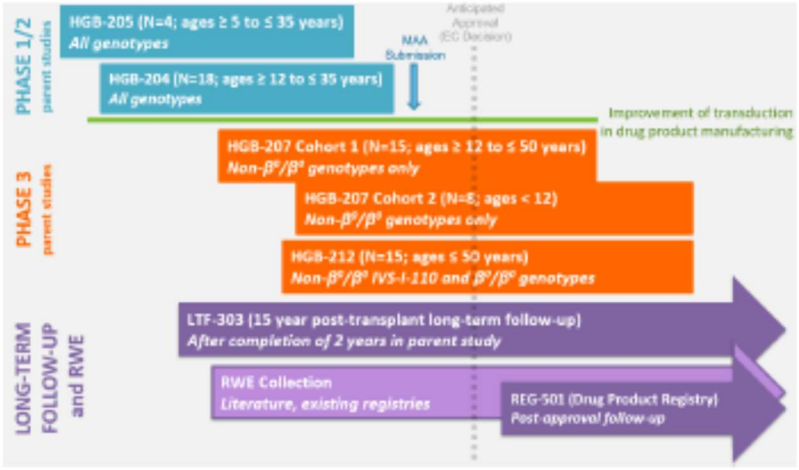
The company is developing another gene therapy on autologous CD34+ cells in another blood disease, namely in sickle-cell disease.[25] The EPAR mentions study HGB-206 as ongoing for patients with sickle-cell disease, in which n=19 patients were treated as by Dec 13th 2018.

3.2.3. Pharmacokinetic properties

ZYNTEGLO beti-cel is an autologous gene therapy medicinal product consisting of autologous blood progenitor cells that have been genetically modified ex vivo. The nature of ZYNTEGLO is such that studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

3.3. ASSESSMENT OF THE THERAPEUTIC VALUE AND ITS IMPORTANCE

Figure 4: Zynteglo Lifespan Approach to Clinical Evidence Generation for Transfusion Dependent β-Thalassemia



Note: The numbers of subjects given reflects the number planned for each group specified

ref[26]

► The phase 1 / 2 studies are HGB-205 and HGB-204. For the CHMP, the data lock was set on December 13th 2018.

► The phase 3 studies are HGB-207 with 2 cohorts and HGB-212. The phase 3 studies are carried out with the commercially available presentation of ZYNTEGLO; the production process was adapted to increase the average number of functional $\beta^{A\text{-}T87Q}$ – globin gene copies (source : FINOSE report). For the EMA, data lock of the phase 3 study data was set on December 13th 2018. At this moment in time, very few data from phase 3 studies were known (4 evaluable patients).

► LTF-303. The long-term follow-up study LTF-303 is fed by the above mentioned studies. After completion of 2 years in the parent study, study patients entered LTF-303. Results from the follow-up study are presented in this report as being the most recent data available. Data lock March 3rd 2020 in the present submission file.

► As control *efficacy* data Bluebird used the two years of retrospective pre-study enrolment for each individual patient. Hereto existing registries in the participating expert centres of thalassaemia were consulted. In the scheme above, this is given as RWE. For control *safety* data of standard of care, literature search in Embase, Medline and five conference website was done for articles reporting on clinical practice studies in Italy, France, Germany, Greece, the United States and the United Kingdom.

► REG-501. For study patients with the non β°/β° genotype and an age of 12 years or above, additional long-term safety and efficacy are collected at the request of the EMA in a registry of real-life data, called REG-501. Because of the conditional marketing autorisation, Bluebird is to submit interim data on an annual basis, for a period of 5 years.

3.3.1. Evidence in clinical trials

Study data phases 1 / 2 and 3 with the above data cuts were used for EMA licensing and are mentioned in the SPC. In this report however, outcome data are used with the most recent data lock available March 3rd 2020.

The CHMP used for pooled efficacy analysis the phase 1 / 2 studies in so far they included the non-β^0/β^0 genotype. The CHMP did not include phase 3 data in the pooling because very few patients were included at that time. For pooled pharmacodynamic analysis, however, all study data were used. In this report, pooling of efficacy data of all study patients phases 1 / 2 and 3 is done in LTF-303, the long-term follow-up study. Of note, the most important pharmacodynamic parameter for the CHMP was the quantification of β^{A-T87Q}-globin in blood.

As the clinical trials HGB-204 and HGB-205 were initiated als phase 1 / 2 trials, the initial study protocols did not include quality of life endpoints. After beti-cel was accepted into Priority Medicines scheme (PRIME) by the EMA, both studies were included as relevant evidence in the application for market authorization. At that time HGB-205 was already completed and almost all patients in HGB-204 had already been treated with beti-cel. Given the importance of quality of life data for health technology assessments, however, the EQ-5D measure was added to the parent study protocol post-commencement. Consequently, only 2 patients treated in HGB-204 had data able to represent changes from pre-treatment baseline measurement (of which only one had non-β^0/β^0-genotype and who did not achieve TI). The majority of patients treated in HGB-204 only had quality of life questionnaire data from the month 6 visit onwards.

The HGB-207 and HGB-212 clinical studies were the phase 3 pivotal studies including quality of life endpoints from onset. At the March 2020 datacut, only 11 patients from the HGB-207 and HGB-211 studies had data available at month 12 and month 24 across all quality of life instruments. All other patients in these trials had not been followed-up long enough to have this dataset available until month 24.

All studies were open-label and single-arm.

3.3.1.1. EFFICACY

Element from the EPAR

CHMP conclusion on the efficacy in the benefit/risk assessment (EPAR):

2.5.5. Conclusions on the clinical efficacy

The number of patients is low with limited follow-up time for patients in Phase 3 studies, but the overall presented data show clinically relevant and meaningful results by achieving TI in 11 out of 14 patients in studies HGB-204 and HGB-205 and 4 of 5 evaluable patients in study HGB-207. The preliminary data from study HGB-207 are consistent with early results and demonstrate improvement in total Hb levels to be achieved.

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

- In order to confirm the efficacy and safety of Zynteglo in patients 12 years and older with TDT who do not have a β^0/β^0 genotype, the MAH should submit interim and final data on Study HGB-207.
- In order to confirm the efficacy and safety of Zynteglo in patients 12 years and older with TDT who do not have a β^0/β^0 genotype, the MAH should submit interim and final data from patients with a severe non-β^0/β^0 genotype such as IVS-I-110/IVS-I-110 and IVS-I-110/β^0 from Study HGB-212.
- In order to confirm the efficacy and safety of Zynteglo in patients 12 years and older with TDT who do not have a β^0/β^0 genotype, the MAH should submit interim data and the 5 years follow-up results of study LTF-303.

The CAT considers the following measures necessary to address issues related to efficacy:

- Non-interventional post-authorisation safety and efficacy study: In order to further characterise and contextualise the long-term safety and efficacy of Zynteglo in patients 12 years and older with TDT who do not have a β^0/β^0 genotype, the MAH should conduct and submit the results of a study based on data from a product registry (REG-501) and use data on patients treated with transfusions and/or HLA-matched allogenic HSCT treated patients from an established European registry as a comparator group.

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

Analysis of the trials on which the efficacy is based on

In all the cohort trials, the same inclusion criteria for **non β°/β°** genotype β-thalassaemia patients were used. The same definition of **transfusion-dependent thalassaemia** (TDT) was used in all the cohort trials namely patients receiving at least 100 mL/kg/year of packed RBCs or 8 or momre transfusions per year in each of the 2 years prior to enrolment.

Studies phase 1 / 2, dose finding studies[27]

HGB-205

This was a single-arm study and multisite study in Thailand, Australia and the United States. Study HGB-205 was designed to primarily assss the safety and pharmacodynamic endpoints. Patients received ZYNTEGLO finished product form identical as in study HGB-204. Study HGB-205 also included sickle cell anaemia patients (off-label).

N=7 patients were enrolled and treated, 4 adolescents with TDT and 3 adolescents/young adults with sickle cell anaemia. The 4 patients with TDT were all of non-β^0/β^0 genotype.

HGB-204

This was a single-arm study in Hôpital Necker in Paris designed to primarily assess the safety and pharmacodynamic endpoints. Patients received ZYNTEGLO finished product identical as in study HGB-205.

N=18 patients were treated, 15 adults and 3 adolescents. 10 had non-β^0/β^0 genotype TDT (on-label) and 8 the most severe form β^0/β^0 genotype (off-label) TDT. Patients age was between 12-35 years.

Studies phase 3

HGB-207

This study is ongoing. It is a single-arm study and multisite study in France (Marseille), Germany, Italy, Thailand, United States and United Kingdom. Patients received the commerically available form of ZYNTEGLO beti-cel. There were 2 cohorts of patients with TDT all of them presenting the non-β^0/β^0 genotype. Cohort 1 included patients ≥ 12 and ≤ 50 years of age (on-label), whereas cohort 2 includes patients <12 years of age (off-label).

N=15 patients were treated in cohort 1 and N=8 patients in cohort 2. The number of patients enrolled in the study before the moment of beti-cel infusion was not given.

HGB-212

This study is ongoing. It is a single-arm study and similar to study HGB-207, except on one point: β^0/β^0 genotype is being studied as well as the IVS-I-110 mutation. Similar to the β^0-allele, the IVS-I-110 allele is widely recognized as producing little to no β-globin. Thus subjects with β^0/IVS-I-110 or IVS-I-110/IVS-I-110 genotypes were excluded from study HGB-207 and grouped with the β^0/β^0 subjects here in study HGB-212. The applicant of this submission considered IVS-I-110 mutation as β^+ as this mutation has phenotypic characteristics of both β^0 and β^+. The β^0 and β^+ aspects of this mutation was discussed in the *Gemeinsamer Bundesausschuss* on March 24th 2020 in Berlin; it was concluded that β^0/IVS-

I-110 or IVS-I-110/IVS-I-110 genotypes were to be considered as non-β^0/β^0 and were therefore within the label of ZYNTEGLO.[28] This study has, like HGB-207, two age cohorts with the same age classes.

N=6 non-β^0/β^0 TDT patients (on-label) and N=9 β^0/β^0 TDT patients (off-label) were treated as of March 2020. The number of patients enrolled is not known. As to the 6 non-β^0/β^0 subjects, 4 were in cohort 1 and 2 in cohort 2.

Long-term follow-up study LTF-303

The long-term follow-up study LTF-303 is still ongoing. Study patients treated with beti-cel who have completed any of the above studies are enrolled in study LTF-303 for an additional 13 years of follow-up, for a total of 15 years after beti-cel infusion. Therefore, study LTF-303 has the longest follow-up period being 72 months post-beti-cel infusion, at the latest moment of analysis: March 3rd 2020.

The LTF-303 includes at data lock n=23 TDT patients ≥ 12 years with a non-β^0/β^0 genotype and n=9 patients ≥ 12 years with the β^0/β^0 genotype.

As to the n=23 non-β^0/β^0 genotype patients with TDT ≥ 12 years old, this is less than the summation of the number of patients in HGB-205 (n=4) + HGB-204 (n=10) + HGB-207 (n=15) + HGB (n=4) making a total of n=33 patients in the above studies. In other terms, long-term data are available only for 23/33 study patients, at data lock December 2020.

Comparator(s) and justification of the choice and doses (according to the Belgian context)

Each study patient was its own control, namely in the period of 2 years before enrolment in the study. This is considered appropriate as no patient is expected to become transfusion-free in this progressive blood disease.

The use of repeated blood transfusions and iron chelation therapy is the comparator in the relative effectiveness assessment, as this is the current standard treatment for these patients without beti-cel infusion in the Netherlands and Belgium.

Population studied and target population

Main inclusion criteria used in all the cohort studies HGB-205, HGB-204, HGB-207 and HGB-212 (EPAR):

1. Patients aged ≤ 50 years
2. Diagnosis of transfusion-dependent β-thalassaemia (TDT) with a history of at least 100 mL/kg/year of packed RBCs in the 2 years preceding enrolment, or be managed under standard thalassaemia guidelines[2] with ≥ 8 transfusions of packed RBCs per year in the 2 years preceding enrolment.
3. Clinicallly stable and presenting a Karnofsky performance status of ≥ 80 for adults or a Lansky performance status of ≥ 80 for aédolescents or children and eligible to undergo an HSCT.
4. Treated and followed for at least 2 years in a specialized centre that maintained detailed medical records on RBC transfusions, in-hospital stays and iron chelators.

Main exclusion criteria for all the studies HGB-205, HGB-204, HGB-207 and HGB-212 (EPAR):

1. Presence of the β^0/β^0 genotype in studies HGB-205 and HGB-207. Similar to β^0-alleles, the IVS-I-110 mutation is widely recognized as producing little to no β-globin. Thus subjects with β^0/IVS-I-110 or IVS-I-110/IVS-I-110 genotypes were excluded from study HGB-207 and grouped together with β^0/β^0 subjects in study HGB-212.
2. Positive testing for HIV-1, HIV-2, HBV or HCV.
3. A white blood cell count < $3x10^9$/L and/or platelet count <$100x10^9$/L not related to hypersplenism.
4. Prior HSCT.
5. Advanced liver disease, as for e.g. MRI of the liver demonstrating clear evidence of cirrhosis.
6. Estimated GFR < 70 mL/min/1,73 m^2 as determined using the CKD-EPI creatinine equation for ≥18 years of age and Bedside Schwartz equation calculator for < 18 years of age.
7. Any condition that would render the patient ineligible for HSCT, as determined by the attending transplant physician or investigator.
8. Prior receipt of gene therapy.
9. A known and available HLA-matched family donor.
10. Any contraindications to the use of G-CSF and plerixafor during the mobilization of the hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning.

The study had 7 distinctive stages numbered from 0 to 6:

0. Pre-treatment. In this stage, study HGB-207 allowed intensive blood transfusions just before autologous HSCT in order to diminish the ineffective erythropoiesis. So-called "hypertransfusions" regimen as given with an allogeneic HSCT.
1. HSC mobilization. The HSC mobilization was organized approximately 2 months before beti-cel infusion. Each patient underwent HSC mobilization with a granulocyte colony-stimulationg factor G-CSF e.g. filgrastim or lenograstim, as well as with plerixafor MOZOBIL. The use of plerixafor in this situation was off-label.
2. Apheresis. Peripheral blood mononuclear cells were collected by apheresis. A total of 2 mobilization cycles could be performed if needed, and each mobilization cycle could include up to 3 apheresis days. However, patients whose drug product failed to meet specifications for any raison underwent repeat apheresis and manufacture of new beti-cel. Apheresis products were processed for ZYNTEGLO production but also kept as rescue cells if needed in case of ZYNTEGLO graft failure. Alternativetly to apheresis, a bone marrow harvest by puncture was allowed to procure HSC for rescue.
3. Stem cell processing. Selection of HSC, transduction with the vector, freezing, testing and batch release was performed at the Bluebird manufacturing site.
4. Myeloablation. The myeloablative conditioning of the patient occurred one week before the beti-cel infusion. From stage 4 on, the patient was hospitalized in the haematological intensive care ward. After the transduced stem cells are dispositioned for clinical use and the patient's eligibility was confirmed by laboratory tests, performance status and adverse events review, myeloablative conditioning with busulfan was carried out. Busulfan was given at a dose of 3,2 mg/kg IV daily, for 4 consecutive days. For children a lower posology was allowed, as guided by the target AUC of busulfan. It was followed by at least 48 hours of washout of busulfan.
5. Beti-cel infusion. This occurred at day 1 of the protocol. Thawed beti-cel was

administered via IV infusion at a dose of ≥ 5 million CD34+ cells/kg body weight tot he study patient.

6. In-patient stay. Finally, an in-patient stay at the intenstive care unit and subsequently haematology ward for 3 weeks up to 6 weeks as a whole.

The different stages of the treatment for all study patients are given in the figure below.

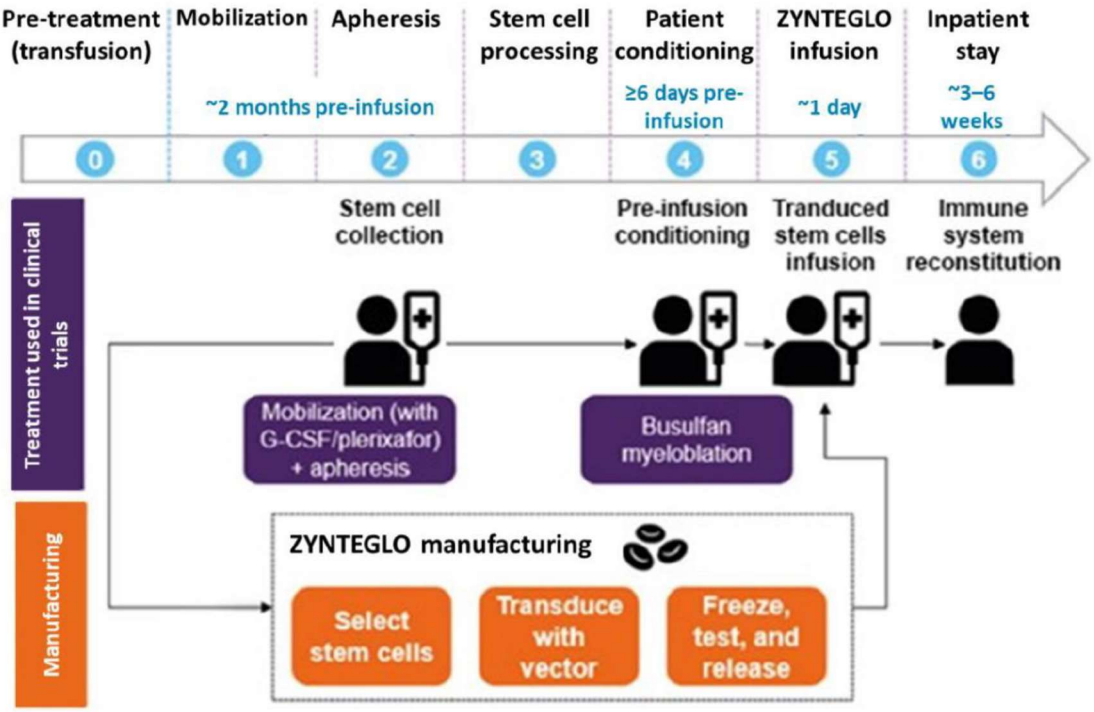


Figure 1 Overview of the Zynteglo manufacturing and treatment pathway (Reference: Company's submission material [2]

ref[29]

Criteria of efficacy in the trials

Primary efficacy endpoint

For the *pooled* EMA analysis of efficacy with studies HGB-204, HGB-205 and HGB-207[3] as well as for study HGB-207 *on its own*, the primary endpoint was the proportion of patients who met the definition of transfusion independence (TI). TI is defined as a weighted average Hb concentration of ≥ 9 g/dL without any packed RBC transfusions for a continuous period of ≥ 12 months at any time during the study after drug product infusion.

[3] During the CHMP procedure, no patient was included in phase 3 study HGB-212.

Secondary efficacy endpoints for study HGB-207

- Characterisation of patients achieving TI, among others, Duration of TI and Time from beti-cel infusion to last RBC transfusion, and time to reach TI
- Characterisation of transfusion reduction (TR)
- Weighted average nadir Hb during the 2 years prior to enrolment compared to weighted average nadir Hb from 12 months post-DP infusion through the month 24 visit
- Characterisation of use of iron chelation such as
  - proportion of patients who have discontinued iron chelation therapy for at least 6 months
  - change in dose of iron chelation therapy from baseline, for those patients not discontinuing chelators for at least 6 months.
- Evaluation of the change in iron burden over time.

Exploratory efficacy endpoints for study HGB-207

- Evaluation of health-related quality of life with PedsQL for children, with PedsQL and EuroQol-5D for adolescents and EuroQol-5D, FACT-BMT and SF-36 v2 for adults.
- Assessment of growth and puberty parameters, bone density, diabetes, endocrine evaluations and neurocognitive development (< 18 years)
- Assessment of improvement in effective erythropoiesis
- Correlations of pre-treatment variables, amongst others, of drug product vector copy number, with response obtained
- Measures of health resource utilization comparing number of transfusions, number of hospitalizations, and iron chelation usage from 12 months post-beticel infusion through 24 mont visit with the annual average of corresponding parameters during the 2 years of enrolment.

Results of the main trials

a) Patient characteristics

Phase 3 study HGB-207

- CHMP analysis with data lock February 2018: n=14
- ≥ 12 years
- Non β^0/β^0 TDT

Mobilisation/apheresis details (EPAR)

Table 21: Mobilisation/Apheresis Details for Study HGB-207 (ITT Population)

Parameter	Statistic	Splenectomized (N=5)	Not Splenectomized (N=9)	Overall (N=14)
Number of Mobilization Cycles / Subject				
1	n (%)	3 (60.0)	9 (100.0)	12 (85.7)
2	n (%)	2 (40.0)	0	2 (14.3)
G-CSF Average Daily Dose (µg/kg/day) [1]	N	5	9	14
	Mean (SD)	6.46 (2.135)	10.23 (0.721)	8.89 (2.286)
	Median	5.44	10.00	9.86
	Min, Max	5.1, 10.2	9.3, 11.6	5.1, 11.6
Plerixafor Average Daily Dose (mg/kg/day) [1]	N	5	9	14
	Mean (SD)	0.246 (0.0069)	0.241 (0.0168)	0.243 (0.0139)
	Median	0.245	0.235	0.242
	Min, Max	0.24, 0.25	0.22, 0.28	0.22, 0.28
Number of Apheresis Procedures Performed per Mobilization Cycle [2]	N	5	9	14
	Mean (SD)	2.60 (0.418)	1.89 (0.333)	2.14 (0.497)
	Median	2.50	2.00	2.00
	Min, Max	2.0, 3.0	1.0, 2.0	1.0, 3.0

Most of the patients (12/14) had only 1 cycle of CD34+-cell mobilization and a minority had 2 cycles (2/24). The dose of granulocyte-colony stimulating factor was median 9,9 µg/kg/day with range 5,1-11,6 mg/kg/day. The dose of plerixafor MOZOBIL was median 0,24 mg/kg/day with range 0,22-0,28 mg/kg/day. Per mobilization phase, patients underwent subsequently 2 apheresis procedures on the median, with range 1-3 apheresis procedures.

Parameter	Statistic	Splenectomized (N=5)	Not Splenectomized (N=9)	Overall (N=14)
Number of CD34+ Cells Collected (Cells×10^6/kg)	N	5	9	14
	Mean (SD)	15.38 (4.061)	26.21 (7.602)	22.34 (8.344)
	Median	16.56	23.70	21.59
	Min, Max	8.9, 18.8	12.3, 35.1	8.9, 35.1
Number Of CD34+ Cells Sent for Transduction (Cells×10^6/kg)	N	5	9	14
	Mean (SD)	12.37 (3.585)	19.40 (7.068)	16.89 (6.850)
	Median	13.52	17.60	15.53
	Min, Max	6.4, 15.7	10.5, 30.9	6.4, 30.9
Number Of CD34+ Cells Sent for Rescue (Cells×10^6/kg)	N	5	9	14
	Mean (SD)	3.01 (1.003)	7.49 (4.352)	5.89 (4.112)
	Median	2.73	6.10	4.80
	Min, Max	2.1, 4.7	2.4, 15.7	2.1, 15.7

On the average, 22 million CD34+-cells/kg body weight were collected (n=14), 17 million cells/kg were sent for transduction and beti-cell production, and 6 million cells/kg were sent for a rescue procedure (if required).

Drug product dosing and infusion details (EPAR)

Table 22: Drug Product Dosing and Infusion Details, by Age Group and Sex (TP)

Parameter	Statistic	Age <12	Age 12 to <18	Age >=18	Sex M	Sex F	Overall (N=10)
Duration of Hospitalization (days) [1]	N	0	2	6	3	5	8
	Mean (SD)		53.0 (5.66)	42.3 (5.61)	50.0 (6.56)	42.0 (6.20)	45.0 (7.17)
	Median		53.0	43.5	49.0	43.0	44.0
	Min, Max		49, 57	32, 49	44, 57	32, 49	32, 57
Number of Drug Product Lots Administered							
1	n (%)	0	4 (100.0)	5 (83.3)	4 (100.0)	5 (83.3)	9 (90.0)
2	n (%)	0	0	1 (16.7)	0	1 (16.7)	1 (10.0)
3	n (%)	0	0	0	0	0	0
4	n (%)	0	0	0	0	0	0
Total Cell Dose (CD34+ cells x 10^6/kg)	N	0	4	6	4	6	10
	Mean (SD)		9.70 (6.551)	8.77 (2.984)	6.88 (1.176)	10.65 (5.235)	9.14 (4.414)
	Median		7.20	8.00	7.20	9.45	7.65
	Min, Max		5.0, 19.4	5.2, 13.6	5.2, 7.9	5.0, 19.4	5.0, 19.4

On the average, 9 million transduced CD34+-cells/kg (n=10) were infused as beti-cel with a minimum of 5 million cells/kg and a maximum of 19 million cells/kg body weight.

Autologous graft details (EPAR)

Parameter	Statistic	Age <12	Age 12 to <18	Age >=18	Sex M	Sex F	Overall (N=10)
Time to Neutrophil Engraftment (days) [4]	N	0	3	6	4	5	9
	Mean (SD)		24.7 (5.77)	21.7 (3.78)	22.8 (4.99)	22.6 (4.51)	22.7 (4.42)
	Median		26.0	21.5	22.5	24.0	24.0
	Min, Max		18, 28	17, 26	18, 28	17, 28	17, 28
Time to Platelet Engraftment (days) [5]	N	0	1	6	3	4	7
	Mean (SD)		51.0 (-)	43.0 (4.00)	46.3 (4.04)	42.5 (5.07)	44.1 (4.74)
	Median		51.0	44.0	44.0	44.5	44.0
	Min, Max		51, 51	35, 46	44, 51	35, 46	35, 51
Time to Platelet Engraftment [5]							
<=30 days	n (%)	0	0	0	0	0	0
>30 to <=60 days	n (%)	0	1 (25.0)	6 (100.0)	3 (75.0)	4 (66.7)	7 (70.0)
>60 to <=90 days	n (%)	0	0	0	0	0	0
>90 days	n (%)	0	0	0	0	0	0
Subjects with Neutrophil Engraftment Success [6]	n (%)	0	3 (75.0)	6 (100.0)	4 (100.0)	5 (83.3)	9 (90.0)
Subjects with Platelet Engraftment Success [7]	n (%)	0	1 (25.0)	6 (100.0)	3 (75.0)	4 (66.7)	7 (70.0)

[4] Defined as the first of 3 consecutive absolute neutrophil count (ANC) laboratory values >= 0.5 x 10^9/L obtained on different days after a post-transplant value of <0.5 x 10^9/L. At the time of data-cut, one subject has not yet reached successful engraftment due to insufficient follow-up.
[5] Defined as the first of 3 consecutive platelet count laboratory values >= 20 x 10^9/L obtained on different days after a post-transplant value of <20 x 10^9/L, while no platelet transfusions were administered for 7 days immediately preceding and during the evaluation period.
[6] Defined as achieving neutrophil engraftment by Day 42 and not receiving back-up cells at any time during the neutropenic phase. At the time of data-cut, one subject has not yet reached successful engraftment due to insufficient follow-up.
[7] Defined as achieving platelet engraftment at any time during the study.

The time to neutrophil engraftment was 23 days on the average (n=10) and the time to platelet engraftment was 44 days, or more than a month (n=10). The proportion of patients with successful neutrophil engraftment at day 42 was 90% (9/10) and with successful platelet engraftment at any time of the study was 70% (7/10).

<u>Pooled analysis HGB-205, HGB-204 and HGB-207</u>

- CHMP analysis with data lock February 2018: respectively n=4, n=10 and n=10, for a total of n=24
- ≥ 12 years
- non β^0/β^0 TDT

Parameter	Statistic	Phase 1/2 Studies: HGB-204 Non-β⁰/β⁰ (N = 10)	HGB-204 β⁹/β⁹ (N = 8)	HGB-204 All Genotypes (N = 18)	HGB-205 Non-β⁰/β⁰ (N = 4)	Pooled Non-β⁰/β⁰ (N = 14)	Pooled All Genotypes (N = 22)	Phase 3 Studies: HGB-207 Non-β⁰/β⁰ (N = 10)	HGB-212 β⁹/β⁹ (N = 1)	All Studies Non-β⁰/β⁰ (N = 24)	All Studies All Genotypes (N = 33)
Age at starting iron chelation (years)											
	N	10	8	18	4	14	22	10	1	24	33
	Mean	9.7	5.8	7.9	5.0	8.4	7.4	6.0	4.0	7.4	6.9
	(SD)	(7.07)	(5.37)	(6.51)	(4.97)	(6.72)	(6.26)	(4.24)	(-)	(5.83)	(5.61)
	Median	7.5	3.5	6.5	3.5	7.0	6.0	4.5	4.0	6.5	5.0
	Min, Max	2, 26	2, 18	2, 26	1, 12	1, 26	1, 26	2, 16	4, 4	1, 26	1, 26
Pre-treatment baseline annualized pRBC transfusion volume (mL/kg/year)											
	N	10	8	18	4	14	22	10	1	24	33
	Mean	164.06	196.11	178.31	174.96	167.18	177.70	204.31	160.21	182.65	185.23
	(SD)	(30.419)	(50.022)	(42.294)	(25.606)	(28.602)	(39.287)	(38.583)	(-)	(37.346)	(40.050)
	Median	151.28	182.59	169.05	181.85	154.78	171.15	211.29	160.21	171.11	171.73
	Min, Max	140.0, 234.5	124.4, 273.2	124.4, 273.2	138.8, 197.3	138.8, 234.5	124.4, 273.2	158.7, 251.3	160.2, 160.2	138.8, 251.3	124.4, 273.2
Pre-treatment baseline annualized pRBC transfusion frequency (#/year)											
	N	10	8	18	4	14	22	10	1	24	33
	Mean	13.45	14.44	13.89	12.13	13.07	13.57	17.75	12.50	15.02	14.80
	(SD)	(1.817)	(1.935)	(1.883)	(1.181)	(1.730)	(1.885)	(3.981)	(-)	(3.667)	(3.274)
	Median	13.75	13.75	13.75	12.50	13.00	13.00	17.75	12.50	14.00	14.00
	Min, Max	10.0, 16.5	12.5, 17.5	10.0, 17.5	10.5, 13.0	10.0, 16.5	10.0, 17.5	11.5, 24.5	12.5, 12.5	10.0, 24.5	10.0, 24.5
Pre-treatment baseline weighted average nadir Hb that preceded pRBC transfusions (g/dL)											
	N	10	8	18	4	14	22	10	1	24	33
	Mean	8.73	9.38	9.02	9.46	8.94	9.10	9.42	9.72	9.14	9.21
	(SD)	(1.014)	(0.431)	(0.855)	(1.479)	(1.155)	(0.967)	(0.767)	(-)	(1.022)	(0.900)
	Median	9.11	9.43	9.31	9.44	9.11	9.31	9.63	9.72	9.43	9.52
	Min, Max	7.0, 9.8	8.7, 10.1	7.0, 10.1	8.1, 10.8	7.0, 10.8	7.0, 10.8	7.5, 10.2	9.7, 9.7	7.0, 10.8	7.0, 10.8
Pre-treatment baseline iron burden[3]											
Liver iron content (mg/g)											
	N	10	8	18	4	14	22	10	0[4]	24	32
	Min, Max	1.2, 26.4	0.4, 17.0	0.4, 26.4	3.9, 14.0	1.2, 26.4	0.4, 26.4	1.0, 19.61		1.0,19.61	0.4, 19.61
Cardiac T2* measurement (msec)											
	N	10	8	18	4	14	22	10	0[4]	24	32
	Min, Max	27, 54	10, 37	10, 54	29, 46	27, 54	10, 54	35.30, 50.92		27, 54	10, 54
Serum ferritin (pmol/L)											
	N	10	7	18	4	14	21	10	0[4]	24	31
	Min, Max	1643, 8629	748, 7267	748, 8629	2139, 7097	1643, 8629	748, 8629	349, 10020		349, 10020	349, 10020

Data as of 22 February 2018 for Study HGB-207 and 07 March 2018 for all other studies.
Source: Table 2.1.3; Table 2.1.4, Listing 2.2.6.5, Listing 2.2.6.6, Listing 2.2.6.7, Interim CSR HGB-207 Listing 16.2.6.7.2, Interim CSR HGB-207 Listing 16.2.6.8, Interim CSR HGB-207 Listing 16.2.6.9
Note: Retrospective pre-treatment transfusion history (pre-treatment baseline annualized pRBC transfusion volume, pre-treatment baseline annualized pRBC transfusion frequency, and pre-treatment baseline weighted average nadir Hb that preceded pRBC transfusions) were collected from the 2 years prior to date of informed consent.
[1] Other genotype reported as: *HBB*:c.92+1G>T & Unknown. The unknown allele is an unidentified β+ mutation of S since this subject is able to produce some endogenous HbA.
[2] Age at β-thalassemia major diagnosis is calculated as (date of diagnosis - date of birth + 1) / 30.4375
[3] Pre-treatment baseline iron burden values are defined as the last value prior to initiation of conditioning.
[4] Due to the limited follow-up time for the 1 treated subject in Study HGB-212, iron burden data was not included for this subject in this module.

Study patients (n=24) started iron chelators for TDT at the age of 7 years (mean). They had during the 2 preceding years before beti-cel infusion a baseline weighted average nadir Hb that preceded blood transfusions of 9,1 g/dL (mean) with a minimum of 7,0 and a maximum of 10,8 g/dL. Liver iron content was between 1,0 and 19,6 mg/gram. Cardiac T2* measurement was between 27 and 54 msec. Serum ferritine levels were between 349 and 10.020 pmol/L.

Study patients (n=24) received in the 2 years prior to beti-cel infusion on the average 183 mL/kg/year packed RBC transfusions, with a minimum of 139 and a maximum of 251. The mean number of yearly transfusion episodes was 15 with a minimum of 10 and a maximum of 24.

It was further observed, for the following study population (the most complete one)

- data lock March 2020
- ≥ 12 years
- Non β^0/β^0 TDT

See next table. As of the March 2020 datacut, there were 35 patients 12 years or older and with non β^0/β^0 enrolled in clinical studies, of which 33 were treated with beti-cel. It is noted that 2 patients dropped out prior to beti-cel infusion. One in study HGB-207 because of pregnancy after mobilisation and one in study HGB-204 on investigator decision after the mobilisation phase.

	HGB-205	**HGB-204**	**HGB-207**	**HGB-212**
Number of patients	4	10	15	4
CD34+-cell dose median (min-max) Million cells/kg	10 (9-14)	7 (5-13)	7 (5-19)	8 (6-10)
Age at diagnosis TDT Months Median (min-max)	3 (1-30)	68 (0-315)	12 (3-84)	6 (0-8)
Age at 1st RBC transfusion Months Median (min-max)	21 (1-84)	30 (0-132)	10 (4-84)	8 (6-12)
Age at established regular RBC transfusions Months Median (min-max)	21 (1-168)	72 (8-312)	84 (6-216)	10 (6-48)
Annual number of transfusions min-max	- (10-13)	14 (10-16)	17 (11-37)	27 (17-39)
Age at start iron chelator Years Median (min-max)	3 (1-12)	7 (2-26)	4 (0-17)	3 (2-5)

b) Primary outcome

The primary outcome, transfusion independence (TI) as defined above, in the pooled patient population and the 4 individual studies was given for the following study population

- data lock January 2020
- ≥ 12 years
- Non β^0/β^0 TDT

Of the n=33 patients, n=32 were evaluable for the primary objective TI.

Table 6 TI for non-ß⁰/ß⁰ patients ≥ 12 years of age in HGB-204, HGB-205, HGB-207 and HGB-212

Trial acronym; author, year	Patients treated; N	Patients evaluable for TI; N	TI at any time; n (%), 95%CI	Patients with TI at Month 60; n (%), 95%CI
HGB-204	10	10	8 (80) 44.4-97.5	5 (100) 47.8-100.0
HGB-205	4	4	3 (75) 19.4-99.4	2 (100) 15.8-100.0
HGB-207	15	15	14 (93.3) 68.1-99.8	0 (0) -
HGB-212	4	3	2 (66.7) 9.4, 99.2	0 (0) -
Overall	33	32	27 (84.4) 67.2-94.7	7 (100) 59.0-100.0

Abbreviations: CI, confidence interval; TI, transfusion independence
Source: bluebird bio; Clinical Study Reports HGB-204, -205,[92, 93] TLFs of HGB -207, -212 ***(figures are from the new data cut - 2020)***[109, 114, 115]

Overall, **TI at any time** of the study was **84%** (27/32) with 95% CI 67% to 95%. **TI at month 60** after beti-cel infusion was **100%** (7/7) with 95% CI 59% to 100 %. This was observed with a median follow-up of 35 months (range 1-72 months) at data lock. The studies HGB-207 and HGB-212 are ongoing, as mentioned before, and the number of patients reaching the moment of 60 months post-beti-cel infusion is to increase.

All study patients who achieved TI remained thus without any packed RBC transfusions and presented a weighted average Hb level ≥ 9 g/dL for a continous period of ≥ 12 months, according to the definition of TI.

Comparative data. In the 2 years preceding beti-cel infusion, 0% of the study patients were TI. This difference is clinically relevant in patients who were transfusion-dependent before.

c) Secondary outcomes

The secondary efficacy endpoints in the phase 3 studies HGB-207 and HGB-212 are pooled with the phase 1 / 2 studies HGB-204 and HGB-205.

So, it concerns the following study population

- data lock January 2020
- ≥ 12 years
- Non β^0/β^0 TDT

- Characterisation of patients achieving TI by, amongst others, duration of TI and time from beti-cel infusion to TI

  ■ Duration of TI

  The duration of TI is counted from the moment of the 12th month after the last packed RBC transfusion. Moments of packed RBC transfusion are given in red below. The duration of transfusion-free periods is given for every individual patient in blue (n=33), for TI-responders and for not (yet) TI-responders.

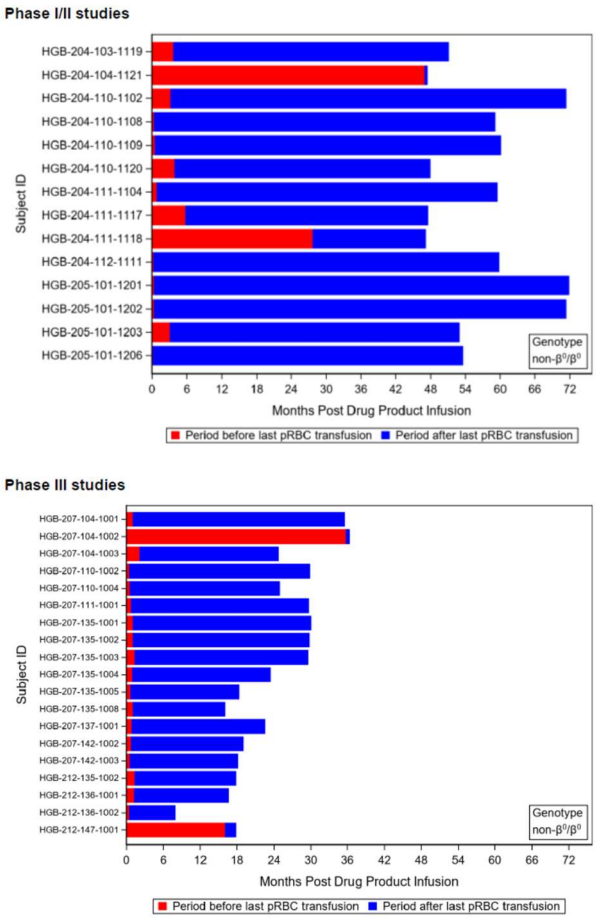


Figure 15 Duration of RBC transfusion period in non-β^0/β^0 patients ≥ 12 years of age

Abbreviations: pRBC, packed red blood cells
Source: bluebird bio; Clinical Study Report LTF-303[101]

These individual results are clinically relevant in patients who were transfusion-dependent before.

- Time from beti-cel infusion to the last RBC transfusion, and time to reach TI

Table 7 Time from beti-cel, infusion to last RBC transfusion, and time to reach transfusion independence (TP; TI patients only)

Trial acronym; author, year	N	Time from beti-cel infusion to last RBC transfusion before reaching TI, months	Time to reach TI, months
HGB-204	8	**Mean (SD):** 2.33 (2.098) **Median (min-max):** 2.00 (0.3-5.8)	**Mean (SD):** 17.60 (2.541) **Median (min-max):** 17.1 (15.0-20.9)
HGB-205	3	**Mean (SD):** 0.32 (0.137) **Median (min-max):** 0.36 (0.2-0.4)	**Mean (SD):** 15.15 (0.427) **Median (min-max):** 14.92 (14.9-15.6)
HGB-207	14	**Mean (SD):** 0.98 (0.431) **Median (min-max):** 0.94 (0.5-2.2)	**Mean (SD):** 15.79 (0.854) **Median (min-max):** 15.39 (15.0-17.9)
HGB-212	2	**Mean (SD):** 1.35 (0.093) **Median (min-max):** 1.35 (1.3, 1.4)	**Mean (SD):** 15.67 (0.000) **Median (min-max):** 15.67 (15.7-15.7)
Overall	27	**Mean (SD):** 1.33 (1.331) **Median (min-max):** 0.92 (0.2-5.8)	**Mean (SD):** 16.25 (1.721) **Median (min-max):** 15.64 (14.9-20.9)

Abbreviations: RBC, red blood cells; SD, standard deviation; TI, transfusion independence
Source: bluebird bio; Clinical Study Reports HGB-204, -205, new data cut Table 2.2.3.1.1.[92, 93, 109]

The time from beti-cel infusion to the last RBC transfusion before reaching TI in TI patients only, was on average 1 month with a minimum of 0 months and a maximum of 6 months.

The time to reach the TI took on average 16 months after beti-cel infusion, with a minimum of 15 months and a maximum of 21 months.

Concerning patients who achieve TI but do not achieve to maintain a weighted average of Hb ≥ 9,0 g/dL (5,59 mmol/L) in approximately 17% of patients, Dutch specialists were asked two questions:[30]
1° What is considered to be the normal Hb value i.e. considered in term of pre-transfusion Hb in Dutch clinical practice for TDT patients? Answer: Hb > 5,5 – 6,0 mmol/L (9 g/dL).
2° What criteria should be assessed to determine when a patient requires transfusion again, apart for the Hb level? Answer: extramedullary hematopoiesis, comorbidity, general performance and quality of life.

- Characterisation of transfusion reduction (TR)

  For the 5/33 patients who did not achieve TI, reductions of 100%, 86%, 84%, 57% and 46% in transfusion volumes were observed, as compared to the 2 years before beti-cel infusion.

  For the 5/33 patients who did not achieve TI, reductions of 100%, 77%, 75%, 9% and 41% in annual transfusion frequency was observed, as compared to the 2 years before beti-cel infusion.

  TI being the preferable outcome measures, Dutch clinical specialists were therefore asked what percentage/change in reduction in transfusions they consider to be *clinically relevant* for TDT patients. Answer: Preferably 100 % reduction being not transfusion dependent anymore after gene therapy or HSCT is applied. However, 50% reduction of transfusion frequency is also clinically relevant, as the patient benefits from lesser/shorter visits to the day care clinic and a lower iron loading burden with accompanied lower dosage of iron chelation therapy.

  In other terms, in the light of this clinical comment, among the 5/33 patients having a reduction in RBC transfusions, 3/5 patients had a relevant degree of transfusion reduction.

- Weighted average nadir Hb during the 2 years prior to enrolment compared to weighted average Hb during TI through the month 24 visit

  The median weighted average Hb level in patients achieving TI was 11,8 g/dL with a minimum of 9,4 g/dL and a maximum of 13,3 g/dL. In a descriptive way, the applicant states that this was equal or higher than the weighted average nadir Hb level when they were still on transfusions. Before, it ranged from 7,0 to 11,0 g/dL. Not all study patients have reached the month 24 visit moment, as mentioned before, only 20/33 reached that moment.

  Of note are the Hb levels in healthy individuals.[31] For healthy girls aged 11-19 years, mean Hb level is 13,5 g/dL with lower limit of normal 12,0 g/dL and for boys aged 11-14 years, mean Hb level is 14,0 g/dL with lower limit 12,0 as well. For boys aged 15-19 years, mean Hb level is higher, 15,0 g/dL, with lower limit of 13,0 g/dL.

  In other terms, the Hb levels in ZYNTEGLO treated patients, ranging 9,4 – 13,3 g/dL, did not reach the lower limit in healthy youngsters (13,5 or 14,0 g/dL). However, the observed range of Hb levels is within the range recommended for TDT patients in general, not undergoing ZYNTEGLO treatment (i.e. polytransfusions and iron chelation) as internationally recommended.[3]

- Characterision of use of iron chelation such as
  - proportion of patients who have discontinued iron chelation therapy for at least 6 months
  - change in dose of iron chelation therapy from baseline for those patients not discontinuing chelation for at least 6 months.

  After beti-cel infusion, patient iron levels were managed at physician discretion. This implies e.g. that physicians used phlebotomy instead of iron chelation therapy when the platelet count was too low to allow taking iron chelators.

  Studies HGB-205 and HGB-204
  Of the 14 non β0/β0 patients, 4/14 had stopped iron chelation for at least 6 months. The time from stopping iron chelation to the last visit was median 27 months, with range 11-42 months. Of the 14 patients, 3 patients received phlebotomy to remove iron.

  Studies HGB-207 and HGB-212
  Of the 19 non β0/β0 patients ≥ 12 years who completed the month 6 visit, 11/19 had stopped iron chelation. 9/19 patients had stopped for at least 6 months. The time from stopping iron chelation to the last visit for at least 6 months was median 18 months, with range 8-35 months. Of the 19 patients, 8 patients received phlebotomy to remove iron.

- Evaluation of the change in iron burden over time

The following data are solely given for the TI-responders being the n=27/33 of the pooled analysis 2020.

Summary of Iron Parameters Over Time (TP)
TI Subjects: Non-b0/b0 Genotype and >=12 Years of Age

Parameter	Statistic	Baseline (N=27)	Month 12 (N=27)	Month 24 (N=20)	Month 36 (N=12)	Month 48 (N=11)	Month 60 (N=7)	Year 6 (N=1)
LIC (mg/g)	N	26	23	19	4	10	3	1
	n < 7 mg/g	14	10	10	2	7	3	1
	% < 7 mg/g	53.8	43.5	52.6	50.0	70.0	100.0	100.0
Cardiac T2* (msec)	N	27	23	19	5	9	3	1
	n > 20 msec	27	22	19	5	9	3	1
	% > 20 msec	100.0	95.7	100.0	100.0	100.0	100.0	100.0
Serum Ferritin (ng/mL)	N	27	26	20	12	11	7	1
	n < 1000 ng/mL	4	4	9	10	10	6	1
	% < 1000 ng/mL	14.8	15.4	45.0	83.3	90.9	85.7	100.0

These data are to be compared with reference values for liver iron content, cardiac MRI T2*values and serum ferritin levels. Reference levels are given in the next Table.

Table 10 Reference levels for serum ferritin, liver iron content and cardiac T2*

	Serum ferritin[125-127]x,x,x	Liver iron content[128-130]	Cardiac T2*[27]
	ng/mL	mg Fe/g dry	ms
Reference level	20-200 (women) 20-500 (men)	0-2	>20
Elevated risk	1000-2500	7-15	10-20
Highly elevated risk	>2500	>15	<10

From these 2 tables, it can only be observed that on the long run, the few evaluable patients n=11 (month 48) and n=7 (month 60) all have values outside the risk area.

d) Exploratory outcomes

- Evaluation of health-related quality of life with PedsQL for children, with PedsQoL and EuroQol-5D-Y for adolescents and EuroQol-5D-3L, FACT-BMT and SF-36 v2 for adults.

  According to a protocol amendment, all questionnaires were to be collected from month 6 visit onwards. The reason was that the early studies HGB-204 and HGB-205 were initially considered as phase I/II studies and not as pivotal studies. Given the importance of quality of life-data for health technology assessments, the EuroQol-5D measure was added to the trials post-commencement. Also, this explains why several study patients did not have baseline quality of life measure. This was endorsed by PRIME and CHMP, which implied that the worsening of QoL in the first weeks/months after beti-cel infusion was *not to be reported*. So it was mentioned in the 2019 interim report of HGB-207 that "subjects show a trend towards returning to baseline levels on the administered HRQoL questionnaires by their month 12 visit". (page 10)

  The following Table gives the results for 9/33 pooled patients who were TI and 2/33 pooled patients who were non TI.

Table 13 HRQoL scores for TI & Non-TI patients from studies HGB-207 & HGB-212 who were ≥12 years with non-β^0/β^0 genotype, change from baseline to Month 12 & Month 24

Parameter	Statistic	TI Patients					Non-TI Patients				
			Month 12		Month 24			Month 12		Month 24	
		BL Value	Value	Change from BL	Value	Change from BL	BL Value	Value	Change from BL	Value	Change from BL
SF-36 (PCS)	N	9	9		5		2	2		1	
	Mean (SD)	53.83 (4.58)	54.64 (4.53)	0.81 (4.83)	56.22 (2.802)	1.87 (4.5103)	51.860 (1.54)	43.31 (12.08)	-8.55 (10.54)	49.40 (-)	-3.55 (-)
SF-36 (MCS)	N	9	9		5		2	2		1	
	Mean (SD)	50.85 (6.79)	52.37 (7.56)	1.528 (8.22)	55.67 (3.12)	6.94 (8.65)	50.14 (3.12)	54.13 (4.63)	3.99 (1.51)	35.86 (-)	-12.07 (-)
Peds-QL (total score, parent)	N	7	6		4		0	0		0	
	Mean (SD)	67.70 (15.37)	74.64 (9.95)	8.51 (15.26)	77.17 (13.84)	1.90 (11.45)	-	-	-	-	-
Peds-QL (total score, patient)	N	7	6		4		0	0		0	
	Mean (SD)	71.74 (13.56)	81.34 (6.79)	10.14 (17.26)	80.98 (8.89)	7.61 (9.39)	-	-	-	-	-
EQ-5D-3L*	N	9	9		5		2	2		1	
	Mean (SD)	84.3 (11.54)	91.2 (4.63)	6.9 (11.93)	97.8 (4.38)	15.2 (12.70)	87.5 (3.54)	75.0 (7.07)	-12.5 (10.61)	75.0 (-)	-10.0 (-)
EQ-5D-Y*	N	8	7		4		0	0		0	
	Mean (SD)	74.6 (19.96)	92.4 (3.55)	14.3 (19.24)	91.5 (7.77)	15.8 (14.86)	-	-	-	-	-
FACT-BMT	N	9	9		5		2	2		1	
	Mean (SD)	124.38 (12.08)	128.60 (12.21)	4.23 (16.99)	130.80 (7.56)	5.12 (12.45)	131.83 (1.65)	135.00 (0.00)	3.17 (1.65)	114.00 (-)	-19.00 (-)
FACT-G	N	9	9		5		2	2		1	
	Mean (SD)	93.04 (9.13)	96.07 (8.86)	3.04 (13.03)	97.20 (5.85)	3.20 (10.85)	98.17 (1.18)	101.50 (2.12)	3.33 (3.30)	87.00 (-)	-12.00 (-)

*EQ5D-3L scores reflect visual analog scale (VAS) component of EQ-5D instrument
Abbreviations: HRQoL, Health-Related Quality of Life; SF-36, Short-Form 36; PCS = Physical component summary; MCS = Mental component summary; PaedsQol, The Paediatric Quality of Life Inventory; FACT-BMT, Functional Assessment of Cancer Therapy – Bone Marrow Transplantation; FACT-G, Functional Assessment of Cancer Therapy; BL = baseline; TI = transfusion independent
Source: bluebird bio; Integrated summary of efficacy tables (HGB-207 & HGB-212)[134-138]
Please note: Table 2.2.16.3 includes subjects <12, 207-138-1001 is 11 years old. The numbers for EQ-5D-Y in this table are not for >=12 years.

No firm conclusions on QoL can be drawn from these data because of pauciness of data. A question is asked to the company on this issue.

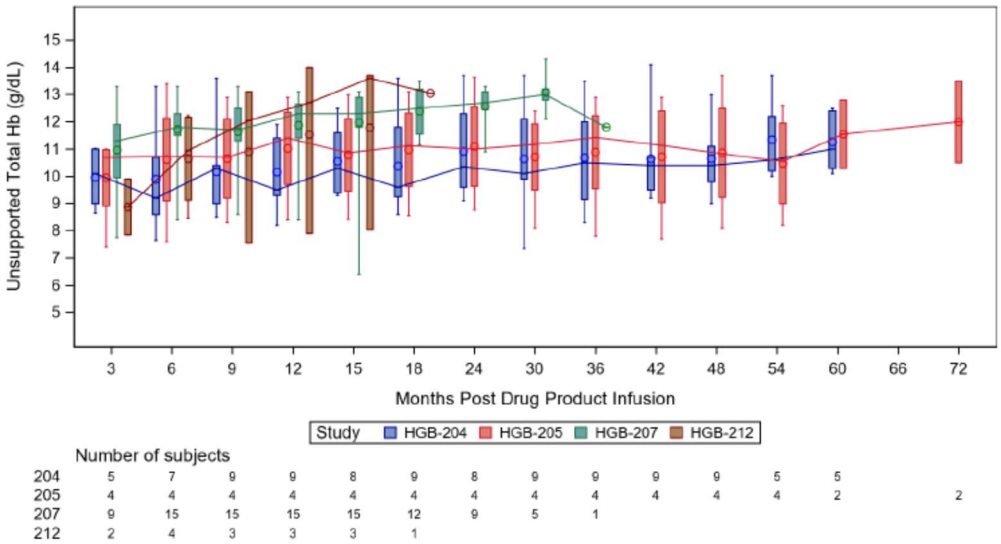
- Assessment of growth and puberty parameters, bone density, diabetes, endocrine evaluations and neurocognitive development (< 18 years)

HGB-207

14 patients underwent Tanner staging at screening, a standard test in pre-puberty and during puberty in youngsters. Seven patient were considered pre-pubertal at the time of beti-cel infusion and 4 patients were undergoing puberty and 1 patient was post-pubertal. These data are incomplete for the moment.

- Assessment of improvement in effective erythropoiesis

Figure 48 Total Hb production for patients who had not received a pRBC transfusion in the prior 60 days



Abbreviations: Hb, haemoglobin; TI
The markers represent the medians. The bars represent the interquartile ranges.
Unsupported total Hb level is defined as the total Hb measurement level without any acute or chronic pRBC transfusions within 60 days prior to the measurement date.
Source: bluebird bio; PDISE[224]

For 22/33 pooled patients who had not received packed RBC transfusion in the prior 60 days, unsupported Hb levels were in the range of the International Guidelines[2] and hence appropriate.

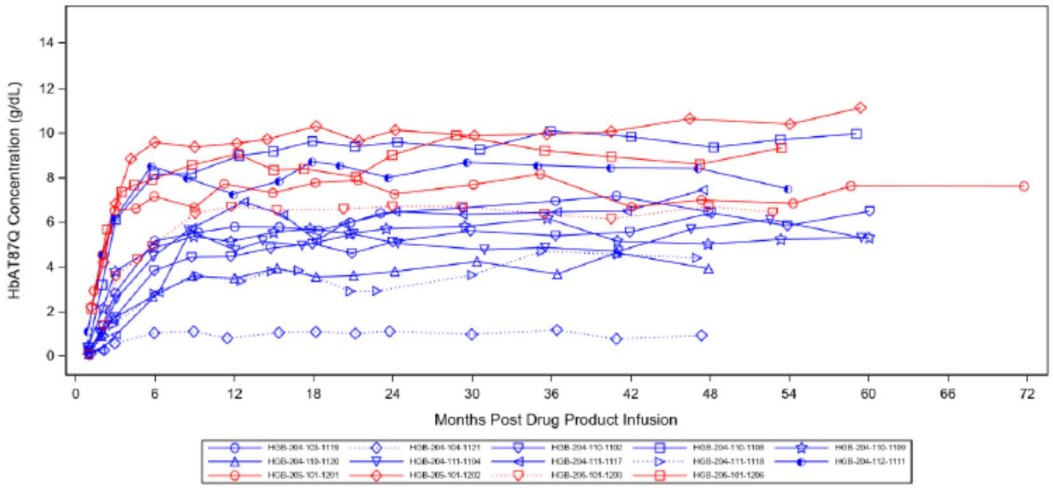
In TI-responders in the 4 studies, it was shown that about 50% had normal absolute reticulocyte counts in long-term data. This result suggests that achieving TI induces a normalisation of erythropoeisis hyperproductivity and thus disappearance of ineffective erythropoiesis in half of the study patients. The clinical specialist designated by the applicant in Belgium to inform the Institute, commented that dyserythropoiesis after beti-cel treatment is to be looked for in clinical practice.

- Correlations of pre-treatment variables, amongst others, of drug product vector copy number, with response obtained

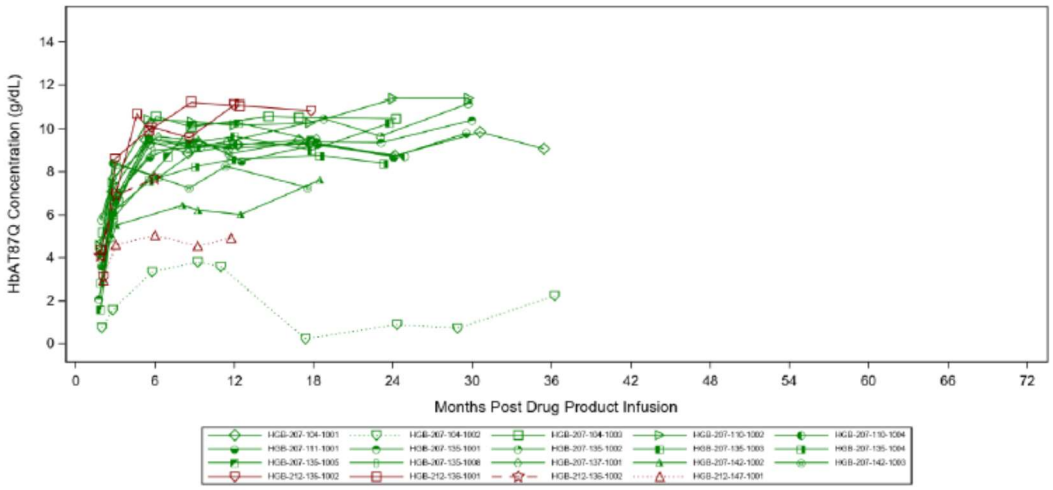
No correlations were given, but the next figure shows a stable transgene HbA^{T87Q} over time in the 4 individual studies.

Figure 50 HbA^{T87Q} in PB over time for treated non-ß^{0}/ß^{0} patients ≥ 12 years of age with TDT [226]

Phase I/II studies



Phase III studies



Abbreviations: PB, peripheral blood; TDT, transfusion-dependent ß-thalassaemia
Note: Patients who achieved TI are represented with solid lines, patients who did not achieve TI are represented with dotted lines, and patients who are not yet evaluable for TI due to short follow-up are represented with dashed lines.
Source: bluebird bio;[226]

These results indicate stable integration of the lentiviral vector in the bone marrow and stable transgene expression in the erythroid lineage derived from transduced HSC as given by the levels of HbA^{T87Q}. No clinical conclusions can be drawn from these figure; the data in this figure are only of pharmacodynamics nature.

- Measures of health resource utilization comparing number of transfusions, number of hospitalizations, and iron chelation usage from 12 months post-beticel infusion through 24 mont visit with the annual average of corresponding parameters during the 2 years of enrolment.

  See sources in the health economic section.

Comparative elements and justification

Study patients presenting non-β^0/β^0 TDT had in the 2 years prior to beti-cel infusion a mean number of 15 transfusion sessions per year, with a minimum of 10 and a maximum of 24. The average observed is similar to Dutch and Belgian patients today; however, the range in the study population is wider than expected in practice.

As to efficacy assessment, each study patient was its own control, namely in the period of 2 years before enrolment in the study. This period was characterised by polytransfusions and iron chelation therapy, as it is the standard of care. The proportion of TI in the pooled patient population 84% with 95% CI 67% to 95% (n=32) was clinically relevant, as compared to before beti-cel infusion being 0% of patients. This was the primary endpoint. This effect ran in parallel with secondary outcomes: duration of TI (n=33) expressed in months after beti-cel infusion (versus zero months before); time to reach TI of on average 16 months, with a minimum of 15 months and at a maximum of 21 months. Of note is that patients up to 6 months after beti-cel infusion received packed RBC, namely up to the moment their HSC produced enough RBC to live further without exogenous RBC. Before beti-cel infusion, the degree of transfusion reduction was 0%.

By indirect comparison with patients undergoing the standard of care (polytransfusions and iron chelator therapy), none is expected to reduce the transfusion burden, none expected even absence of transfusion. The observed results with ZYNTEGLO are therefore to considered clinically relevant.

What about other clinical outcomes?

- Reduction of mortality? No difference in mortality was observed in comparison with standard of care;. All patients treated with beti-cel were alive.
- Reduction in iron chelator therapy? The data are not conclusive although are suggestive for less need of iron chelation therapy. The data are difficult to interpret because some patients were treated for iron overload, not by iron chelators, but by phlebotomy. The reason is that phlebotomy is preferred after HSCT because iron chelators may aggravate the low platelet count.
- Reduction of iron burden over time? The data are not conclusive because few patients were evaluable at at month 48 (n=11) and at month 60 (n=7).
- Increase in quality of life? The data are not conclusive because no data collection was reported in the first 6 months after beti-cel infusion. This is the period after HSCT during hospital stay, including intensive care stay in strict isolation, where quality of life is expected to be aggravated. The data from month 6 on were only explorative and, besides, on small numbers of patients.

3.3.1.2. ADVERSE EVENTS

EPAR element

CHMP conclusion on the safety in the benefit/risk assessment (EPAR):

2.6.3. Conclusions on the clinical safety

Overall, due to the limitations in the safety database it is not possible to fully discriminate between effects caused by Zynteglo and those by the concomitant treatment/HSCT procedure. Nevertheless, adverse reactions have been described specifically for the mobilisation/apheresis, myeloablative conditioning and product related in the SmPC. Common AEs that may be caused by Zynteglo may also be missed due to the limited number of patients included in the safety database. Furthermore, the safety data were pooled across studies, TDT genotypes, cell doses and manufacturing processes. No apparent differences in the safety profile have been observed based on these factors, although patient numbers are low. Similarly, a conclusion on the effect of intrinsic factors (age, race, gender, genotype) on the safety profile of Zynteglo is complicated by low patient numbers.

Overall, the safety profile seems to be in line with that what is known for HSCT. As treatment with Zynteglo encompasses an HSCT procedure, the risks associated with mobilisation and conditioning are also part of the benefit:risk of Zynteglo. This includes the risk for secondary malignancies, as is illustrated by the event of myelodysplasia in an SCD patient, VOD (5 serious events) and impairment of fertility.

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

- In order to confirm the efficacy and safety of Zynteglo in patients 12 years and older with TDT who do not have a β^0/β^0 genotype, the MAH should submit interim and final data on Study HGB-207.
- In order to confirm the efficacy and safety of Zynteglo in patients 12 years and older with TDT who do not have a β^0/β^0 genotype, the MAH should submit interim and final data from patients with a severe non-β^0/β^0 genotype such as IVS-I-110/IVS-I-110 and IVS-I-110/β^0 from Study HGB-212.
- In order to confirm the efficacy and safety of Zynteglo in patients 12 years and older with TDT who do not have a β^0/β^0 genotype, the MAH should submit interim data and the 5-year follow-up results of study LTF-303.

The CAT considers the following measures necessary to address issues related to safety:

- In addition, as a condition to the MA, a non-interventional post-authorisation safety and efficacy study should be conducted in order to further characterise and contextualise the long-term safety and efficacy of Zynteglo in patients 12 years and older with transfusion-dependent β thalassaemia (TDT) who do not have a β^0/β^0 genotype. The MAH should conduct and submit the results of a study based on data from a product registry (REG-501) and use data on patients treated with transfusions and/or HLA-matched allogenic HSCT treated patients from an established European registry as a comparator group.

The registry will specifically address the risk of delayed platelet engraftment, insertional oncogenesis, loss of response to gene therapy and neutrophil engraftment failure. Interim data on the registry should also be submitted at each annual renewal of the conditional marketing authorisation.

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

The patient pool for which safety data are discussed in this report, is the group of n=48 TDT patients of the EPAR, with data lock on December 13th 2018. It concerns the studies HGB-205, HGB-204, HGB-207, HGB-212 and LTF-303. The CHMP used safety data from the ongoing study in sickle-cell disease as supportive data (study HGB-206).

From the moment of informed consent to month 24, the highest percentage of patients

with adverse events was from the moment of initiation of myeloablation to neutrophil engraftment. The lowest percentage was from the informed consent to the initiation of stem cell mobilization. No events were reported between month 24 and month 60 at the CHMP (2019).

The median follow-up duration was 35 months with a minimum of 1 month and maximum of 72 months.

Most frequent adverse reactions and severity

Table 14 Overview of most frequent reported AEs attributable to treatment

Type of AEs	Mobilisation/apheresis	Myeloablative conditioning	Beti-cel
Most frequent AEs (≥10%)	• Thrombocytopenia • Hypocalcaemia • Headache • Peripheral sensory neuropathy • Nausea • Bone pain	• Febrile neutropenia • Neutropenia • Thrombocytopenia • Leukopenia • Anaemia • Decreased appetite • Insomnia • Headache • Expistaxis • Pharyngeal inflammation • Stomatitis • Nausea • Vomiting • Diarrhoea • Abdominal pain • Anal inflammation • Constipation • Dyspepsia • Gingival bleeding • Pyrexia • Fatigue • Mucosal inflammation • Venoocclusive liver disease • Alanine aminotransferase increased • Aspartate aminotransferase increased • Blood bilirubin increased • Vaginal haemorrhage • Alopecia • Skin hyperpigmentation • Pruritus	• Abdominal pain
AEs (1-10%) presented by System Organ Class	• Blood and lymphatic system disorders • Metabolism and nutrition disorders • Psychiatric disorders • Nervous system disorders • Cardiac disorders • Vascular disorders • Respiratory, thoracic and mediastinal disorders • Gastrointestinal disorders	• Infections and infestations • Blood and lymphatic system disorders • Endocrine disorders • Metabolism and nutrition disorders • Psychiatric disorders • Nervous system disorders • Eye disorders • Ear and labyrinth disorders • Cardiac disorders	• Blood and lymphatic system disorders • Vascular disorders • Respiratory, thoracic and mediastinal disorders • Musculoskeletal and connective tissue • General disorders and administration site conditions • Gastrointestinal disorders
	• Skin and subcutaneous tissue disorders • Musculoskeletal and connective tissue disorders • General disorders and administration site conditions • Investigations • Injury, poisoning and procedural complications	• Vascular disorders • Respiratory, thoracic and mediastinal disorders • Gastrointestinal disorders • Hepatobiliary disorders • Skin and subcutaneous tissue disorders • Musculoskeletal and connective tissue • Renal and urinary disorders • Reproductive system and breast disorders • General disorders and administration site conditions • Investigations • Injury, poisoning and procedural complications	

Abbreviations: AEs, adverse events
Source: SmPC beti-cel[80],[140]

Most study patients experienced the following adverse events: thrombocytopenia (85%), anaemia (77%), stomatitis (67%), alopecia (64%), nausea (61%), vomitus (59%) and neutropenia (56%).

Of these adverse events, the following were reported as grade 3 or 4 of severity: thrombocytopenia, anaemia and vomitus. Were reported as adverse events of grade 1 or 2 of severity: alopecia, nausea and vomitus.

Description of selected adverse events according to the SPC:

- Bleeding

  Bleeding is a potential complication of thrombocytopenia subsequent to myeloablation and treatment with beti-cel. A risk of bleeding exists before platelet engraftment and may continue after platelet engraftment in patients who have continued thrombocytopenia. Although neutrophils engrafted as expected, platelet engraftment was delayed. Platelet engraftment is defined as 3 consecutive platelet values ≥ 20 x 10^9/L on 3 different days after beti-cel infusion with no platelet transfusion administered during 7 days before. The median day of platelet engraftment in study patients (n=39; data lock March 2018) was day 41, with a range of 19 days and 191 days. The CHMP noted that in the allogenic HSCT, the median time for platelet engrafting was 30 days based on literature data.

- Hepatic veno-occlusive disease (VOD)

  Patients not receiving prophylaxis for VOD appeared to be at an increased risk for developing VOD. Twelve % of patients presented serious VOD, 80% of which did not receive prophylaxis for VOD. Patients with TDT may present a higher risk of VOD following myelablation compared with other patient populations.

- Infusion related reactions to ZYNTEGLO

  Pre-medication for infusion reactions was managed at physician discretion in the studies. Infusion related reactions to beti-cel were observed in 12% of patients and occurred on the day of infusion. All reactions, which were of mild severity, resolved. These included abdominal pain, dyspnoea, hot flush and non-cardiac chest pain.

Serious adverse reactions

No deaths have been reported in the clinical study program of beti-cel.

Fourty-nine %, or one patient out of two, reported a serious adverse event, for a total of 31 serious adverse events. Of these 31, 10 events occurred prior to beti-cel infusion and were attributed to study procedures, HSC mobilization, apheresis or unknown reasons. The following 21 serious adverse events occurred in 13 patients:

- Infections : 9, such as e.g. cellulitis, diarrhoea and salmonella sepsis
- Bleeding event: 1. Hypotensive shock due to epistaxis bleeding due to low platelet count at day 11 post-infusion
- Thrombotic events: 2. An intracardiac thrombus and a vena cava thrombosis, both resolved.
- Hepatic events: 4. Four cass of hepatic veno-occlusive disorder that were attributed to busulfan conditioning by the investigators
- Hypoglycaemia: 1. The episode of hypoglycaemia resolved.
- And 4 other serious adverse events: a transfusion reaction to platelet transfusion, serious anaemia, a major depression and major hypoxia all of which resolved.

Withdrawal because of adverse reactions

There were no adverse events leading to discontinuation or withdrawal from the studies. As ZYNTEGLO is a once-in-time treatment, withdrawal from study medication is out of the question. A question is asked to the company how many patients withdrew from the moment of study enrollment to the moment of beti-cel infusion.

Main adverse effects of the reference therapy

The reference therapy consists of life-long use of polytransfusions and iron chelators. The applicant made a literature review on adverse events of the standard of care, being repeated life long transfusions and iron chelation therapy. Aside from transfusion complications such as iron overload in various organs, transfusion reactions, allo-immunisation, iron chelation therapy on itself[32],[33] gives the following adverse events at a frequency ≥ 10%: arthralgia, myalgia, nausea, abdominal pain, vomiting, chromaturia, increased creatinine levels and injection site reactions (subcutaneous desferrioxamine). No formal comparison on toxicity or safety profiles in comparison with beti-cel was further made.

For the patients' association OSCAR, it is obvious that beti-cel does not lead to graft-versus-host disease because the patient's own cells are used (as opposed to allogeneic stem cell transplantation). A less aggressive chemotoxicity scheme is used with beti-cell as opposed to allogeneic stem cell transplantation.

Comparative elements and justification

The EPAR states that « due to limitations in the safety database, it was not possible to fully discriminate between effects caused by ZYNTEGLO and those by the concomitant treatment/HSCT procedure. » (page 122). This discrimination may seem artificial because the patient either undergoes beti-cel infusion and the entire transplant program around either not : he/she continues polytransfusions and iron chelator therapy. This stresses the importance that the safety discussion of beti-cel contains a safety discussion on the entire HSCT procedure, including stem cell mobilisation, iatrogenic bone marrow ablation and engraftment.

As to safety reports from the literature on allogenic HSCT, the CHMP stated that graft-versus-host disease may occur, whereas none occurred in the ZYNTEGLO program (EPAR page 118). This is explained by the autologous nature of beti-cel.

In general, the CHMP noted that the safety profile of ZYNTEGLO was « in line with what is known for HSCT » (EPAR page 122). Nevertheless, a delayed platelet engraftment of median 41 days was observed with ZYNTEGLO, as compared with 30 days in the literature. Delayed platelet engraftment is the sole important identified risk in pharmacovigilance. (EPAR page 142). This contrasts with the timely neutrophil engraftment. Neutrophil engraftment failure is therefore an important potential risk in pharmacovigiliance but not an identified risk.

In the early phase of the procedure, HSC are to be collected. As an adjunct for HSC mobilization, plerixafor MOZOBIL was systematically used in the studies. This use is off-label for this kind of procedure. The CHMP mentioned the off-label use of plerixafor but considered its use safe in a ZYNTEGLO procedure because it minimally increased safety risks in children. There is one exception, however, where the use of plerixafor may increase the safety risk in children : presence of splenomegaly. Splenomegaly is a common feature in TDT patients and mobilisation of HSC with

plerixafor has been reported to be involved in splenic rupture (EPAR page 121). This reported risk on plerixafor in the literature was not observed in the ZYNTEGLO studies.

As mentioned before, the safety comparison with the standard of care – life long RBC transfusions and iron chelators – was descriptive and not a formal comparison.

3.3.1.3. APPLICABILITY

Limitations in the use :

Contra-indications – interactions – special precautions

Contra-indications

The contra-indications for ZYNTEGLO treatment are in essence the contra-indications to the mobilisation agents and the myeloablative conditioning agents. Previous treatment with HSC gene therapy is also a contra-indication, meaning that beti-cel therapy is to be given once in a lifetime. Pregnancy and breast-feeding are contra-indications, as wel as hypersensitivity to beti-cel or to any of the excipients.

Interactions

► No formal drug interactions studies have been performed. Beti-cel is not expected to interact with the hepatic cytochrome P-450 family of enzymes and drug transporters.

► Drug-drug interactions between iron chelators and the myeloablative conditioning agent must be considered, as some iron chelators are myelosuppressive.

► There is no clinical experience with the use of erythropoeisis-stimulating agents in patients treated with beti-cel.

► The safety of immunisation with live viral vaccines during or following beti-cel treatment has not been studied.

Special precautions

► Standard procedures for patient management for HSC mobilization, myeloablation and HSC transplantation are to be followed. For the latter, this includes, amongst others, prophylactic use for hepatic veno-occlusive disease with ursodeoxycholic acid or defibrotide, mucositis treatment with oral solutions, prophylactic use of anti-epileptics and antifungals.

► Restarting iron chelators after beti-cel infusion may be necessary, but must be avoided for 6 months after infusion. Phlebotomy can be used in stead of iron chelation.

► Any blood product given within 3 months after ZYNTEGLO infusion should be irradiated.

► Engraftment failure as measured by neutrophil engraftment.
In the clinical trials no patient failed to engraft neutrophils. It is a potentially severe risk, defined as failure to achieve 3 consecutive absolute neutrophile counts ≥ 500 cells/µL, by day 43 after beti-cel infusion. In the clinical studies with beti-cel, neutrophils engrafted at a median of 19 days, with a range of 13 to 38 days (n=42; data lock March 2018). The back-up collection of transduced CD+34 cells of the patient was meant to deal with this risk at day 43.

► Delayed platelet engraftment
Although the CHMP found no correlation between delayed platelet engraftment and bleeding risk, the risk of bleeding is to be particularly followed and treated with platelet infusions if necessary, according to standard guidelines.

► False positive HIV-tests
Because the lentiviral vector is composed of parts of the human immunodeficiency virus (HIV), although modified, some commercial PCR assays may recognise a piece of HIV protein used to make beti-cel. Patients are to be informed of testing false positively for HIV.

► Risk of insertional oncogenesis
Patients should be monitored annually for leukaemia or lymphoma for 15 years post-infusion with beti-cel.

► Infertility
Because of infertility due to the procedure of myeloablation, cryopreservation of spermatocytes or punctured ovary follicle cells should be organised. The patient is to be informed on life-long infertility after ZYNTEGLO beti-cel infusion.

Comparative elements and justification

For the alternative treatment option being the standard of care, namely life-long repeated RBC transfusions and iron chelators, the precautions mentioned above are not needed. There is no infertility problem and no need to check for malignancies, although liver cancer can occur in patients undergoing the standard of care and have iron load in the liver.[34] The above mentioned precautions with ZYNTEGLO are typical measures for any patient undergoing autologous HSCT and two measures are specific for ZYNTEGLO: the precaution on a delayed platelet engraftment and the risk of insertional oncogenesis.

A special precaution to take care of with repeated RBC transfusions is for instance to check for allo-immunisation or the prevention of transfusion reactions. Special precautions to take care of with iron chelators is the monitoring of chelator toxicity.[35] It consists, amongst others, to look during follow-up visits for an increase in creatinine levels (deferasirox); neutropenia and agranulocytosis (deferiprone); growth retardation (deferoxamine); opportunistic infections (deferoxamine); ototoxicity and neurotoxicity.[36]

No formal comparison between the applicability of ZYNTEGLO beti-cel and standard of care has been carried out.

3.3.1.4. PRACTICAL USE

Aspects of administration

ZYNTEGLO beti-cel must administered in a qualified treatment centre by a physician with experience in HSC transplantation and in the treatment of patients with transfusion-dependent thalassemia.

Mobilisation of stem cells and apheresis
HSC mobilisation is essential to generate sufficient CD34+ HSC. After apheresis, the medicinal product is manufactured in a specialised lab. In the clinical trial program (March 2020 datacut), 2 patients out of 35 dropped out after stem cell mobilisation.

Too few CD34+ cells
The minimum target number of CD34+ HSC to be collected is 12 million/kg body weight. If during manufacturing of beti-cel, a minimal quantity of 5 million CD34+ cells/kg is not met, the patient must undergo one additional cycle of mobiliations and apheresis, or more than once cycle if needed. These cycles are separated by at least 14 days, in order to obtain more CD34+ cells for additional manufacture. In the clinical program (March 2020 datacut), too few CD34+ cell collection was not observed.

Back-up CD34+ cells
A back-up collection of 1,5 million CD34+ cells or more is required if collected by apheresis or 100 million TNC/kg or more if collected by bone marrow harvest. The cryopreserved CD34+ cells may be needed in on of the three following situations : 1° too few CD34 cells before ZYNTEGLO infusion ; 2° primary engraftment failure ; 3° loss of engraftment after the infusion of beti-cel.

Myeloablation
A 4-day course of myeloablation is required in a strict isolation room of the haematology intensive ward. Full-myeloablation must be administered, in a sterile isolation room, before infusion of beti-cel. Patients should maintain hemoglobin levels ≥ 11 g/dL for 30 days prior to the myeloablative conditioning. Iron chelators are to be stopped at least 7 days prior to myeloablation. Prophylaxis for hepatic veno-occlusive disease is recommended. For some myeloablative conditiong schemes, prophylactic use of anti-convulsive agents is needed. There must be a minimum of 48 hours of washout before beti-cel infusion.

Shelf life
The shelf life for the lentiviral vector (thus without the patient stem cells) is 24 months frozen. The shelf life of ZYNTEGLO (with the patient stem cells) is 1 year when frozen at the maximum of minus 140 °C, in the vapour phase of liquid nitrogen until ready for thaw and administration. Once thawed, it can be kept at room temperature for a maximum of 4 hours.

ZYNTEGLO infusion
Beti-cel is for autologous use and should be administered once. It is shipped from the manufacturing facility to centres in the European Union. The infusion should be completed as soon as possible an not more than 4 hours after thawing. Each infusion bag is to be administered in less than 30 minutes. More than one bag of beti-cel may be needed. The entire volume of each infusion bag should be infused. Flush of all beti-cel remaining in the infusion bag and any associating tubing is to be done with at least 50 mL of 0,9 % sodium chloride solution to ensure as many cells as possible are infused into the patient.

Hospital stay
After beti-cel infusion, the patient stays 3 to 6 weeks in hospital. During the hospital stay, he is initially treated in an strict isolation room of the haematological intensive ward, until signs of CD34+ cell graft functioning.

Comparative elements and justification

The alternative treatment is the standard of care being repeated packed RBC transfusions and iron chelators life-long. The clinical state of this therapy is cumbersome as given in studies measuring its ease of use. Repeated transfusions necessitate a visit to the one-day clinic at a frequency of more than once a month. Although iron monitoring as well as chelation therapy have improved in the past decade, strict adherence is required and frequent monitoring are the rule.[35]

ZYNTEGLO beti-cel treatment is a heavy treatment in the early months because of the nature of autologous HSC transplantation. No formal comparison of ease of use has been made with the standard of care.

3.3.1.5. DEGREE OF EVIDENCE, RISK OF BIAS AND GRADE-SCALE

The degree of evidence is single-cohort studies.

Risk of Bias

The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews – Checklist for Case Series is used to determine the Risk of Bias.

The single-arm trial results hereunder only contain the data of patients ≥ 12 years with the non-β_0/β_0 genotype who received the gene therapy infusion with ZYNTEGLO beti-cel. The risk of bias is in this case of single-arm trial acceptable. Of note is that, for the studies HGB-207, HGB-212 and LTF-303, the company "is to provide comprehensive data relevant to the initial indication including long-term safety and efficacy data" (*EPAR page 136/142*) in the context of the condition marketing authorisation. Data lock January 2020.

Table Risk of Bias

	HGB-205	**HGB-204**	**HGB-207**	**HGB-212**	**LTF-303**
Were there clear criteria for inclusion in the case series?	Yes, but gene transfer carried out with slightly other production process	Yes, but gene transfer carried out with slightly other production process	yes	yes	yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	yes	yes	yes	yes	yes
Were valid methods used for identification of the condition for all participants included in the case series?	yes	yes	yes	yes	yes
Did the case series have consecutive inclusion of participants?	yes	yes	yes	yes	yes
Did the case series have complete inclusion of participants?	Unclear as to number of patients eligible and subsequently prepared with myeloablation	idem	idem	idem	Yes, it is the long-term study of previous one-arm trials (and of future treated
Was there clear reporting of the demographics of the participants in the study?	yes	yes	yes	yes	yes

Was there clear reporting of clinical information of the participants?	yes	yes	yes	yes	yes
Were the outcomes or follow up results of cases clearly reported?	No: no QoL data reported in the first 6 months after beti-cel infusion	idem	idem	idem	yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	yes	yes	yes	yes	yes
Was statistical analysis appropriate?	Yes as to descriptive statistics. No inference test for within-patient comparison before beti-cel (efficacy) nor with control groups[4] in literature (safety).	idem	idem	idem	idem

[4] The control groups were treated with repeated red blood cell transfusions and iron chelation therapy.

Table GRADE evidence profile

GRADE Evidence profile of the in-patient comparison (*efficacy*) in β-thalassaemic patients ≥ 12 years with genotype non-β_0/β_0
Data lock January 2020.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Inprecision	Other	Cohort after beti-cel	Same patient before beti-cel	Relative (95% CI)	Absolut (95% CI)		
Red Blood Cell Transfusion independency[5], proportion of patients n (%)												
4+1 pooling	Single-armwithin-patient[6]	Not serious[7]	Not serious	Not serious[8]	Not serious		HGB-205 3/4 (75%) HGB-204 8/10 (80%) HGB-207 14/15 (93%) HGB-212 2/3 (67%) Pooled 27/32[9] (84%)	0/32 (0%)	RR: 0.17 (95% CI 0.08-0.36)	84% (95% CI 67-95)	⊕⊕◯◯ LOW	CRUCIAL
Decrease of Red Blood Cell transfusions 6 months through last study visit, median number of less transfusions per patient annualized and median % change from baseline (number of patients) in patients not showing transfusion-independency[10]												

[5] Transfusion independency is attained by definition when without any red blood packed cell transfusion for at least 12 months while maintaining a weighted average nadir Hb level of ≥ 9 g/dL beginning after a preceding 60 days without transfusion.
[6] The default certainty level is set on 'LOW' because of the absence of a controlled trial.
[7] Because of the progressive character of the disease, implying a life-long transfusion program and iron chelator therapy, every patient is his own control who undergoes gene transfer of a functional hemoglobin. Indirect comparison using an untreated control group would not show any patient being independent of red blood cell transfusions (0% expected number). Therefore a single-arm in-patient comparison is acceptable.
[8] Every patient is his own control before beti-cel infusion. Because of the irreversible character of the disease progression, natural improvement to a state of transfusion independency is highly unlikely and even clinically impossible unless patients get an allogeneic transplantation. The label mentions that patients are eligible for allogeneic transplantation but don't get one because a matched donor is lacking. Therefore there is no need of downgrading for indirect evidence.
[9] There were n=32 evaluable patients on n=33 treated patients because of one patient left out in study HGB-212 who was not evaluable.
[10] In clinical standard practice the number of red blood cell transfusions are as follows. In the Netherlands, specialists indicated that on average patients have 15-20 transfusion episodes a year, in order to follow the international standards. Belgian experts indicated approximately 13 transfusion episodes per year, usually every 4 weeks, and for some patients 17 times per year (being every 3 weeks).

4+1 pooling	Single-armwithin-patient	Not serious[11]	Not serious	Not serious[8]	Not serious		HGB-205 -13 -100% (1) HGB-204 -6 -42% (2) HGB-207 -6 -41% (1) HGB-212 -13 -77% (1) Pooled -10 -75% (5)	/	/	-75% (95% CI -100 -10)[12]	⊕⊕◯◯ LOW	CRUCIAL
Discontinuation of iron chelation therapy for at least 6 months, proportion of patients n (%)												
4	Single-armwithin-patient	Not serious[13]	Not serious	Not serious	Not serious		HGB-205 and HGB-204 4/14 (29%) HGB-207 and HGB-212 9/19 (47%) Pooled 13/33 (39%)	0/23 (0%)	RR: 0.61 (95% CI 0.46-0.81)	/	⊕⊕◯◯ LOW	CRUCIAL
QoL : only explorative outcomes at month 12 and month 24												
4	Single-arm within-patient	Not serious	Serious[14]	Very serious[15]	Serious[16]		The QoL data were explorative outcome data and were carried out at month 12 and month 24. QoL data were lacking for the first 6 months, the period of intensive care and bone marrow recuperation.				⊕◯◯◯ VERY LOW	CRUCIAL

CI: Confidence interval

[11] Because of the progressive character of the disease, implying a life-long transfusion program and iron chelator therapy, every patient is his own control who undergoes gene transfer of a functional hemoglobin. Indirect comparison using an untreated control group would not show a reduction in transfusion programs. Therefore a single-arm in-patient comparison is acceptable.
[12] Only data available on n=4 patients.
[13] A controlled trial is lacking. Because of the progressive character of the disease, implying a life-long transfusion program and iron chelator therapy, every patient is his own control. Indirect comparison using an untreated control group would not show any discontinuation of iron chelation therapy for at least 6 months. Therefore a single-arm in-patient comparison is acceptable.
[14] See Table biais: QoL data for the first 6 months were not reported or discarded.
[15] An indirect comparison of QoL would have been possible between ZYNTEGLO-treated patients and control patients continuing their red blood cell transfusion program and iron chelators.
[16] The available QoL data do not lead to a conclusive analysis on clinical relevance.

Because the control values from the literature are unknown, there is no GRADE Evidence profile on the following items:

- Deaths
- Discontinuation due to adverse events
- Serious adverse events.

3.3.2. Real world evidence

As mentioned before, patients treated with ZYNTEGLO are to enrol in a registry for a long-term follow-up on safety and efficacy, up to 15 years of follow-up : REG-501. It includes patients with a non β°/β° genotype TDT and an age of 12 years or above treated outside the context of clinical trials. Because of the conditional marketing autorisation, Bluebird is to submit interim data on an annual basis, for a period of 5 years. A this stage, no formal comparison can be made with the standard of care. The REG-501 study plans to enroll approximately 350 patients over a period of 5 years and is designed to collect longitudinal data on patients with TDT treated with beti-cel. It will be used to meet post-marketing commitments that are required by EMA in the light of their recommendation to conduct long-term follow-up of patients treated with gene therapy drug products to monitor for serious adverse events and adverse events of interest, as well as to asses durability of clinical response.

Off-label use of ZYNTEGLO is not expected at this stage. Clinical specialists indicated that ZYNTEGLO treatment at an age below 12 years is likely to be more attractive given the fact that complications of TDT are not serious at a very young age. This implies that once TI is reached after beti-cel infusion, there will be less need to take care of iron overload.

3.3.2.1. EFFICACY IN PRACTICE

No efficacy data in practice are available of the use of ZYNTEGLO. The first EU-country and at this time, the sole EU-country where ZYNTEGLO is marketed, is Germany.[37]

3.3.2.2. ADVERSE EVENTS

The launch in Germany is on hold since Feb 17th 2021 because of two patients having had the same technology as ZYNTEGLO but for another blood disease: sickle cell anaemia. One developed acute myeloid leukemia 5 years after treatment and another one developed myelodysplastic syndrome.[38] A relationship between these 2 events and insertional oncogenesis is unlikely.[39]

EPAR elements of the Risk Management Plan

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Delayed platelet engraftment
Important potential risks	Insertional oncogenesis Loss of response to gene therapy Neutrophil engraftment failure Splenic rupture
Missing information	Long-term safety and efficacy Use in patients over 35 years of age

An important identified risk of ZYNTEGLO beti-cel in practice is delayed platelet engraftment. Important potential risks are insertional oncogenesis, loss of response to gene therapy, neutrophil engraftment failure and splenic rupture.

3.3.2.3. APPLICABILITY

No other data than those mentioned in the SPC : Contra-indications, interactions and special precautions to be taken.

3.3.2.4. PRACTICAL USE

The patient receives a Patient Alert Card, that states that he should not donate blood, organs, tissues or cells for transplantation at any time in the future.

4.ABBREVIATIONS

Abbreviation	Description
ATMP	Advanced therapeutic medicinal product
CAT	Committee for Advanced Therapies (EMA)
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	Confidence interval
EBMT	European Blood and Marrow Transplantation
eGFR	Estimated glomerular filtration rate
FACT-BMT	Functional assessment of cancer therapy – bone marrow transplantation
FACT-G	Functional assessment of cancer therapy - general
GBA	Gemeinsamer Bundesausschuss
G-CSF	Granulocyte colony-stimulating factor
Hb	haemoglobin
HbA	Adult haemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIC	Hepatic iron concentration
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRQoL	Health-related quality oflife
HSC	Haematopoietic stem cell
HSCT	Haemopoietic stem cell transplantation
LIC	Liver iron content
MRD	Matched related donor
MRI	Magnetic resonance imaging
ms	Milliseconds
PaedsQL	Paediatric quality of life
PCR	Polymerase chain reaction
PRIME	Priority Medicines
RBC	Red blood cells
RWE	Real world evidence
SF-36	Short Form 36
SPC	Summary of Product Characteristics
TDT	Transfusion-dependent thalassaemia
TI	Transfusion independence
TIF	Thalassaemia International Federation
TR	Transfusion reduction
VCN	Vector copy number
VOD	Veno-occlusive disease (of the liver)
WBC	White blood cells
WHO	World Health Organisation

5.REFERENCES

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- EPAR
- Document by a clinical specialist chosen by the applicant. Wet 6 april 2010: Reclame is iedere mededeling van een onderneming die rechtstreeks of onrechtstreeks ten doel heeft de verkoop van producten te bevorderen, ongeacht de plaats of de aangewende communicatiemiddelen.

*** References with an asterisk were not part of the company's submission file.**

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Zorginstituut Nederland

Budget impact analysis of betibeglogene autotemcel (Zynteglo®) for the indication TDT

For reimbursement assessment

Date 31st May 2021
Status Final

Colofon

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Content

1 Introduction

In this report we estimate the additional costs for the pharmaceutical budget if betibeglogene autotemcel or beti-cel (Zynteglo®) will be reimbursed in the Netherlands and in Belgium. Starting points for the budget impact analysis (BIA) are: the licensed indication, the size of the eligible population, the drug costs, the dosing schedule of the drug, the treatment duration and the potential substitution of the current treatment costs.

The focus will be on the patients for whom the Dutch Health Care Institute (ZIN) and the Belgian RIZIV-INAMI concluded an evidence based clinical benefit compared to the standard of care.

1.1 Licensed indication

Betibeglogene autotemcel (Zynteglo®) is licensed for "the treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β°/β° genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen-matched related donor is not available."

1.2 Position within the disease treatment pathway

Dutch and Belgian expertise centres in thalassaemia don't have formal proper treatment guidelines but refer to the international Guidelines for the management of transfusion-dependent thalassaemia.[1] Treatment options consist of two pathways: 1) repeated transfusions of red blood cells (RBC) and iron chelators, 2) allogeneic HSCT and subsequently if necessary, iron chelators for existing pre-transplant iron overload. Current treatment for TDT patients is described in the report about the relative effectiveness. In summary; patients who do not receive an allo-HSCT are given a lifelong regimen of RBC transfusions (to maintain an appropriate Hb-level) plus iron chelation (to minimise the risk of iron-related complications). As the indication of beti-cel concerns patients 12 years and older for whom HSCT is appropriate but who do not have an HLA-matched related HSC donor, RBC transfusions and iron chelation therapy are considered the standard of care in this population and will therefore be included in the BIA. Allo-HSCT is not considered as a comparator treatment and therefore is not included in this BIA.

2 Starting points and assumptions

2.1 Number of eligible patients

The applicant reported that because of the rarity of TDT, limited epidemiology data is available in the literature, especially literature discussing Dutch incidence and prevalence. Therefore, the applicant based the size of the eligible population for the Netherlands on Dutch key opinion leader (KOL) input[2, 3] and an in-field enquiry conducted in May/June 2020 by the Dutch Hemoglobinopathy Professionals (LWvHB, Landelijke Werkgroep voor Hemoglobinopathie Behandelaars).[4] For the eligible population in Belgium the applicant used data from a survey with two clinical experts, one treating adult patients and one paediatric/adolescent patients.

2.1.1 The Netherlands

The applicant assumed that the number of eligible Dutch patients for beti-cel treatment consists of a prevalent pool of TDT patients (who are primarily adult patients) plus new incident cases (who could be immigrants or TDT patients for whom a previous HSCT was not successful).[2] These calculations are visually presented in Figure 1 for adult patients and in Figure 2 for adolescent patients, which show the expected treatment algorithm after the introduction of beti-cel, along with the expected patient numbers in the first year. The applicant assumed that the prevalence of β-thalassaemia in the Netherlands in 2020 was between 150 and 200 patients.[2,3] Dutch KOLs indicate that of those patients, approximately one-third of the adult patients are transfusion-dependent.[2,3] To verify this assumption and to have current and accurate numbers, an in-field enquiry on request of the applicant was conducted by the Dutch Hemoglobinopathy Professionals (LWvHB), represented by Prof B.J. Biemond. This analysis shows that there are a total of 66 patients with TDT in the Netherlands ≥12 years.[4]

There were 65 *adult patients*.[4] Of these patients as estimated by their treating physicians 57 patients (88%) would be eligible for autologous HSCT (not for allogeneic HSCT). The enquiry further showed that 14 of these patients (25%) have a non-β^0/β^0 genotype and would therefore be eligible to receive beti-cel (Figure 1). To verify this percentage the applicant asked the National Reference Laboratory for Haemoglobinopathies to perform a database search in October 2020.[5] This search, with data from 2007 onwards showed the following genotypes in the data of 71 transfusion-dependent beta-thalassemia patients (intermedia or major): 46 β^0/β^0, 22 β^0/β+ and 3 β^+/β^+, showing a split of 35% patients with a non-β^0/β^0 and 65% patients with a β^0/β^0 genotype at diagnosis in the Netherlands.[5, 6] The applicant assumed that the percentage (25%) as found in their in-field inquiry is the most appropriate to use. Because the uncertainty about this percentage ZIN asked the Dutch clinical experts about this issue during the consultation. In their response the clinical experts say that the data from the six Dutch expert clinics are the most reliable for estimating the real number of TDT patients. Laboratories are not fully informed about the need for transfusions in patients that are analysed. The Dutch clinical experts think that the proportion of patients that have a non-β^0/β^0 genotype will be closer to 25% than 35%. ZIN will therefore use the 25% assumption in this BIA.

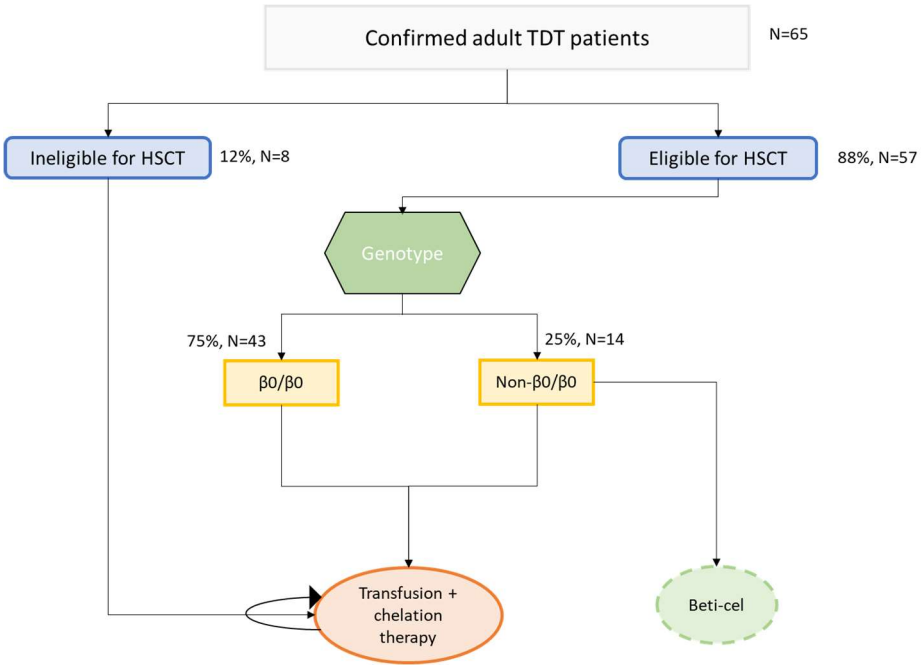

Figure 1 Treatment algorithm and patient distribution for adults (≥18 years of age) in the Netherlands
Source: interview KOL[2]

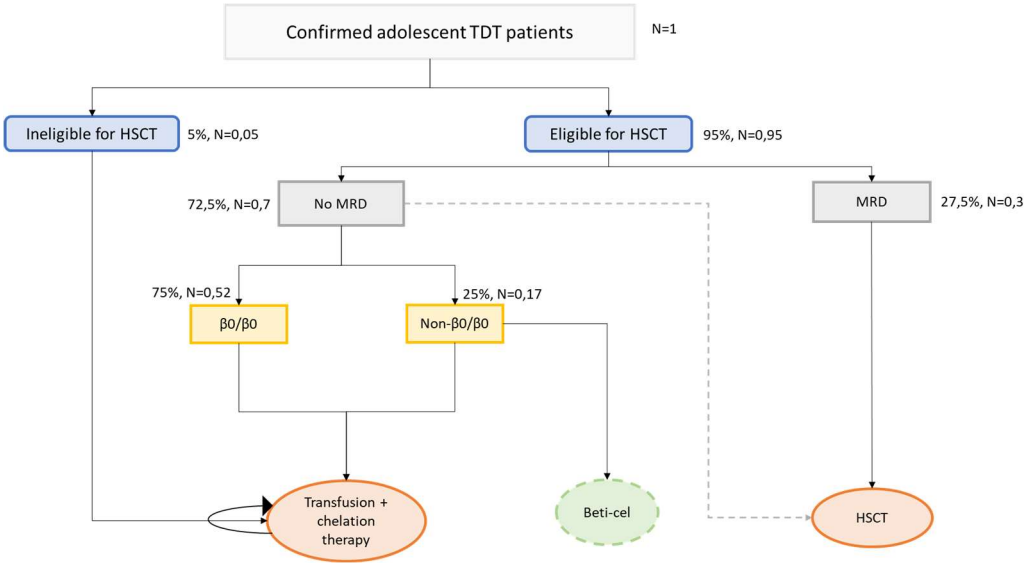

Figure 2 Treatment algorithm and patient distribution for adolescents (12-18 years of age) in the Netherlands

Source: interview KOL[3]

As mentioned above, the applicants in-field enquiry conducted by the applicant in collaboration with the LWvHB[4] showed that there is currently 1 *adolescent TDT patient* in the Netherlands. Of these patients it has been estimated that 95% (n=0.95) will be eligible for HSCT[3] and, in turn, between 70-75% (n=0.7) of these

patients will not have a matched related donor (MRD).[7] Since the enquiry only reported 1 adolescent patient and reported that 25% of the patients have a non-β^0/β^0 genotype[4], this results in a total of 0.17 (25%*0.7) adolescent TDT non-β^0/β^0 patient that is potentially eligible for receiving beti-cel.
Based on a published report by the National Institute for Public Health and the Environment[8] and the opinion of the two Dutch clinical experts, the applicant indicates that each year 3-5 patients are diagnosed with β-thalassaemia (newborns and immigrants). For newborns born in the Netherlands, screening for β-thalassemia is foreseen in heelprick testing. This is not done in Belgium. For people not subject to heelprick screening, the diagnosis is made, or at least suspected, at a later age of the child, usually during the first year of life. Of these 3-5 patients approximately 50% are transfusion dependent.[3] Therefore in this BIA it is assumed that there will be 4 new β-thalassaemia patients per year, of which 2 (50%) are transfusion dependent. Keeping in mind the distributions used for the calculation of the prevalence, the applicant expects that a maximum of 0.44 *newly diagnosed TDT patient* is eligible for beti-cel per year (88%*25%*2).

Based on the data as provided above, the applicant estimated that a total of ***14.17*** patients (14 adults and 0.17 adolescent) from the prevalent pool in the Netherlands will be eligible for treatment with beti-cel. The Dutch clinical experts that were consulted by the applicant indicate that not all eligible patients will receive beti-cel because it is an intensive treatment. They assume that only 64.3% of the eligible patients will be treated (***9.11 patients***). From the 0.44 incident patients only ***0.29*** will be expected to actually receive beti-cel in the base case scenario.
ZIN asked the Dutch clinical experts about this assumption during the consultation and in their response the clinicians confirmed that treatment with beti-cel is not without risks. Besides the exposure to the chemotherapy, the patients will also have a very low or no immune system for a longer period of time. Not all the patients will be in a sufficient condition to undergo such an intensive treatment with beti-cel. Age can become a contra-indication as well, due to the cumulative toxicity. Health benefits (years without blood transfusions) will become smaller if a patient is older. Despite all these factors the Dutch clinical experts expect that the proportion of patients eligible for treatment with beti-cel will be a little bit higher than 64,3%. In a scenario the applicant presents the results if all prevalent (n=14.17) and incident (n=0.44) patients will be treated.
The applicant further assumes that during the first three years all the 9.11 prevalent patients will be treated. That is what the clinical experts expected as well. ZIN therefore assumes that 3 prevalent patients will be treated per year during the first 3 years. This is in line with the assumption of the Dutch clinical experts.[2,3] The distribution of the applicant was different (they start with 2 patients in the first year) but it is not clear for ZIN why this distribution was chosen. From year 4 onwards only the incident patients will be treated. A 10 year time horizon was chosen by the applicant to show the effect of beti-cel over a longer time horizon. ZIN prefers a shorter time horizon in BIAs (3 year is a common time horizon in Dutch BIAs). In this report, ZIN will present the budget impact during a 5 year time horizon. In the cost-effectiveness analysis the impact of beti-cel treatment during a long time horizon is analysed.

2.1.2 *Belgium*

For Belgium the applicant asked HICT to support in the development of the budget impact model and the collection of country specific data for that model. For the collection of country specific data HICT did a survey with one Belgian paediatric expert (Prof. Ferster, Huderf) and one expert in treating adult patients (Dr. Benhiat, Erasme ULB).[9] From the answers in this survey and the available literature[10,11] the applicant concluded that there were about 7-8 TDT cases per 1,000,000 persons in Belgium in 2020. This corresponds to *86.6 patients* diagnosed with TDT in Belgium.

Of this prevalent patient pool 20% of patients (n=17) are adolescent and 43% are adults (≥18 years, n=37), according to the clinical experts.[9] This means in Belgium approximately *54 TDT patients* are of interest as per the licensed indication of beti-cel (see Figure 3).

If patients are candidates for HSCT, these can only be performed in JACIE-accredited (academic) centres. Some patients (often new immigrants) are not treated in academic centres and/or do not receive a genotype test (due to lack of insurance)[9], and will be treated with RBC transfusions and chelation therapy. It is assumed that *36 patients* are treated in academic centres and receive the genotype test.[12] [9]

According to the applicant no Belgian historical or current data is available regarding the split between non-β^0/β^0 and β^0/β^0 genotypes. Therefore the applicant assumed that about 50% of the TDT patients should have a non-β^0/β^0 genotype,[9, 13-15] resulting in *18 non-β^0/β^0 TDT patients* in Belgium (see Figure 3).

The applicant assumed that 75% of the adolescent population and 90% of the adult population has no HLA-matched related donor. This assumption was based on literature[16, 17] and confirmed by the Belgian clinical experts[9]. This results in a total of 6 adolescent and 8 adult patients potentially eligible for beti-cel per the licensed indication (see Figure *Figure* 3).[9] Thus, *14 patients in total.*

The annual incidence of thalassemia was assumed to be *about 2-3 new TDT* diagnoses per year. This was based on the literature and validated by the Belgian clinical experts.[8, 11, 18] It is assumed there are 2,5 new patients per year, of which *0.94 patient* (2,5*75%*50%) is eligible for treatment with beti-cel. From the 0.94 incident patients only *0.63* will be expected to actually receive beti-cel in the base case scenario.
The applicant assumes that during the first three years the prevalent pool of patients will be treated. ZIN assumes 3,33 prevalent patients (and 0,63 incident patients per year) will be treated per year during the first three years. So, from year 4 onwards only the incident patients will be treated. A 10 year time horizon was chosen by the applicant to show the effect of beti-cel over a longer time horizon. RIZIV prefers a shorter time horizon in BIAs (3 year is a common time horizon in Belgian BIAs). ZIN therefore will present the budget impact during a 5 year time horizon. In the cost-effectiveness analysis the impact of beti-cel treatment during a long time horizon is analysed.

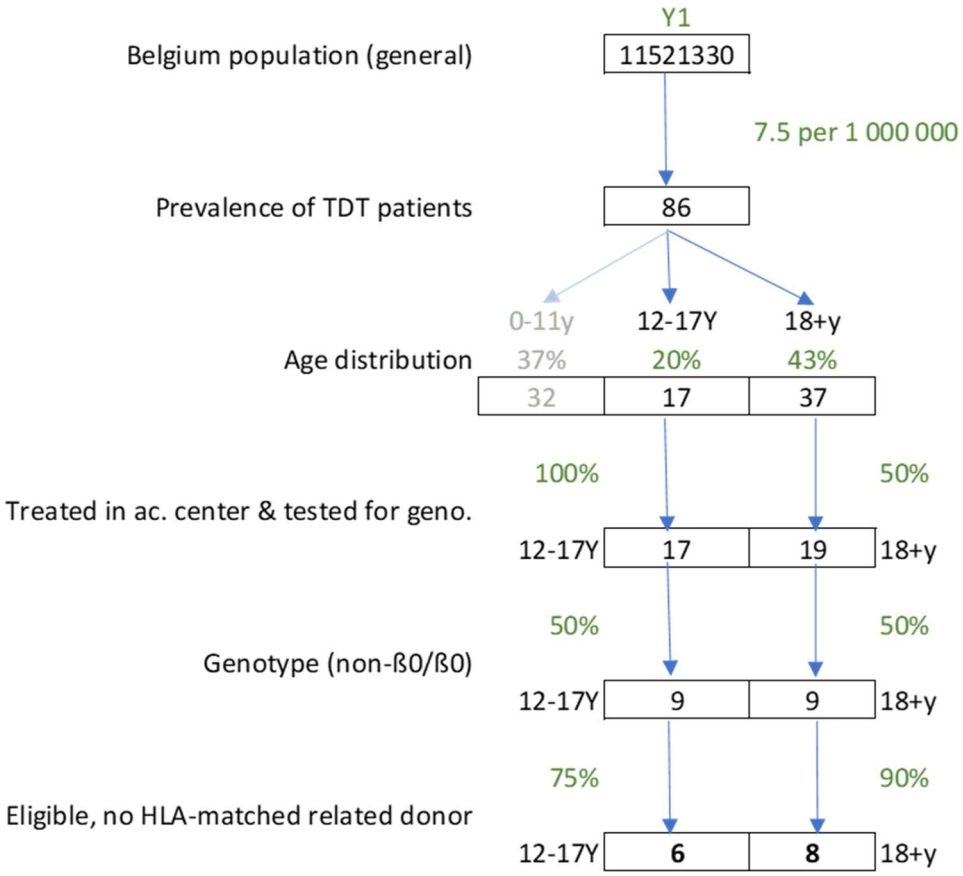

Figure 3 Prevalence estimates of TDT patients eligible for beti-cel in Belgium

In table 1 the parameters used by the applicant to estimate the eligible population are summarized. These are mentioned for both The Netherlands and Belgium, and ZIN comments on potential different assumptions between the countries.

Table 1 Parameters used by the Applicant to estimate the Eligible Population

Parameter	**Netherlands**		**Belgium**		**ZIN Commentary**
	Value	*Reference*	*Value*	*Reference*	
Prevalence of β-thalassaemia in 2020	150-200 patients	Dutch KOL[2,3]: Bart Biemond (adults) Frans Smiers (adolescents)	7-8/ million persons= 86 patients	Belgian expert opinion and literature	Numbers are comparable between both countries.
Proportion transfusion-dependant	33%= **66 patients** of which 65 adults and 1 adolescent	Dutch KOL[2,3]: Bart Biemond (adults) Frans Smiers (adolescents) Applicants analysis with the Dutch Hemoglobino-pathy Professionals	86 patients, see above, of which **54** aged >=12 years	See above and expert opinion	Numbers are comparable between both countries.

Parameter	Netherlands		Belgium		ZIN Commentary
	Value	*Reference*	*Value*	*Reference*	
		(LWvHB)[4]			
Treated in academic centres and tested for genotype	100%= **66 patients**	Assumed by ZIN because not mentioned in the BIA by the applicant.	100% in adolescents=17 patients and 50% in adults=19 patients. In total **36 patients**	Belgian clinical experts	This distinction was not mentioned in the Dutch BIA. Therefore ZIN assumed 100% of the 66 TDT patients as estimated by the clinical experts in the Netherlands were treated in academic centres.
Proportion eligible for autologous HSCT (not for allogeneic HSCT)	88% in adults and 69% in adolescents (= 57 adult patients and 0.7 adolescents) = **57.7 patients**	Dutch KOL[2,3]: Bart Biemond (adults) Frans Smiers (adolescents) Applicants analysis with the Dutch (LWvHB)[4]	90% in adults (n=17,1) 75% in adolescents (n=12,75) = **29.85 patients**	Belgian clinical experts	Proportions are comparable.
Proportion of adults and adolescent patients that have a non-β^0/β^0 genotype	25% = **14.17 patients**	Applicants analysis with the Dutch LWvHB[4] and database search by National Reference Laboratory for Haemoglobinopathies (oct 2020)[5]	50%= **14.93 patients**	Belgian clinical experts Danjou et al., 2015 Barberio et al., 2016 Colah et al., 2010	The Dutch database search by National Reference Laboratory for Haemoglobinopathies (Oct 2020)(6) resulted in a percentage of 35%. Dutch clinical experts confirmed the 25% during the consultation by ZIN.
Proportion of eligible patients that will be treated with beti-cel	64.3% = **9.11 patients**	Assumption Dutch clinical experts because beti-cel is an intensive treatment	50% of adolescents and 90% of the adults = **10 patients**	Assumption Belgian clinical experts	In the base case ZIN assumes that not all the eligible patients in the Netherlands and Belgium will be treated. In a scenario all prevalent eligible patients

Parameter	Netherlands		Belgium		ZIN Commentary
	Value	*Reference*	*Value*	*Reference*	
					are treated with beti-cel.
Market uptake beti-cel	Prevalent pool will be treated during the first 3 years, equally divided ≈**3 prevalent patients per year**	Assumption Dutch clinical experts and ZIN	Prevalent pool will be treated gradually during the first 3 years≈ **3.33 prevalent patients per year**	Assumption Belgian clinical experts and ZIN	ZIN agrees, no comments on this

In table 2 the estimated number of patients that will receive beti-cel during the following five years are summarized. As can be seen from this table two scenarios are outlined. The applicants scenario, assuming that only 64,3% of all eligible patients will be treated with beti-cel. And an alternative scenario, assuming that all eligible patients will be treated with beti-cel during the upcoming years. Both scenarios are presented for the Netherlands and for Belgium.

Table 2 Number of Patients receiving beti-cel under Applicant and Alternative scenario

	Description	Year 1	Year 2	Year 3	Year 4	Year 5
Applicant base case scenario (64.3% of patients will be treated with beti-cel)						
The Netherlands	Total eligible patients	Prevalent: 14.17	Incident: 0.44	Incident: 0.44	Incident: 0.44	Incident: 0.44
	Incident patients treated with beti-cel Transfusion independent (TI; 85%) Transfusion reduced (TR; 15%)		0.29 0.25 0.04	0.29 0.25 0.04	0.29 0.25 0.04	0.29 0.25 0.04
	Prevalent patients treated with beti-cel TI (85%) TR (15%)	3.11 2.64 0.47	3 2.55 0.45	3 2.55 0.45	NA	NA
	Prevalent and incident patients not treated with beti-cel (SoC)	11.06 (=14.17-3.11)	8.21 (=11.06-3 +0.15)	5.36 (=14.17-9.11 +0.15+0.15)	5.51 (=5.36 +0.15)	5.66 (=5.51 +0.15)
Belgium	Total eligible patients	Prevalent: 14.93	Incident: 0.94	Incident: 0.94	Incident: 0.94	Incident: 0.94
	Incident patients treated with beti-cel TI (85%)		0.63 0.54	0.63	0.63 0.54	0.63 0.54

	TR (15%)		0.09	0.54 0.09	0.09	0.09
	Prevalent patients treated with beti-cel TI (85%) TR (15%)	3.33 2.83 0.50	3.33 2.83 0.50	3.33 2.83 0.50	 NA	 NA
	Prevalent patients not treated with beti-cel (SoC)	11.60	8.58 (=11.60-3.33+0.31	5.87 (=8.58-3.33+0.62)	6.18 (=5.87+0.31)	6.49 (=6.18+0.31)
Alternative scenario (all the patients will be treated with beti-cel)						
Netherlands	Total eligible patients	Prevalent: 14.17	Incident: 0.44	Incident: 0.44	Incident: 0.44	Incident: 0.44
	Incident patients treated with beti-cel TI (85%) TR (15%)		0.44 0.37 0.07	0.44 0.37 0.07	0.44 0.37 0.07	0.44 0.37 0.07
	Prevalent patients treated with beti-cel TI (85%) TR (15%)	4.72 4.01 0.71	4.72 4.01 0.71	4.73 4.02 0.71	0	0
	Patients not treated with beti-cel (SoC)	9.45	4.73	0	0	0
Belgium	Total eligible patients	Prevalent: 14.93	Incident: 0.94	Incident: 0.94	Incident: 0.94	Incident: 0.94
	Incident patients treated with beti-cel TI (85%) TR (15%)		0.94 0.80 0.14	0.94 0.80 0.14	0.94 0.80 0.14	0.94 0.80 0.14
	Prevalent patients treated with beti-cel TI (85%) TR (15%)	4.98 4.23 0.75	4.98 4.23 0.75	4.97 4.22 0.75	0	0
	Patients not treated with beti-cel (SoC)	9.95	4.97	0	0	0

NA, Not Applicable

The applicant expects that within 2 to 4 years the indication will be broadened to paediatric patients <12 years of age and patients with a β^0/β^0 genotype. This will probably result in much more eligible patients and thus a higher budget impact. There will also be a chance that patients with a matched related donor want to be treated with beti-cel. The Dutch clinical experts confirmed this and they mentioned

that this will especially be the case in adult patients. Allogen SCT with a HLA matched donor has its risks, like graft failure and graft versus host disease. These risks depend on the co-morbidities in patients, and these are mostly present in adults. If in the future beti-cel might become available for patients with a HLA matched donor as well, than this will of course have an impact on the budget.

2.2 Substitution of current treatment

The current treatment pathway in the Netherlands and in Belgium and the anticipated place of beti-cel in this treatment pathway is shown in table 1 and 2. Beti-cel is expected to replace a lifelong regimen of RBC transfusions and chelation therapy in patients who are eligible for HSCT but have no matched related donor, are at least 12 years of age, and have a non-β^0/β^0 genotype.
Maybe in the near future luspatercept becomes a treatment option in these patients in the Netherlands as well. If so, this will probably be a treatment option before starting beti-cel and only for adults. This is not included in the estimation of the budget impact because luspatercept is not available yet, it is not the standard of care and it is not integrated in clinical guidelines yet. Excluding luspatercept from this BIA might result in an overestimation of eligible patients for beti-cel.
As the aim of treatment with beti-cel is to achieve transfusion independence (TI), it is expected that the introduction of beti-cel will significantly reduce the prevalent pool of TDT in the coming years. Although the majority of the prevalent pool of TDT patients is expected to be treated, some patients might not be willing to be treated with beti-cel as it is an intensive treatment.[2,3,9] These patients will remain on SoC treatment with transfusions and chelation therapy in the base case scenario (see Table 2 for eligible patient number). In an extra scenario we show the number of patients and budget impact if all eligible prevalent and incident patients will receive beti-cel (see table 2).

2.3 Costs per patient per year

Beti-cel treatment costs
In table 3 the costs for beti-cel treatment in the Netherlands and Belgium are presented as estimated by the applicant. These costs consist of pre-transplant costs, the costs of beti-cel itself, the costs of the transplant and hospitalization, and post-transplant monitoring costs.
Usually in the Netherlands only the drug costs are included in the BIA. But due to the fact that beti-cel treatment is only possible with the pre-transplant, transplant and monitoring activities, these costs are also included in this BIA. Those are direct drug-related activities. For the Netherlands these costs for the BIA do only cover the DBC tariffs for the corresponding treatments and days in hospital, but are excluding travel costs and costs for cryopreservation. Travel costs are excluded as these should not be included in the Dutch BIA, and cryopreservation costs are considered to be related to AEs, which are also excluded from the BIA. In the Netherlands these costs are studied in the cost-effectiveness analysis.
For Belgium the same strategy was used and only the direct drug-related costs were included in the BIA. In an extra scenario, specifically for Belgium, extra costs were added such as adverse event costs. This is the budget line 3 analysis in Belgium.
The Belgian unit cost for the medical resource use is obtained from NIHDI. All reimbursed drug unit costs are obtained directly from NIHDI website. For non-reimbursed drugs www.bcfi.be is consulted. For each drug, the cheapest option is chosen. The unit costs were collected in July 2020. The drug usage of each therapy is obtained from the dosing regime in the SPC, supplemented with information from

guidelines, treatment schedules and expert opinion.[9]The medical resource usage includes administration, visits, lab tests & monitoring and is obtained through expert opinion.[63] The cost for hospitalisation is collected from national data as published by the Belgian government (APR-DRG data).[19]

As beti-cel is a one-time treatment, the total costs for beti-cel treatment are assumed to be the annual cost for beti-cel per patient, and are only applied once, in the first year.

Table 3: Costs per TDT patient for treatment with beti-cel

	Netherlands	***Belgium***
Pre-transplant costs	€9,044	€5,638
Hospitalization	€41,708	€45,822
Beti-cel	**€1,575,000 (excl. VAT)**	**€1,669,500 (incl. 6% VAT)**
Post-transplant monitoring	€8,700	€5,557
Total costs per beti-cel treatment	**€1,634,453**	**€1,726,517**

Blood transfusion and iron reduction therapy costs
The costs for RBC transfusion are calculated based on the cost for the first unit/bag of blood, the cost for the subsequent units, and the number of units used per transfusion, resulting in a total cost per transfusion. The annual costs for blood transfusion are then calculated by multiplying the cost per transfusion with the number of transfusions per year, which differ for the transfusion dependent and the transfusion reduced patients included in the Dutch BIA (15 vs 3.79 transfusions per year respectively).[2,5,20] In table 4 the estimation of the annual transfusion costs are outlined. During the consultation the Dutch clinical experts confirmed the annual number of blood transfusions is approximately 15. Because TDT patients will get a blood transfusion every 3-5 weeks. The clinical experts mentioned they were not able to give an indication about the mean number of RBCs in the TR patients, because they had never seen a beti-cel treated patient yet. The 3.8 RBCs is a result from the clinical trials, and can be explained as follows: transfusion-reduced patients sometimes have an appropriate Hb-level and sometimes they have not. So sometimes these patients need a RBC and other times they don't. Therefore the mean number of 3.8 RBCs per year for TR patients seems clinically plausible.

Table 4 RBC transfusion costs

Transfusion costs	**Costs (€)**	**Source**
First unit	€ 422	Red blood cells per unit, laboratory costs, outpatient visit
Subsequent unit	€ 280	Red blood cells per unit, laboratory costs
Number of bags per transfusion	3,5	KOL input[2]
Annual number of transfusions for transfusion dependent patients	15	KOL input[2,5,20]
Annual number of transfusions for transfusion reduced patients	3,8	Pooled beti-cel trial data (74.75% reduction of transfusions)
Annual transfusion cost for transfusion dependent patient	**€ 16.840**	
Annual transfusion cost for transfusion reduced patient	**€ 4.252**	

In the Belgian BIA it was assumed that blood transfusions are typically done every 4 weeks (13 times per year on the average).[9] The resource use per blood transfusion was based on evaluation of several Belgian hospital invoices. The number of blood packs was estimated by the experts to be 3 to 4 packs for adolescents and adults.[9]

Patients who receive regular blood transfusions need iron reduction therapy to keep their iron levels under control. The annual chelation therapy costs consist of the drug costs and monitoring costs.
The distribution between various chelation therapies is based on KOL input. In the vast majority of patients, oral chelation therapy is given. Dose is dependent on body weight. The average body weight in the beti-cel clinical trials is used for the calculations. Chelation therapy costs differ between transfusion dependent patients and transfusion reduced patients. This is because transfusion reduced patients receive a decreased dosage of chelation therapies. For transfusion dependent patients, iron reduction is done by using iron chelation therapies: oral iron chelation such as desferasirox (Exjade®) or subcutaneous iron chelation such as deferoxamine-mesilaat (Desferal®).

Table 5 RBC transfusion costs and chelation therapy costs

	Netherlands	Belgium
Annual transfusion cost for transfusion dependent patient	€ 16,840	€ 11,421
Annual transfusion cost for transfusion reduced patient	€ 4,252	€4,094
Annual chelation therapy cost for transfusion dependent patient	€ 27,609	€ 26,016
Annual chelation therapy cost for transfusion reduced patient	€ 20,897	€ 17,287

Patients who have been treated with beti-cel, need to be treated with iron chelation therapy after beti-cel treatment, for a period of 2 years, in order to normalize their iron levels (i.e. the iron normalization period). During the iron normalization period, phlebotomy can also be used as one of the options to normalize iron levels. From the cost-effectiveness analysis as described in the PE-report, it can be seen that this 2-year duration of iron normalization is an uncertain parameter. It can be shorter (1 year) or longer (3 years), it depends on a patient's condition. In this BIA a 2-year duration is used, like the base-case analysis in the CEA. But we should keep in mind that if this duration is longer, the budget impact will increase as well.

Total costs per patient per year
Patients who do not receive beti-cel treatment (yet) are assumed to *be transfusion dependent* and they receive a lifelong treatment with RBC transfusions and chelation therapy. Annual costs are the same each year (NL: € 44,449, BE: € 37,437), and consist of annual blood transfusion costs (NL: € 16,840, BE: € 11,421) plus annual chelation therapy costs (NL: € 27,609, BE: € 26,016).
The patients who receive beti-cel treatment have beti-cel treatment costs in the first year. After beti-cel treatment, it is assumed that patients become either transfusion independent or transfusion reduced.
Transfusion independent patients do not receive any transfusions anymore after beti-cel treatment, but do receive iron chelation therapy or phlebotomy for 2 years (the iron normalization period) to reduce their iron levels (NL: € 18,540, BE: € 18,940). This cost is therefore included in the first year and in the second year. In the third year, no costs are incurred anymore for iron normalization. The total costs for transfusion independent patients are therefore € 1,652,993 (NL) and € 1,745,457 (BE) in the first year (NL: € 1,634,453 plus € 18,540, BE: € 1,726,517

plus € 18,940), € 18,540 (NL) and € 18,940 (BE) in the second year and € 0 in the third year.

Table 6 Total annual costs per treatment per year

Patient group and treatment	Costs (€) in first year	Costs (€) in second year	Costs (€) in third and any subsequent year
TD: Transfusion dependent patients on SoC with transfusions plus chelation therapy - Netherlands - Belgium *Consists of RBC transfusion costs + chelation therapy costs*	 € 44,449 € 37,437	 € 44,449 € 37,437	 € 44,449 € 37,437
TI: Transfusion dependent patients on beti-cel treatment - after which they become **transfusion independent** - no treatment after 2 years iron normalisation period - Netherlands - Belgium *Consists of: beti-cel treatment costs all allocated to the first year, no RBC transfusion costs, iron normalisation period costs of 2 years starting in first year.*	 € 1,652,993 € 1,745,457	 € 18,540 € 18,940	 € 0 € 0
TR: Transfusion dependent patients on beti-cel treatment - after which they become **transfusion reduced** – RBC transfusion and chelation therapy, including first two years of iron normalisation period costs - Netherlands - Belgium *Consists of: beti-cel costs all allocated to first year, RBC transfusion costs (at reduced frequency) immediately from first year onwards, 2 years of iron normalization period costs starting in first year, after which chelation therapy costs for transfusion reduced patients are added*	 € 1,657,245 € 1,749,562	 € 22,792 € 23,034	 € 25,150 € 21,381

For patients who become *transfusion reduced after beti-cel treatment*, costs of RBC transfusion plus chelation therapy are included in the BIA. Transfusion reduced patients still get RBC transfusions after beti-cel treatment, however at a reduced frequency and therefore reduced costs compared with transfusion dependent patients. They also have the iron normalization period, similar as the transfusion independent patients described above (€ 18,540 in the first and second year), after which they continue to receive iron chelation therapy, at reduced dosages and therefore reduced costs compared with the transfusion dependent patients (€ 20,897). The first year of beti-cel treatment therefore consists of the cost of beti-cel (total costs including transplantation), annual blood transfusion costs and annual iron normalization costs. The second year consists of annual blood transfusion costs and annual iron normalization costs. The third and any subsequent year consists of annual blood transfusion costs and annual chelation therapy costs for TR patients.

2.4 Assumptions

The following assumptions and uncertainties should be considered for this BIA:

- The costs of treatment are based on full adherence and maximum treatment duration of transfusion and chelation therapy.
- For some of the cost inputs there are differences between costs for adults and adolescents. For those cases the costs for the adults have been selected

for the BIA, as the majority of the prevalent TDT patients are adults and it is not possible to predict what percentage of the newly diagnosed patients will be adolescent or adult (as these could be immigrants). As the costs for adults are always higher than the costs for the adolescents, this is a conservative approach resulting in the maximum total costs.

- A number of additional costs have been included in the BIA which usually are not included in a Dutch budget impact analysis: besides pharmaceutical costs, costs for beti-cel administration, hospitalization and monitoring are included, as well as costs for outpatient visits for RBC transfusions. The BIA also takes into account the effect of beti-cel treatment, by adding costs for transfusion and chelation therapy for patients who become transfusion reduced after beti-cel treatment.
- The exact uptake of beti-cel per year is difficult to predict. Although the number of beti-cel treatments per year in this BIA have been confirmed by Dutch and Belgian KOLs.[2,3]
- It is assumed by the Dutch and Belgian KOLs, that not all TDT patients who are eligible for beti-cel treatment based on the label of beti-cel, are willing to receive the treatment, due to the intensity of the treatment. This is mostly related to the pre-conditioning regimen with chemotherapy. This assumption is taken into account in the base-case. As requested by ZIN, a scenario analysis is added by the applicant where it is assumed that all eligible patients according to the label, also receive beti-cel treatment.
- According to the Dutch and Belgian BIA guidelines, the budget impact should be calculated for the first three years. The applicant decided to also present the budget impact results for a longer time horizon, i.e. the first 10 years after market entry of beti-cel, to show the characteristic curve in expected budget impact, due to the one-time treatment. ZIN decided to only present a 5-year time horizon, because long time uncertainties can be better analysed in the CEA instead of a BIA.
- See table 1 for all the assumptions made to estimate the eligible patient population in Belgium and the Netherlands.

2.5 Scenario analyses

The applicant performed a scenario to study the impact of including all the prevalent and incident patients for beti-cel treatment (instead of 64.3% in the base case). ZIN performed an additional scenario to analyze the impact of less treatment effectiveness, assuming 25% of the treated patients will be TR instead of 15%. Furthermore, the applicant analyzed two scenario's in which a payment scheme is used. The applicant proposed two types of payment schemes: a value-based payment-over-time (VBPoT) model and an outcomes-rebate model. Being aware of the multiple therapies expecting to reach the market in the coming years, the applicant believes it would be helpful to introduce a payment scheme that spreads the budget impact over a longer time period.

VBPoT model

Since the applicant believes in a payment model that shares risk with the health care system and where the payments are directly tied to the value delivered to patients, they propose a value-based payment-over-time (VBPoT) model for beti-cel. In this model the total cost is distributed over 5 annual payment instalments (€315,000 each year), with 80% of the total amount tied to continued demonstration of treatment success. For beti-cel the clinically most relevant outcome for patients is freedom of transfusions (Dutch KOL opinion).[2,3] The first

payment is made upon treatment start (month 0) for all patients. The 4 remaining payments are only made if treatment with beti-cel is successful (TI). This scenario is only done for the Netherlands.

Outcomes-based rebate model
Another scenario that is presented by the applicant, as an alternative for VBPoT, concerns an outcome based rebate model. In this model the total beti-cel cost is paid at T=0 (beti-cel infusion). If a patient does not achieve TI or does not remain TI during month 19 to 24 after beti-cel infusion, the applicant offers an 80% rebate at T=25 months. Therefore, an additional analysis is presented in which the costs and budget impact of beti-cel are calculated based upon this scheme.

3 Budget impact results

In this chapter the budget impact as a result of the introduction of beti-cel for the treatment of TDT patients is presented for both The Netherlands and Belgium. First the gross budget impact is estimated (budget line 1 in Belgium), second the net budget impact is estimated in which current treatment costs are substituted (budget line 2 in Belgium). Some scenario's will be presented as well: 1) all prevalent patients will be treated, 2) value-based payment-over-time (VBPoT) model for beti-cel is used and 3) outcomes-based rebate model is used.

3.1 Gross and net drug budget impact- base case scenario

The Netherlands
Table 7 shows the budget impact as a result of the introduction of beti-cel in the Netherlands, based on the annual treatment costs per patient and the annual patient numbers per treatment.

In the current world without beti-cel, the total cost of treatment for TDT patients ≥12 years of age with a non-β^0/β^0 genotype is approximately € 630,000 in year 1 increasing to € 649,400 in year 2 and € 669,000 in year 3. In the new world with beti-cel, the total cost of treatment for Dutch TDT patients ≥12 years of age with a non-β^0/β^0 genotype is € 5.6 million in year 1 increasing to € 5.9 million in year 2 and then decreasing to € 5.8 million in year 3. After the third year, the costs are decreasing significantly compared with the first three years (table 6) as the complete prevalent pool of eligible TDT patients is expected to be treated within the first three years. The net budget impact (new world minus costs current world) is approximately € 5 million in year 3.

Belgium
Table 8 shows the budget impact as a result of the introduction of beti-cel in Belgium, based on the annual treatment costs per patient and the annual patient numbers per treatment.

In the current world without beti-cel, the total cost of treatment for TDT patients ≥12 years of age with a non-β^0/β^0 genotype is approximately € 559,000 in year 1 increasing to € 594,000 in year 2 and € 629,000 in year 3. In the new world with beti-cel, the total cost of treatment for Belgian TDT patients ≥12 years of age with a non-β^0/β^0 genotype is € 6.3 million in year 1 increasing to € 7.3 million in year 2 and then decreasing to € 7.2 million in year 3. After the third year, the costs are decreasing significantly compared with the first three years (table 7) as the complete prevalent pool of eligible TDT patients is expected to be treated within the first three years. The net budget impact (new world minus costs current world) is approximately € 6.6 million in year 3.

Table 7 Netherlands base case - not all eligible patients are expected to receive treatment

Current world - World without beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 629.842	€ 649.400	€ 668.957	€ 688.515	€ 708.073
Beti-cel	€ 0	€ 0	€ 0	€ 0	€ 0
Total	**€ 629.842**	**€ 649.400**	**€ 668.957**	**€ 688.515**	**€ 708.073**
New world - World with beti-cel (budget line 2)					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 491.606	€ 364.926	€ 238.247	€ 244.914	€ 251.581
Beti-cel TI	€ 4.363.902	€ 4.677.326	€ 4.680.292	€ 465.160	€ 417.883
Beti-cel TR	€ 778.905	€ 822.762	€ 835.039	€ 101.602	€ 103.669
Total beti-cel (budget line 1)	€ 5.142.807	€ 5.500.088	€ 5.515.331	€ 566.762	€ 521.552
Total	**€ 5.634.413**	**€ 5.865.015**	**€ 5.753.578**	**€ 811.676**	**€ 773.134**
Annual budget impact (budget line 2)	**€ 5.004.570**	**€ 5.215.615**	**€ 5.084.620**	**€ 123.161**	**€ 65.061**

Table 8 Belgium base case - not all eligible patients are expected to receive treatment

Current world - World without beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 558.934	€ 594.125	€ 629.316	€ 664.507	€ 699.698
Beti-cel	€ 0	€ 0	€ 0	€ 0	€ 0
Total	**€ 558.934**	**€ 594.125**	**€ 629.316**	**€ 664.507**	**€ 699.698**
New world - World with beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 434.269	€ 321.209	€ 219.755	€ 231.361	€ 242.966
Beti-cel TI	€ 4.939.643	€ 5.935.790	€ 5.946.018	€ 1.006.375	€ 952.774
Beti-cel TR	€ 874.781	€ 1.043.759	€ 1.056.522	€ 194.356	€ 195.454
Total beti-cel (budget line 1)	€ 5.814.424	€ 6.979.549	€ 7.002.540	€ 1.200.731	€ 1.148.228
Total	**€ 6.248.694**	**€ 7.300.758**	**€ 7.222.295**	**€ 1.432.091**	**€ 1.391.194**
Annual budget impact (budget line 2)	**€ 5.689.759**	**€ 6.706.633**	**€ 6.592.979**	**€ 767.584**	**€ 691.497**

3.2 Scenario analyses

3.2.1 All the prevalent and incident patients will be treated with beti-cel

The Netherlands
In table 9 the budget impact is presented if all the eligible Dutch patients will be treated with beti-cel (instead of 64.3% as in the base case). The annual budget impact for the entire patient group in the Netherlands is € 7.6 million in the first year, increasing to € 8.2 million in the second year and then reducing to € 8 million in the third year. After these three years, the annual budget impact is much lower, at € 175.000 in year four, declining to € 85.000 in year five.

Belgium
In table 10 the budget impact is presented if all the eligible Belgian patients will be treated with beti-cel (instead of 64.3% as in the base case). The annual budget impact for the entire patient group in Belgium is € 8.5 million in the first year, increasing to € 10 million in the second year and then reducing to € 9.8 million in the third year. After these three years, the annual budget impact is lower, at € 1.1 million in year four, declining to € 1 million in year five.

3.2.2 25% of the treated population will be transfusion reduced (TR) instead of 15%: beti-cel is less effective

As can be seen from the results in table 11 and 12, the impact of changing the proportion TR patients after beti-cel treatment with 10% on the pharmaceutical budget is minimal.

3.2.3 Budget impact in case the applicants value-based payment-over-time (VBPoT) model for beti-cel is used- only for the Netherlands

The VBPoT scenario is included in the BIA model by distributing the total cost over 5 annual payment instalments (€ 315.000 per year) for all transfusion independent patients. As the VBPoT model ties 80% of the total amount to continued demonstration of treatment success, for transfusion reduced patients only € 315.000 is paid in the first year, with no other payments made as these patients do not reach transfusion independence. As can be seen from table 13, this payment model results in more spread costs during the years. And of course cumulatively it will result in less costs and a smaller budget impact.

3.2.4 Budget impact in case the applicants outcomes-based rebate model is used- only for the Netherlands

In this model the total beti-cel cost is paid at T=0 (beti-cel infusion). If a patient does not achieve TI or remains TI during month 19 to 24 after beti-cel infusion, the applicant offers an 80% rebate at T=25 months. In the BIA this is implemented as a rebate in year 3 after beti-cel treatment for the transfusion reduced patients. The rebate is € 1.260.000 (80% of € 1.575.000), which results in a total cost of € -1.234.850 in the third year after beti-cel treatment, consisting of the rebate plus annual costs for transfusions and chelation therapy for the transfusion reduced patients. As can be seen in table 14 the annual budget impact in the first three years is 5, 5.2 and 4.5 million euro, while already from the fourth year onwards the annual costs in a world without beti-cel are higher than when beti-cel is introduced in the market (table 14).

Table 9 Netherlands scenario - all eligible patients are expected to receive treatment

Current world - World without beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 629.842	€ 649.400	€ 668.957	€ 688.515	€ 708.073
Beti-cel	€ 0	€ 0	€ 0	€ 0	€ 0
Total	**€ 629.842**	**€ 649.400**	**€ 668.957**	**€ 688.515**	**€ 708.073**
New world - World with beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 419.599	€ 209.799	€ 0	€ 0	€ 0
Beti-cel TI	€ 6.645.858	€ 7.324.567	€ 7.331.344	€ 699.536	€ 625.153
Beti-cel TR	€ 1.175.815	€ 1.298.879	€ 1.318.193	€ 164.329	€ 167.659
Total beti-cel	€ 7.821.674	€ 8.623.446	€ 8.649.536	€ 863.865	€ 792.812
Total	**€ 8.241.272**	**€ 8.833.245**	**€ 8.649.536**	**€ 863.865**	**€ 792.812**
Annual budget impact	**€ 7.611.430**	**€ 8.183.845**	**€ 7.980.579**	**€ 175.350**	**€ 84.739**

Table 10 Belgium scenario - all eligible patients are expected to receive treatment

Current world - World without beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 558.934	€ 594.125	€ 629.316	€ 664.507	€ 699.698
Beti-cel	€ 0	€ 0	€ 0	€ 0	€ 0
Total	**€ 558.934**	**€ 594.125**	**€ 629.316**	**€ 664.507**	**€ 699.698**
New world - World with beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 372.498	€ 186.062	€ 0	€ 0	€ 0
Beti-cel TI	€ 7.388.519	€ 8.863.313	€ 8.863.609	€ 1.489.765	€ 1.409.753
Beti-cel TR	€ 1.306.923	€ 1.570.817	€ 1.587.413	€ 302.066	€ 303.848
Total beti-cel	€ 8.695.442	€ 10.434.130	€ 10.451.022	€ 1.791.831	€ 1.713.601
Total	**€ 9.067.940**	**€ 10.620.192**	**€ 10.451.022**	**€ 1.791.831**	**€ 1.713.601**
Annual budget impact	**€ 8.509.006**	**€ 10.026.067**	**€ 9.821.706**	**€ 1.127.324**	**€ 1.013.904**

Table 11 Netherlands scenario - 25% of treated patients is TR

Current world - World without beti-cel

Treatment	Y1	Y2	Y3	Y4	Y5
SoC (transfusions and chelation)	€ 629.842	€ 649.400	€ 668.957	€ 688.515	€ 708.073
Beti-cel	€ 0	€ 0	€ 0	€ 0	€ 0
Total	**€ 629.842**	**€ 649.400**	**€ 668.957**	**€ 688.515**	**€ 708.073**
New world - World with beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 491.606	€ 364.926	€ 238.247	€ 244.914	€ 251.581
Beti-cel TI	€ 3.855.606	€ 4.122.005	€ 4.124.508	€ 405.273	€ 363.558
Beti-cel TR	€ 1.288.508	€ 1.380.805	€ 1.401.385	€ 179.137	€ 182.729
Total beti-cel	€ 5.144.114	€ 5.502.810	€ 5.525.892	€ 584.410	€ 546.287
Total	**€ 5.635.720**	**€ 5.867.736**	**€ 5.764.139**	**€ 829.324**	**€ 797.868**
Annual budget impact	**€ 5.005.878**	**€ 5.218.336**	**€ 5.095.181**	**€ 140.809**	**€ 89.796**

Table 12 Belgium scenario - 25% of treated patients is TR

Current world - World without beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 558.934	€ 594.125	€ 629.316	€ 664.507	€ 699.698
Beti-cel	€ 0	€ 0	€ 0	€ 0	€ 0
Total	**€ 558.934**	**€ 594.125**	**€ 629.316**	**€ 664.507**	**€ 699.698**
New world - World with beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 434.269	€ 321.209	€ 219.755	€ 231.361	€ 242.966
Beti-cel TI	€ 4.359.279	€ 5.231.310	€ 5.240.259	€ 880.980	€ 833.678
Beti-cel TR	€ 1.456.510	€ 1.751.242	€ 1.772.670	€ 337.327	€ 339.318
Total beti-cel	€ 5.815.789	€ 6.982.552	€ 7.012.929	€ 1.218.307	€ 1.172.996
Total	**€ 6.250.058**	**€ 7.303.762**	**€ 7.232.684**	**€ 1.449.667**	**€ 1.415.962**
Annual budget impact	**€ 5.691.124**	**€ 6.709.636**	**€ 6.603.368**	**€ 785.161**	**€ 716.264**

Table 13 Netherlands scenario - Value-based over-time-payment model

Current world - World without beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 629.842	€ 649.400	€ 668.957	€ 688.515	€ 708.073
Beti-cel	€ 0	€ 0	€ 0	€ 0	€ 0
Total	**€ 629.842**	**€ 649.400**	**€ 668.957**	**€ 688.515**	**€ 708.073**
New world - World with beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 491.606	€ 364.926	€ 238.247	€ 244.914	€ 251.581
Beti-cel TI	€ 1.048.062	€ 1.989.486	€ 2.871.652	€ 2.738.520	€ 2.769.743
Beti-cel TR	€ 188.585	€ 207.322	€ 219.599	€ 51.362	€ 53.429
Total beti-cel	€ 1.236.647	€ 2.196.808	€ 3.091.251	€ 2.789.882	€ 2.823.172
Total	**€ 1.728.253**	**€ 2.561.735**	**€ 3.329.498**	**€ 3.034.796**	**€ 3.074.754**
Annual budget impact	**€ 1.098.410**	**€ 1.912.335**	**€ 2.660.540**	**€ 2.346.281**	**€ 2.366.681**

Table 14 Netherlands scenario - outcomes-based rebate scenario

Current world - World without beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 629.842	€ 649.400	€ 668.957	€ 688.515	€ 708.073
Beti-cel	€ 0	€ 0	€ 0	€ 0	€ 0
Total	**€ 629.842**	**€ 649.400**	**€ 668.957**	**€ 688.515**	**€ 708.073**
New world - World with beti-cel					
Treatment	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
SoC (transfusions and chelation)	€ 491.606	€ 364.926	€ 238.247	€ 244.914	€ 251.581
Beti-cel TI	€ 4.363.902	€ 4.677.326	€ 4.680.292	€ 465.160	€ 417.883
Beti-cel TR	€ 778.905	€ 822.762	€ 242.839	-€ 1.107.998	-€ 1.723.331
Total beti-cel	€ 5.142.807	€ 5.500.088	€ 4.923.131	-€ 642.838	-€ 1.305.448
Total	**€ 5.634.413**	**€ 5.865.015**	**€ 5.161.378**	**-€ 397.924**	**-€ 1.053.866**
Annual budget impact	**€ 5.004.570**	**€ 5.215.615**	**€ 4.492.420**	**-€ 1.086.439**	**-€ 1.761.939**

4 Conclusion

The costs per patient for beti-cel are all made in the year of beti-cel treatment, due to the one-time administration. However, the annual budget impact will reduce after several years, as the total pool of patients with TDT, eligible for beti-cel treatment in both the Netherlands and Belgium, will probably be reduced due to the introduction of beti-cel. It is expected that the prevalent pool will be treated in the first 3 years after introduction of beti-cel to the market. This leads to only incident cases to be treated with beti-cel in the years following this period, resulting in a lower budget impact in following years.

For the Netherlands, the budget impact is approximately € 5 million per year during the first three years, confirming that the majority of the costs will be made in the first three years, when the prevalent patient pool is treated. In year 4 and 5 the costs will be decreasing to €123,000 and € 65,000 respectively.
The same trend is seen for Belgium, where the reimbursement of beti-cel results in a budget impact of €5.7 million, €6.7 million and €6.6 million in the first 3 years of reimbursement, when the prevalent patients are treated with beti-cel, with a much smaller budget impact in the following years, €767,000 and €691,000 in year 4 and 5.

After discussions with ZIN and RIZIV, for the Netherlands two payment models have been included as scenario analyses. When applying the VBPoT model, payments for beti-cel are spread over a period of 5 years. The budget impact of the first three years is €1.1 million in the first year and €2.7 million in the third year. The budget impact is lower compared with the base case as the VBPoT model ties 80% of the total amount to continued demonstration of treatment success.
In the outcomes-based rebate scenario, the same trend is seen as in the base case: the annual budget impact is highest in the first three years after introduction of beti-cel on the market. In this scenario, annual costs of SoC are higher than the annual costs of the world with beti-cel already from the fourth year onwards, due to the rebate that is given for transfusion reduced patients.
Although these scenarios have not been calculated for Belgium, it can be expected that, based on the same principles, a similar trend would occur for Belgium.

The applicant expects that within 2 to 4 years the indication will be broadened to paediatric patients <12 years of age and patients with a β^0/β^0 genotype. This will probably result in much more eligible patients and thus a higher budget impact. There will also be a chance that patients with a matched related donor want to be treated with beti-cel. If in the future beti-cel might become available for patients with a HLA matched donor as well, than this will of course have an impact on the budget.
In the near future luspatercept might become a treatment option in these patients in the Netherlands as well. If so, this will probably be a treatment option before starting beti-cel and only for adults. Including luspatercept in this BIA might result in less eligible patients for beti-cel and thus a lower budget impact.

The discussion of the concept of this budget impact report was completed by the Scientific Advisory Board of Zorginstituut Nederland at its meeting on 31 May 2021 and by the Belgian Commission Reimbursement of Medicines at its meeting on 1 June 2021.

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Zorginstituut Nederland

Pharmaco-economic report for betibeglogene autotemcel (Zynteglo®) for the treatment of transfusion-dependent B-thalassaemia (TDT)

Part of reimbursement assessment

Datum 31st May 2021
Status Final

Colofon

Zaaknummer	2020033958
Volgnummer	2021007263
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Inhoud

Summary (English summary)

The company bluebird bio has submitted for reimbursement a dossier on the orphan medicinal product ZYNTEGLO® beti-cel. ZYNTEGLO® contains autologous CD34+ cell enriched hematopoietic stem cells, genetically modified via lentiviral vector mediated transduction encoding the βA-T87Q globin gene.

The dossier is submitted within the Beneluxa Pharmaceutical Policy Initiative. For the HTA part, RIZIV-INAMI authors the pharmacotherapeutic part and ZIN the pharmaco-economic part and budget impact for the two countries.

ZIN has analysed the pharmaco-economic dossier as submitted by the manufacturer. This is done to advise the Dutch Minister of Health about the reimbursement of the product. In case of proven clinical benefit, a pharmaco-economic analysis is obligated in The Netherlands. In Belgium this is not an obligation in the reimbursement procedure, so this pharmaco-economic report will focus on the Dutch situation. In a scenario-analysis the cost-effectiveness of betibeglogene autotemcel (Zynteglo®) in the Belgium situation will be studied.

The cost-effectiveness analysis is done for the patients within the registered indication for betibeglogene autotemcel: 'Treatment of patients 12 years old and older with transfusion-dependent β-thalassaemia who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen-matched related hematopoietic stem cell donor is not available.'

ZIN concluded (after being advised by the WAR) that there is a therapeutic clinical benefit of beti-cel compared to standard of care in patients with transfusion-dependent B-thalassaemia (TDT).

Economic Evaluation
The applicant performed an economic evaluation using a cost-effectiveness analysis and a cost-utility analysis. A DICE-model is used. The study is done from a societal perspective over a lifetime horizon. Discounting of 4% for future costs and 1.5% for future effects is used.

Comparative treatment
Beti-cel is compared with standard of care (blood transfusions and iron chelation therapy).

Results
From this cost-effectiveness analysis the applicant concludes that patients treated with beti-cel gain 11.6 additional QALYs over lifetime compared to SoC. One-time treatment with beti-cel leads to additional discounted costs of €878,171 compared to SoC, resulting in an ICER of €75,871 per QALY gained for the Netherlands and €67,428 per QALY gained for Belgium.

Conclusion and discussion
ZIN concludes (after being advised by the WAR and BeNeLuXa partners) that betibeglogene autotemcel in the treatment of transfusion-dependent B-thalassaemia (TDT) is not a cost-effective treatment. The ICER as presented by the

applicant might be too low because some very optimistic assumptions about the lifelong effectiveness of beti-cel, which is still very uncertain due to lack of long term effectiveness data. In addition to that, in the CE-model the applicant is very pessimistic about the overall survival of transfusion-dependent (TD) patients.
There are several aspects in the applicants cost-effectiveness analysis (model structure and input data) that that are still very uncertain due to lack of proper data or due to limitations in sensitivity analyses.

Model inputs treatment effectiveness:

- ZIN disagrees with the assumption that all transfusion-independent (TI) patients remain TI for their remaining life. This is very uncertain because the lack of long-term effectiveness data of beti-cel treatment. ZIN requested the applicant to add scenario analyses of decreasing effects in TI patients to explore the impact on the ICER and/or to assume in the base case analysis that a small proportion of the TI patients will decrease to the transfusion-reduced (TR) status in the model. The applicant explored the impact of decreasing from TR to TD status but did not analyse that for the decrease from TI to TR status. The applicant argues that due to the mechanism of action of beti-cel (utilises an ex-vivo approach by adding functional copies of the β-globin gene into the patient's own cells) this corrects the underlying cause of the condition and therefore the chance of secondary graft failure after successful beti-cel treatment seems negligible. The Dutch clinical experts state that the long-term effectiveness as assumed by the applicant is not 100% certain. They say that secondary graft failure of with beti-cel treated stem cells is not plausible, but cannot be excluded because of the limited experience and short follow-up duration.
- Although the two interviewed Dutch clinical experts agreed with the applicants assumption of a 2-year duration of iron normalisation after beti-cel transplantation, this remains an uncertain parameter in the CE-model. The clinical experts stated that the duration of iron normalisation after beti-cel treatment depends among others on the type of iron chelation therapy. The duration will probably vary between 2 and 3 years. In the base case analysis the 2-year duration is used (because most of the patients are treated with phlebotomy) and in a scenario the 3-years duration is used.
- In the base case analysis the model estimated that 36% of the patients treated with beti-cel and 97% treated with standard of care, had iron overload related complications. The applicant checked the clinical plausibility of these percentages with Dutch clinicians and they agreed with these percentages. Although these are still uncertain parameters in the CEA because it is unknown what the long term complications will be after beti-cel treatment.
- Uncertainty exists about the used SMR data of TD patients in the model. These are based on assumptions because a lack of data and these are based on very old studies. Dutch clinical experts confirmed the lack of recent data. ZIN thinks that the used SMR for the TD patients (3.9) might be too high, because standard of care for TDT patients improved a lot during the last decades. Because old data are used (1964-1994) those improvements are not included in the model now, so this might result in a too optimistic cost-effectiveness of beti-cel compared to standard of care.

Model inputs utilities:

All the utility data are based on UK data, because of a lack of Dutch data. Dutch clinical experts stated that the health states descriptions do not differ between the UK and the Netherlands and no other information and data are available. Therefore, ZIN agrees with the used utilities . The impact of variation in these utility values was analysed in sensitivity analyses.

Sensitivity analyses:
ZIN concludes (after reviewing by BeNeLuxa partners) that some essential parameters were not included in the PSA. They all concern short and long term effectiveness parameters (e.g. engraftment success of beti-cel; if transplant failure, % reduced transfusions; relapse after beti-cel transplant in TI patients and TR patients). By excluding these important parameters the uncertainty in the model may be inadequately captured.

Areas of uncertainty:
- There is a lot of uncertainty about the long-term effectiveness of beti-cel, the possibility of adverse events in medium-to-long term, the mortality rate for TD patients and the duration of iron normalisation after beti-cel treatment. Because of these uncertainties the cost-effectiveness estimates are likely to be too optimistic.
- Uncertainty issues are also the small patient numbers and immature evidence base.

Overall, ZIN concludes that beti-cel is not a cost-effective treatment for TDT patients compared to standard of care (lifelong blood transfusions and iron chelation therapy) at a for this disease relevant WTP value of €50.000 per QALY. There is a lot of uncertainty about the long-term effectiveness of beti-cel, the duration of iron normalisation after beti-cel, the mortality rate for transfusion-dependent patients and the possibility of adverse events after beti-cel in medium-to-long term. Because of these uncertainties the cost-effectiveness estimates are likely to be too optimistic, because it is assumed that after beti-cel treatment, bloodtransfusions (and iron chelation therapy) are not needed anymore for the rest of a patient's life. Related to that patients treated with beti-cel develop less iron overload complications and are assumed to live much longer. When we assume the applicants (too optimistic) deterministic ICER of €75,871 per QALY the price of beti-cel should decrease with approximately 20% to drop below the WTP value of €50.000 per QALY.

The discussion of the concept of this pharmacoeconomic report was completed by the Scientific Advisory Board of Zorginstituut Nederland at its meeting on 31 May 2021 and by the Belgian Commission Reimbursement of Medicines at its meeting on 1 June 2021.

Samenvatting (Dutch summary)

De fabrikant bluebird bio heeft een vergoedingsaanvraag gedaan en heeft een dossier ingediend betreffende het weesgeneesmiddel ZYNTEGLO beti-cel. ZYNTEGLO bestaat uit hematopoïetische stamcellen die worden afgenomen bij de patiënt. Deze cellen worden gemodificeerd door een virus dat codeert voor gezonde kopieën van het beta-globine gen.

Het dossier is ingediend binnen het Beneluxa Pharmaceutical Policy Initiatief. RIZIV-INAMI is auteur van het farmacotherapeutische deel en ZIN is auteur van het farmaco-economische deel en de budgetimpactanalyse voor de twee landen.

ZIN heeft het farmaco-economische dossier van de fabrikant beoordeeld. Dit is gedaan om de Nederlandse minister van Volksgezondheid te adviseren over de vergoeding van dit geneesmiddel. Als er sprake is van een therapeutische meerwaarde, dan is een farmaco-economische analyse verplicht in Nederland. In België is dit geen verplichting in de vergoedingsprocedure, daarom zal dit farmaco-economisch rapport voornamelijk focussen op de Nederlandse situatie. In een scenario-analyse zal de kosteneffectiviteit van betibeglogene autotemcel (Zynteglo®) in de Belgische situatie bekeken worden.

De kosteneffectiviteitsanalyse werd gedaan voor patiënten binnen de geregistreerde indicatie van betibeglogene autotemcel: 'Behandeling van patiënten van 12 jaar en ouder met transfusie-afhankelijke β-thalassaemie zonder β^0/β^0 genotype, en voor wie een hematopoïetische stamcel transplantatie mogelijk is maar voor wie geen humaan leukocyt antigeen (HLA)-compatibele verwante HSC-donor beschikbaar is.'

ZIN concludeert (na advisering door de WAR) dat er een therapeutische meerwaarde is van beti-cel ten opzichte van standaard zorg bij patiënten met transfusion-dependent B-thalassaemia (TDT).

Economische Evaluatie
De registratiehouder heeft een economische evaluatie uitgevoerd door middel van een kosteneffectiviteits-en kostenutiliteitsanalyse. Daarbij is gebruik gemaakt van een DICE-model. De analyse is uitgevoerd vanuit het maatschappelijk perspectief. De gekozen tijdshorizon is levenslang. Er is een discontering toegepast van 4% op toekomstige kosten en 1,5% op toekomstige effecten.

Vergelijkende behandeling
In de economische evaluatie is betibeglogene autotemcel vergeleken met standaardzorg (bloedtransfusies en ijzerchelatietherapie).

Resultaten
In de kosteneffectiviteitsanalyse concludeert de registratiehouder dat patiënten die behandeld worden met beti-cel levenslang 11.6 extra QALYs winnen vergeleken met standaardzorg. Eenmalige behandeling met beti-cel leidt tot extra (verdisconteerde) kosten van €878.171 vergeleken met standaardzorg, resulterend in een ICER van €75,871 per gewonnen QALY voor Nederland en €67,428 per gewonnen QALY voor België.

Conclusie en discussie
Zorginstituut Nederland concludeert na advisering door de WAR en de BeNeLuXa partners dat betibeglogene autotemcel bij de behandeling van transfusie-afhankelijke B-thalassemie (TDT) geen kosteneffectieve behandeling is. De IKER zoals gepresenteerd door de registratiehouder lijkt te positief omdat er erg optimistische aannames zijn gedaan over de levenslange effectiviteit van beti-cel, wat erg onzeker is vanwege het gebrek aan gegevens over lange termijn effectiviteit. Daarnaast wordt de algehele overleving van transfusie-afhankelijke patiënten erg pessimistisch ingeschat. Er zijn verschillende aspecten van de kosteneffectiviteitsanalyse (modelstructuur en analysetechniek, inputgegevens, validatie en gevoeligheidsanalyses, en resultaten) die nog erg onzeker zijn vanwege gebrek aan data of door beperkingen in gevoeligheidsanalyses.

<u>Model inputgegevens over behandeleffecten:</u>
- ZIN kan zich niet vinden in de aanname dat alle transfusie-onafhankelijke (TI) patiënten hun hele leven transfusievrij blijven. Dit is erg onzeker vanwege het gebrek aan lange termijn effectiviteitsgegevens van behandeling met beti-cel. ZIN verzocht de registratiehouder om scenario analyses toe te voegen waarin afnemende effecten van TI patiënten worden meegenomen, om te onderzoeken wat de invloed op de IKER is en/of aan te nemen in de base case analyse dat een klein deel van de TI patiënten zal verplaatsen naar de transfusie gereduceerde (TR) status in het model. De registratiehouder heeft onderzocht wat de invloed is van het veranderen van TR naar TD status maar heeft niet gekeken naar de verandering van TI naar TR status. De registratiehouder beargumenteert dat vanwege het werkingsmechanisme van beti-cel de onderliggende oorzaak van de ziekte wordt aangepakt en dat daardoor de kans op secundaire afstoting na succesvolle beti-cel behandeling verwaarloosbaar is. De Nederlandse klinische experts geven aan dat de lange termijn effectiviteit zoals aangegeven door de registratiehouder niet 100% zeker is. Ze zeggen dat secundaire afstoting niet waarschijnlijk is, maar dat dit niet helemaal buiten beschouwing gelaten kan worden vanwege de beperkte ervaring en korte termijn follow-up.
- Ondanks dat de twee geïnterviewde Nederlandse klinische experts het eens waren met de aanname van de registratiehouder dat de duur van ijzer normalisatie na de beti-cel transplantatie twee jaar is, blijft dit een onzekere parameter in het KE-model. De klinische experts geven aan dat de duur van ijzernormalisatie ook afhangt van het type ijzer chelatie therapie. De duur zal waarschijnlijk tussen de 2 en 3 jaar zijn. In de base-case analyse wordt een duur van 2 jaar gebruikt (omdat de meeste patiënten aderlating krijgen) en in een scenario wordt 3 jaar gebruikt.
- In de aangepaste base case analyse schatte het model dat 36% van de patiënten behandeld met beti-cel en 97% behandeld met standaardzorg, ijzerovermaat complicaties heeft. De registratiehouder heeft deze percentages gecheckt bij de Nederlandse klinische experts en zij konden zich vinden in deze percentages. Echter blijft dit wel nog een onzekere parameter in het KE-model omdat het onbekend is wat mogelijke lange termijn complicaties kunnen zijn na beti-cel behandeling.
- Onzekerheid bestaat over de gebruikte SMR data in het model. ze zijn gebaseerd op aannames vanwege gebrek aan data en ze zijn gebaseerd op erg verouderde studies. Nederlandse klinische experts bevestigen het gebrek aan recente data, en dit blijft een onzekere parameter in de KEA. ZIN denkt dat de gebruikte SMR voor de transfusie-afhankelijke patiënten (3.9) te hoog zal zijn, omdat de standaard zorg voor TDT patiënten erg verbeterd is de afgelopen decennia. Aangezien er oude data is gebruikt (1964-1994) worden die verbeteringen nu niet in het model meegenomen, en daarom wordt de

kosteneffectiviteit van beti-cel wellicht te positief ingeschat.

Model inputgegevens utiliteiten:
Alle utiliteitsdata zijn gebaseerd op UK gegevens, vanwege een gebrek aan Nederlandse data. ZIN kan zich vinden in de gebruikte utiliteiten omdat de klinische experts aangeven dat de utiliteiten vergelijkbaar zullen zijn en omdat er geen andere gegevens beschikbaar zijn. De invloed van variatie in deze utiliteiten is onderzocht in gevoeligheidsanalyses.

Gevoeligheidsanalyses:
ZIN concludeert (na review door de BeNeLuxa partners) dat sommige essentiële parameters niet zijn meegenomen in de PSA die allen de korte en lange termijn effectiviteit van beti-cel betreffen (engraftment success van beti-cel; als transplantatie faalt, % afname transfusies; terugval na beti-cel transplantatie TI en TR patiënten). Door het niet meenemen van deze belangrijke parameters wordt de onzekerheid in het model niet volledig gevangen.

Punten van onzekerheid:
- Er is veel onzekerheid over de lange-termijn effectiviteit van beti-cel, de mogelijke bijwerkingen op de medium-en lange termijn, de algehele overleving van transfusie-afhankelijke patiënten en de duur van ijzernormalisatie na beti-cel behandeling. Vanwege deze onzekerheden zijn de kosteneffectiviteitsschattingen wellicht te optimistisch.
- Andere onzekerheden zijn de kleine patiënten aantallen en het immature bewijs.

ZIN concludeert dat beti-cel geen kosteneffectieve behandeling is voor TDT patiënten in vergelijking met standaardzorg (levenslang bloedtransfusies en ijzer chelatie therapie) bij een voor deze aandoening relevante referentiewaarde van €50.000 per QALY. Er is veel onzekerheid over de lange termijn effectiviteit van beti-cel, de duur van ijzernormalisatie na beti-cel, de sterftekans voor transfusie-afhankelijke patiënten en het voorkomen van bijwerkingen na beti-cel op de medium tot lange termijn. Vanwege deze onzekerheden zijn de kosteneffectiviteitsschattingen waarschijnlijk te optimistisch, omdat wordt aangenomen dat na behandeling met beti-cel, bloedtransfusies (en ijzerchelatie therapie) niet meer nodig zijn gedurende het resterende leven van de patiënt. Daaraan gerelateerd wordt ervan uitgegaan dat patiënten die behandeld zijn met beti-cel minder ijzerovermaat complicaties ontwikkelen en veel langer leven. Als er wordt uitgegaan van de (te optimistische) deterministische IKER van €75,871 per QALY van de registratiehouder, dan moet de prijs van beti-cel met circa 20% dalen om onder de referentiewaarde van €50.000 per QALY te komen.

De inhoudelijke bespreking is afgerond in de Wetenschappelijke Adviesraad (WAR) van Zorginstituut Nederland in de vergadering van 31 mei 2021 en door de Belgische Commissie Tegemoetkoming Geneesmiddelen (CTG) in de vergadering van 1 juni 2021.

Abbreviations

AE	Adverse events
BIA	Budget Impact Analysis
BoD	Burden of disease
CBS	Centraal Bureau voor de Statistiek
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CUA	Cost-utlitity analysis
DFO	deferoxamine
DFP	deferiprone
DFX	deferasirox
DICE	Discretely integrated condition event
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EVPI	Expected value of perfect information
FACT-BMT	Functional Assessment of Cancer Therapy – Bone Marrow Transplantation
FACT-G	Functional Assessment of Cancer Therapy – General
FDA	Food and Drug Administration
FK	Farmacotherapeutisch Kompas
FSH	Follicle-stimulating hormone
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomular filtration rate
GvHD	Graft versus host disease
Hb	Haemoglobin
HbA	Normal adult haemoglobin
HBB	Haemoglobin Subunit Beta
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCP	Health Care Professional
HCRU	Healthcare resource utilisation
HCV	Hepatitis C Virus
HES	Hospital Episode Statistics
HIC	Hepatic Iron Concentration
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
HSC	Haematopoietic stem cell
HSCT	haematopoietic stem cell transplantation
HTA	Health Technology Assessment
HTLV	Human T-Cell Lymphotropic Viruses
ICER	Incremental cost-effectiveness ratio
KOL	Key opinion leader
LH	Luteinising hormone
LIC	Liver iron content
LN	Natural logarithm
LVV	Lentiviral vector
LWvHB	Landelijke Werkgroep voor Hemoglobinopathie Behandelaars

MRD	Matched related donor
MRI	Magnetic resonance imaging
Ms	Milliseconds
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NTDT	Non-transfusion-dependent thalassemia
NVVH/DHA association	Nederlandse vereniging voor de hematologie / Dutch haematology
NZA	Nederlandse Zorgautoriteit
OWSA	One-way sensitivity analysis
PaedsQL	Paediatric Quality of Life
PAID	Practical Application to Include future Disease costs
PB	Peripheral blood
PCR	Polymerase chain reaction
PE	Pharmaco-economic evaluation
PRIME	Priority Medicines
pRBC	packed red blood cells
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PTT	Prothrombin time
QALY	Quality-adjusted life year
QoL	Quality of life
RBC	Red blood cell
RCT	Randomised controlled trial
RIVM	Rijksinstituut voor Volksgezondheid en Mileu
RWE	Real-world evidence
SAE	Serious adverse events
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SE	Standard error
SF-36	Short Form 36
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
TCRN	Thalassaemia Clinical Research Network
TD/TDT	Transfusion-dependent / transfusion-dependent thalassemia
TI	Transfusion independence
TIF	Thalassaemia International Federation
TP	Transplant population
TR	Transfusion reduction
TTO	Time-trade-off
UCBT	Umbilical cord blood transplantation
UK	United Kingdom
US	United States
VCN	Vector copy number
VOD	Veno-occlusive disease
VBPRoT	Value Based Payment Rebate over Time
WBC	White blood cell
WHO	World Health Organisation
WTP	Willingness to pay
ZIN	Zorginstituut Nederland

1 Introduction

The company bluebird bio has submitted for reimbursement a dossier on the orphan medicinal product ZYNTEGLO® beti-cel. ZYNTEGLO® contains autologous CD34+ cell enriched hematopoietic stem cells, genetically modified via lentiviral vector mediated transduction encoding the βA-T87Q globin gene.

The dossier is submitted within the Beneluxa Pharmaceutical Policy Initiative. For the HTA part, RIZIV-INAMI authors the pharmacotherapeutic part and ZIN the pharmaco-economic part and budget impact for the two countries.

ZIN has analysed the pharmaco-economic dossier as submitted by the manufacturer. This is done to advise the Dutch Minister of Health about the reimbursement of the product. In case of proven clinical benefit, a pharmaco-economic analysis is obligated in The Netherlands. In Belgium this is not an obligation in the reimbursement procedure, so this pharmaco-economic report will focus on the Dutch situation. In a scenario-analysis the cost-effectiveness of betibeglogene autotemcel (Zynteglo®) Belgium situation will be studied.

1.1 Registered indication

The cost-effectiveness analysis should be done for the patients within the registered indication for betibeglogene autotemcel. The registered indication is: 'Treatment of patients 12 years old and older with transfusion-dependent β-thalassaemia who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen-matched related hematopoietic stem cell donor is not available.'

1.2 Disease

β-thalassaemia is a genetic blood disease caused by a defect of the β-globin gene in chromosome 11. It is characterised by a decreased synthesis (β^+ or β^E) or absent synthesis (β°) of the β-globin chains. β-globin chains form together with the ὰ-chains and haem, the physiological haemoglobin molecule : HbA. The IVS-1-10 mutant (see further study HGB-12) has phenotypic characteristics of both β^+ and β°; it is a common β-globin variant in the Mediterranean population.
β-thalassemia presents clinically from early childhood on. The bone marrow expands and extra-medullary haematopoiesis occurs. Anaemia is the typical presentation of a child with β-thalassaemia. The iron absorption is increased, which, together with regular blood transfusions, leads to iron overload. Increased production of erythropoietin-hormone leads to the bone marrow expansion and skeletal changes, as well to a hypermetabolic stage.
β-thalassaemia can be divided into two main groups: non-transfusion dependent and transfusion-dependent. This division is based on the patient's needs for blood transfusions. Patients with the transfusion-dependent form require regular blood transfusions to survive. The treatments with repeated transfusion and iron chelation are life-long.
Patients who are not adequately treated with transfusions and iron chelation therapy, develop serious complications like cardiomyopathy, pulmonary hypertension, osteoporosis, skeletal deformities, arthropathy, hepato-splenomegaly, endocrinopathies, diabetes, delayed puberty and gonadal dysfunction. Untreated, patients will die before the age of 3 years.
See chapter 5.1.1. of the clinical report for a more detailed disease description.

1.3 Epidemiology

It is assumed that the prevalence of β-thalassaemia in the Netherlands in 2020 was between 150 and 200 patients. Of these patients, approximately one-third of the adult patients is assumed to be transfusion-dependent. There were 65 *adult patients* and of these patients it is estimated by their treating physicians that 57 patients (88%) would be eligible for autologous HSCT (not for allogeneic HSCT). An enquiry further showed that 14 of these patients (25%) have a non-β^0/β^0 genotype and would therefore be eligible to receive beti-cel. In Belgium this number is assumed to be approximately 15 patients. See the budget impact analysis for a more detailed description of the number of patients in the Netherlands and in Belgium.

1.4 Decision problem

The pharmaco-economic analysis should answer the question if the use of betibeglogene autotemcel in daily clinical practice is cost-effective, in other words that the costs of investing in betibeglogene autotemcel are outweighed by the health benefits and financial savings. To answer this question an incremental cost-effectiveness ratio of betibeglogene autotemcel compared to the standard of care is estimated by the applicant.

2 Methods

In this chapter we start with an overview of the data sources and literature that were used by the applicant to perform the pharmaco-economic analysis. After that the PICOT and model structure will be described. Then the model inputs will be outlined and we finish with a section about uncertainty analyses.

2.1 Overview of used data sources and literature

2.1.1 Data sources

The applicant used several data sources for the pharmaco-economic analysis. Of course data from the beti-cel trials were used (HGB-204, 205, 207 and 212).[1-4] In the pharmacotherapeutic report these studies are outlined in detail.
Further, *a United Kingdom (UK) chart review study*[5] was performed by the applicant and used as input for the model. A retrospective chart review with cross-sectional patient and caregiver surveys in 9 National Health Service (NHS) centres across the UK was conducted by the applicant to evaluate routine management of TDT, and patient and caregiver health-related quality of life (HRQoL). Eligible patients had a documented diagnosis of TDT (index event) ≥2 years prior to data collection. The observation period was the 2-5 year period prior to data collection or death. Patient-reported outcomes (PRO) were completed at enrolment, including EuroQoL EQ-5D, Work Productivity and Activity Impairment (WPAI), and disease-specific TranQoL. The primary endpoint was the number of blood transfusion episodes per patient per year. In addition, data on comorbidity, pre-transfusion Hb, distribution of iron chelation therapies (oral, SC), serum ferritin, liver iron concentration (LIC) and T2* cardiac iron were collected. The UK chart review study has not been published yet, but will be submitted to a medical journal in the near future.
Another source is *a time-trade-off (TTO) study* that was conducted by the applicant in the UK to inform assumptions around the QoL impact of TDT and beti-cel (presented as "gene therapy"). A total of 207 participants completed the interviews, which were conducted in March 2018 in three locations in England. Vignettes were developed to represent the different health states of TDT, such as TDT with ongoing blood transfusions and iron chelation therapy, as well as the period of time for which patient undergo HSCT or gene therapy (i.e. beti-cel). In addition, several post-transplant health states were included.[6]

2.1.2 Literature review

To populate the model for parameters for which no data was available from the beti-cel clinical trials, the UK chart review study or the vignette study, the applicant conducted a systematic literature review (SLR)[7] in May 2017 and updated in October 2020 to identify available evidence on model inputs such as quality of life, resource use and costs. Five studies concerned CE models and one cost-of-illness model was identified in the SLR. All CE studies related to the evaluation of iron chelation therapies rather than HSCT transplant and were from the UK (n=3)[8-10], Italy (n=1)[12] and the US (n=1)[11]. These studies were used by the applicant to inform the CE model on the inclusion of long-term iron overloading complications: cardiac disease, liver related complications and other complications (including diabetes, hypogonadism, hypoparathyroidism, hypothyroidism).

2.1.3 *Validation of the used data*

Because apparently no specific Dutch and Belgium data are available to populate the PE-model, the applicant sent out a questionnaire to two Dutch key opinion leaders (KOLs)[13-14] and two Belgian KOLs[15] to validate clinical, resource use and cost inputs, model assumptions and discuss the anticipated positioning of beti-cel in TDT. This was further discussed in separate teleconferences. In both countries one clinical expert in paediatric and adolescent patients was included and one with expertise in adult patients.

Besides this, ZIN used two assessment reports from other countries, England and Scandinavian countries, to validate and check data and methods that were used in this Dutch assessment dossier. NICE is working on its appraisal right now and Finose (Finland, Norway and Sweden) already finished its reimbursement report.

2.2 PICOT

2.2.1 *Population*

In the pharmacotherapeutic report it is concluded that beti-cel (Zynteglo®) has clinical benefit in the following population: 'Patients 12 years and older with transfusion-dependent β-thalassaemia who do not have a β°/β° genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen-matched related donor is not available'.
In the pharmacoeconomic model two sources were used for patient baseline characteristics (age, gender, body weight, baseline iron overload levels, history of iron overload complications):
1) baseline data reported for the beti-cel trials HGB-204, 205, 207 and 212[1-4] and
2) data from the United Kingdom (UK) chart review study[5].
The applicant validated these patient characteristics data with Dutch and Belgian key opinion leaders (KOLs)[13-15]. See table 1 for the baseline patient characteristics.
Of the 33 non-β^0/β^0 TDT patients enrolled and evaluated for transfusion-independency (TI) in the HGB-204, 205, 207 and 212 trials, the mean age of the population was 20.6 years and 54.5% were female.[16] The inclusion criteria for these trials were limited to patients aged under 50 years and therefore data regarding the effectiveness of beti-cel is not available for individuals over the age of 50 years. In the UK chart review a total of 165 patients were included (median age at data collection 24.1 [interquartile range (IQR) 11.8-37.2] years; 50% (n=82) male; one patient was deceased).
From the CEA and the model (and table 1) is looks like only patients in the age of 12-35 years are eligible to be treated with beti-cel. The Dutch clinical experts noted that the clinical trial population best presents the Dutch patients. In clinical practice it can be expected that less older patients will be eligible for beti-cel treatment because of more iron complications in older patients due the longer periods of blood transfusions. On the other hand in The Netherlands it is common practice to perform allogenic transplantations in paediatric TDT patients. Therefore the number of patients in the age category of 12-17 years that will be treated with beti-cel is estimated to be less than 10% (see table 1). In the model the age distribution at baseline has been taken from the clinical trial and adjusted according to the above, resulting in: 12-17: 10%; 18-23: 61.3%; 24-29: 8.2%; 30-34: 20.5%; 35-39: 0%; 40-44: 0%; 45-50: 0%.
The applicant also argues that the beti-cel indication does not stipulate an upper age limit for treatment, eligibility should instead be determined based on the individual patient's fitness to safely undergo autologous-HSCT using myeloablative conditioning, provided other criteria for treatment such as transfusion-dependence and genotype are met. In the EPAR it is also mentioned that the observed benefit-risk in the studied population can be extrapolated to the older population (i.e. >35)

as long as transplant eligibility criteria for patients with TDT are met. The applicant emphasizes that the decision to start treatment should be based on specific co-morbid factors known to impact the safety of treatment including myeloablative conditioning, rather than a strict upper age limit in the indication. Although the number of eligible patients for beti-cel treatment older than 35 years will be small, ZIN thinks this is not in line with how it is put into the CE-model. Because in the CEA obviously there is an upper age limit of 35 years now.

The average body weight for adolescents (44.9 kg) and adults (56.9 kg) is obtained from the HGB-204, 205, 207 and 212 clinical trials.[1-4] In addition, average body weight data from the UK chart review study[5] (adolescent: 40.0 kg; adult: 64.0 kg), has been validated as an alternative source by the applicant with the Dutch KOLs. During the consultation process the Dutch clinical experts have indicated that due to the lack of available data from the Dutch patient population, it would be best to use the data from the clinical trials, as on average this seems to reflect the Dutch patient population. Moreover, they have the opinion that these clinical trial patients are also expected to best resemble the eligible patients in the Netherlands, as they have undergone auto-HSCT with beti-cel, whereas those from the UK chart review might not all be suitable for gene therapy through auto-HSCT with beti-cel.
In the model, average body weight is used to calculate iron chelation dosing and related iron chelation drug acquisition costs. Lower bodyweight corresponds to lower doses, and hence lower iron chelation drug costs. So actually the applicant used a conservative approach by using the (lower) average body weights from the HGB-204, 205, 207 and 212 clinical trials in the base case analysis. To evaluate the impact of this choice, the applicant runs a scenario analysis using the (higher) average body weights from the UK chart review study.

ZIN requested the applicant to explain the difference between the UK chart review and the UK HES data. This last one is often used as input in the model, but it is not the same as the UK chart review. The applicant explains that the UK retrospective chart review study evaluated current management pathways for TDT, clinical status, healthcare resource use, the impact of TDT on quality of life (QoL) and work productivity (WPAI) of patients and carers in the UK using an observational mixed-methodology. The results offer insights into the real-world management and clinical status of patients with TDT in the UK. The UK HES cohort study on the other hand was designed to explore the 10-year mortality (2009-2018) and prevalence of co-morbidities in patients with TDT, using Hospital Episode Statistics (HES) data from the National Health Service (NHS) in England.

To assess the iron-overloading complications at baseline in the treated population in the beti-cel clinical studies, the applicant conducted a review of medical history data. As a result of that review the applicant described that none of the patients had liver complications nor diabetes, but two had some element of cardiac complications and two had hypogonadism. However, the applicant reported that the severity of the complications was not serious enough to prevent the patients being enrolled in the study, so it was assumed that all patients had zero iron overload complications at model baseline.
The applicant justifies this assumption by the argument that Dutch clinical experts confirmed that patients are not eligible for treatment with beti-cel if they have severe complications.[2] Hence, it seems to not make sense to include these complications at baseline. Moreover the applicant argues that excluding them from baseline also limits double counting as the risk to develop these complications is already included in the iron level groups.

At baseline (model entry), TDT patients are specified with an iron loading level as a function of serum ferritin, liver iron concentration [LIC], and myocardial T2*. The model uses data from the UK chart review[5] because it contains more recent data and it concerns a larger sample size (N=165) than the clinical trials. The applicant validated its use for the Dutch clinical practice with the Dutch KOLs and they both agreed these iron loading data are representative for the Dutch patients.[13-14] The majority of patients included in the chart review had low iron loading levels in the liver (61%) and heart (88%). Moreover, patients with high cardiac iron loading would not be eligible for beti-cel therapy, therefore the applicant reported that the distribution of Myocardial T2* was adjusted such that no patients in the model had high cardiac iron levels at baseline. The high cardiac iron loading 'category' was set to zero and the other two (low and moderate cardiac iron loading) were recalculated to sum up to 100%.
In table 1 the baseline iron distributions from the clinical trials and from the UK chart review are presented. The UK data show a tendency to slightly lower proportions of patients with high iron levels. In the Netherlands the clinical practice is to transplant all paediatric TDT patients before the age of 12, which has been adjusted in the model as well. This results in a generally older Dutch eligible patient population compared to the clinical trial patients, which gives reason to also assume higher proportions of patients with high iron levels. The applicant therefore decided to include the iron level distributions from the UK chart review in the model.

Table 1 Baseline patient characteristics in beti-cel trials, a UK chart review and data used in the PE-model

Characteristics	HGB-204, 205, 207 and 2012[1-4]	UK Chart Review[c][5]	Model population (base case)[b]
N	33	165	33[b]
Age, mean (SD)	20.6 (6.3) 12-17: 33.3% 18-23: 45.4% 24-29: 6.1% 30-34: 15.2%	Median (IQR): 24.1 (11.8-37.2)	22.8[c] 12-17: 10.0%[a] 18-23: 61.3%[a] 24-29: 8.2%[a] 30-34: 20.5%[a]
Gender, % female	54.5%	50%	54.5%[b]
Body weight (kg), mean	44.9 kg (adolescents) 56.9 kg (adults)	40.0 kg (adolescents) 64.0 kg (adults)	Adolescents: 44.9 kg[b] Adult: 56.9 kg[b]
Pre-treatment iron overload			
Cardiac T2* (msec)	Low iron: 100% Moderate iron: 0% High iron: 0%	Low iron: 88% Moderate iron: 12% High iron: 0%*	Low iron: 88%[c] Moderate iron: 12%[c] High iron: 0%*
Liver iron concentration (LIC) (mg/g)	Low iron: 61% Moderate iron: 27% High iron: 12%	Low iron: 61% Moderate iron: 23% High iron: 16%	Low iron: 61%[c] Moderate iron: 23%[c] High iron: 16%[c]
Serum ferritin (pmol/L)	Low iron: 21% Moderate iron: 58% High iron: 21%	Low iron: 25% Moderate iron: 39% High iron: 36%	Low iron: 25%[c] Moderate iron: 39%[c] High iron: 36%[c]

Abbreviations: Serum Ferritin: low iron, ≤2,247 pmol/L; moderate iron, 2,247 -5,618 pmol/L; high iron, >5,618 pmol/L Liver Iron Concentration: 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, [a]Recalculated to Dutch clinical practice[2] from TI-evaluable patients aged ≥ 12 years and a non-β0/β0 genotype from clinical trials HGB-204, 205, 207 and 212; [b]TI-evaluable patients aged ≥ 12 years and a non-β^0/β^0 genotype from clinical trials HGB-204, 205, 207 and 212; [c]Recalculated to Dutch clinical situation using midpoint age per category; *Patients with high myocardial iron loading (myocardial T2*: <10 ms) are not eligible for beti-cel therapy, hence, this baseline value is set to 0%*

2.2.2 *Intervention*

The intervention is autologous CD34-cells encoding $\beta^{A\text{-}T87Q}$ – globin gene i.e. ZYNTEGLO beti-cel, this is a once in a lifetime infusion. More details about the intervention are described in the pharmacotherapeutic report.

Beti-cel treatment consists of the following steps:[17]

Step 1: Pre-treatment hypertransfusion to maintain a Hb ≥ 11 g/dL: prior to start of beti-cel treatment, patients receive additional blood transfusions (hypertransfusion) to maintain a Hb ≥ 11 g/dL.

Step 2: Mobilisation and apheresis of stem cells: the beti-cel treatment process continues with the harvesting of the patient's own HSCs through a standard peripheral stem cell collection procedure, known as apheresis, following the administration of mobilising agents.

Step 3: Stem cell processing: the collected stem cells are then shipped to an external manufacturing practice facility where they are purified, and functional copies of the gene are inserted using a viral vector delivery system outside the body (ex vivo).

Step 4: Patient conditioning: the patient subsequently undergoes myeloablative conditioning using chemotherapy to make space in the bone marrow.

Step 5: Beti-cel infusion via auto-HSCT: and the quality controlled modified stem cells are shipped back to the qualified treatment centre, where they are given back to the patient through peripheral infusion. This procedure is also known as an autologous HSCT.

Step 6: Inpatient stay for engraftment: after HSCT, patients stay approximately 30 days in the hospital until engraftment occurs and blood values have normalised.

2.2.3 *Comparator*

The comparator population in the pharmacotherapeutic report is based on the clinical trials and is therefore an in-patient comparison of the treatments given in the 2-year period before ZYNTEGLO beti-cel infusion versus the period after infusion for at least 18 months.[1] Besides that, the therapeutic value is based on an indirect comparison, continuation of repeated red blood cell transfusions and iron chelation therapy (lifelong) because this is the current standard of care for TDT patients in the Netherlands and in Belgium.

The comparative treatment used in this pharmaco-economic evaluation is standard of care (SoC), consisting of life-long blood transfusions in combination with iron chelation therapy. Blood transfusions are provided every 3-4 weeks.[13-14] There are three iron chelators available: deferiprone, deferasirox, desferrioxamine. As mentioned before, dosing of iron chelation therapy is based on body weight.[18-20] It is administered orally either 75mg/kg divided in 3 doses a day for deferiprone (DFP) or 14-21mg/kg once daily for deferasirox (DFX)[19-20] or subcutaneously 20-60 mg/kg, 5-7 times per week for desferrioxamine (DFO)[18] depending on body weight. The applicant used the UK chart review of medical records to understand the current real-world routine management and clinical status of patients with TDT in the UK. Of the patients receiving iron chelation therapy at the time of data collection, 58% received DFX, 7% received DFP, 14% received DFO, and the remaining 21% received a combination of chelators at the time of data collection. Table 2 presents the distribution of chelating agents from the UK chart review and from Dutch clinical KOL input as collected by the applicant. Deferasirox appeared to be the most prescribed iron chelator in the Netherlands, only in exceptional cases the patient will be treated with another iron chelator. In the model the input from Dutch KOLs for iron chelator distribution is used. ZIN agrees with this distribution and therefore in the remaining of this report the focus will be on deferasirox as the most important iron chelation therapy in The Netherlands.

Table 2 Distribution of chelating agents from chart review and clinical input

Iron chelator(s)	Mode of administration	UK chart review study	Dutch clinical KOL input
deferasirox	Oral	58%	98%
deferiprone	Oral	7%	1%
desferrioxamine	Subcutaneous	14%	0%
deferiprone and desferrioxamine	Oral and subcutaneous	11%	1%
deferiprone and deferasirox	Oral	5%	0%
deferasirox and desferrioxamine	Oral and subcutaneous	5%	0%

Source: applicants UK Chart Review study[5] Dutch KOLs input[13-14] collected by the applicant

2.2.4 *Clinical outcome measures*

Clinical outcome measures used in the model include both main clinical trial outcomes as well as long-term transplant-related outcomes and complications of iron overload. The outcome measures as used in the pharmacotherapeutic report

[1] Period for at least 16 months after beti-cel was the median duration between the moment of beti-cel infusion and time to reach transfusion-independency. Of note is that packed red blood cells are still given after beti-cel infusion (when the patient is in intensive care) up to 6 months at the latest. As the definition goes for at least 18 months transfusion-free periods, the follow-up.

are as follows:
- Red Blood cells (RBC) aspect: Transfusion-independency [crucial], defined as a weighted average Hb concentration of ≥ 9 g/dL without any packed RBC transfusions for a continuous period of ≥ 12 months at any time after beti-cel infusion. It is the most important clinical outcome because the natural evolution of the disease does not consist of transfusion-free periods.
- Discontinuation of iron chelators for at least 6 months [crucial]
- White blood cells aspect: Recuperation of neutrophil production by the bone marrow after beti-cel infusion [important]. Outcome valid in any hematopoietic stem cell transplantation.
- *Thrombocytes aspect:* Recuperation of platelet production by the bone marrow after beti-cel infusion [important]. Outcome valid in any hematopoietic stem cell transplantation.
- QoL [crucial]
- Serious adverse events [crucial]
- Proportion of patients stopping the study [crucial]

In the model beti-cel transplant related outcomes include transfusion status after transplant (transfusion independent (TI), transfusion reduced (TR)), infertility from myeloablative conditioning and iron normalisation post-transplant. Long-term complications of iron overload are also incorporated in the model. See section 2.4 for further detailed information.

2.2.5 Timehorizon

In the model to evaluate the CE of beti-cel gene therapy for the treatment of patients with TDT, effects and costs are simulated for individual patients with a distribution of ages at the start of the simulation ('model entry') and using a lifetime horizon. The maximum survival age is capped at an age of 100 years.

2.2.6 Type of economic evaluation

If a therapeutic benefit is concluded in the pharmacotherapeutic report in The Netherlands a cost-effectiveness analysis (CEA) and/or a cost-utility analysis should be performed (CUA) by the applicant.
In this economic evaluation the applicant performed a CEA and CUA to analyse the cost-effectiveness of treatment with betibeglogene autotemcel compared to the SoC in the Netherlands (base-case) and Belgium (scenario).

Conclusions about the PICOT:
ZIN agrees with all the aspects of the PICOT that are used by the applicant in the pharmaco-economic evaluation. The CE results in this report give information about the 12 to 35 years aged patients and not about patients older than 35 years.

2.3 Economic model structure

2.3.1 Model-structure and health states

In figure 1 the model structure is presented. A Discretely Integrated Condition Event (DICE) simulation framework is used to evaluate the CE of beti-cel gene therapy for the treatment of patients with TDT. Effects and costs are simulated for individual patients with a distribution of ages at the start of the simulation ('model entry') and using a lifetime horizon. DICE is a method that conceptualizes the course of the disease as a combination of the "conditions" (aspects that persist over time, such as iron levels, age) and "events" (aspects that happen at a point in time, such as transplantation), and accumulates outcomes of interest of each patient simulation. The DICE model is an event-driven model. The course of the disease (TDT) is

represented as a combination of evolving conditions (information in the model) and events (distinct points in time where conditions change). The path diagram (see figure 1) maps out the possible pathways through the model's events, both real-world and modelling. Real-world events correspond to things that happen in real life, and modelling events facilitate model execution or calculations. Figure 1 shows all the events in the model, each one represented by a box.

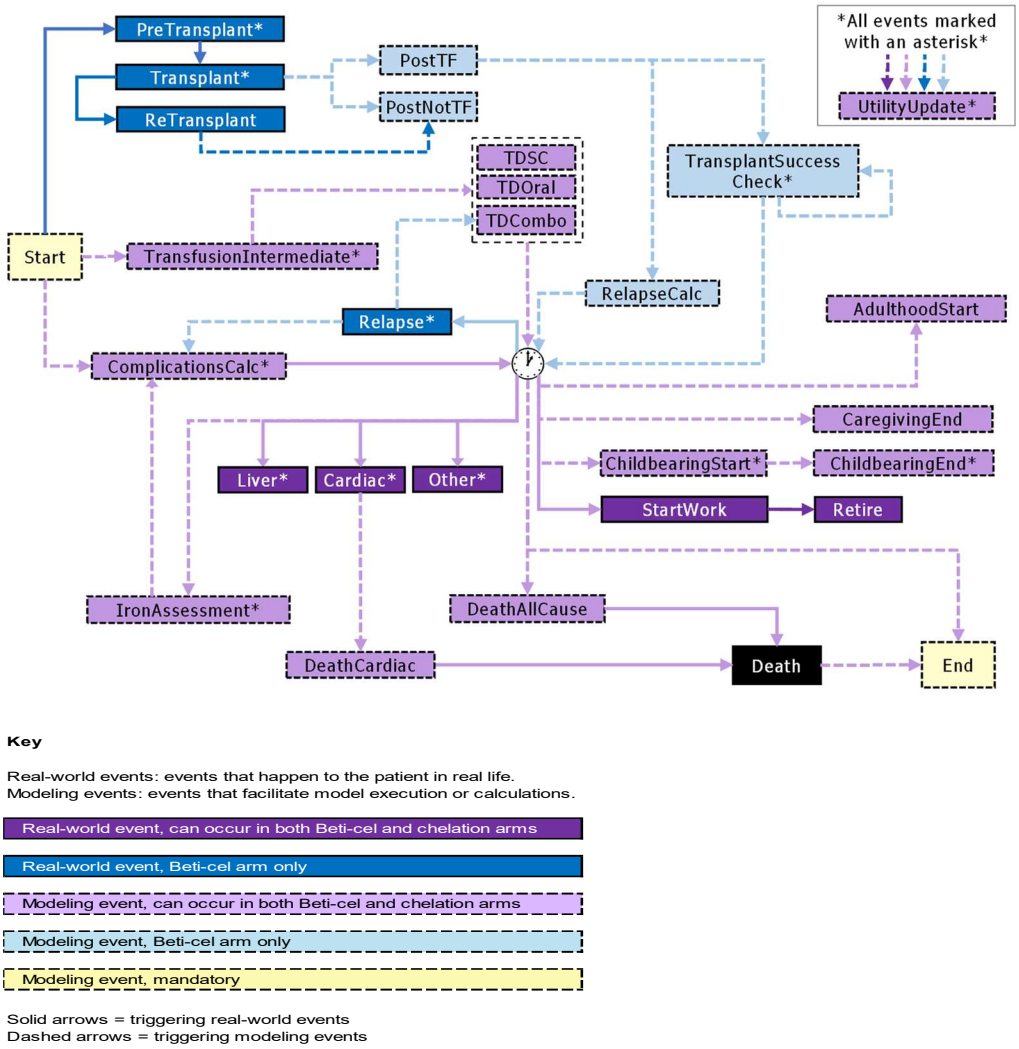

Figure 1: Model structure of the DICE-model for treatment with betibeglogene autotemcel in patients with transfusion-dependent B-thalassaemia (TDT).

As patients age in the model, those who achieve transfusion-independency (TI) are assumed to have survival and utility values closer to the Dutch general population than transfusion-dependent (TD) patients. Patients who are not TI will receive lifelong blood transfusions and iron chelation therapy (at baseline levels or at a reduced frequency). Mortality is assumed to be dependent on age, gender, whether or not the patient is TI as well as the presence of iron overload-related cardiac, liver and endocrine disease (diabetes, hypogonadism). A sequence of major events dictates how this progression will occur during transplant and acute recovery, post-acute recovery, and ongoing ageing (see figure 1).
The applicant argues that using a Markov framework is not preferred in this disease.

They argue that modelling a range of possible iron levels in the three organ systems (cardiac, liver and endocrine) using a Markov framework would have required an unfeasible number of states to capture as a cohort. These would have been multiplied by the number of combinations of iron loading complications, the transfusion requirements of the patient, as well as age and gender, creating hundreds of potential overall health states. Thus, the applicant concludes that it is necessary to use an individual patient modelling approach in order to capture the effects of organ-specific iron overload. Individual simulation also allows timing and order to vary between the various events that occur in this disease. Therefore, a DICE simulation framework was implemented by the applicant. ZIN agrees that the DICE framework is a good approach for the CE analysis in this disease. However a model must appropriately account for uncertainty and this is one of the challenges with DICE models - the degree of computational complexity is challenging.

2.3.2 Cycle duration, cohort size and patient paths

In the model, the path of 600 patients (600 profiles) is simulated. The simulation of one patient starts by the selection of a baseline profile (Table 3). In each analysis, the sequence of selecting the profiles and thus baseline characteristics is random, and hence the baseline characteristics of the 600 simulated patients can vary in each analysis. The sequence is as follows:

- select a patient profile (age, gender) from the Profiles table (Table 3) and generate their specific random draw values (iron overload levels)
- simulate this patient on beti-cel
- simulate this exact same patient (same baseline characteristics) on blood transfusion and chelation.
- select a new patient profile.

The age and gender distributions observed in the HGB-204, 205, 207 and 212 trials (Table 1) are used to weigh each profile (see adjusted shares in Table 3). A cardiac, liver and serum iron overload level (low, moderate or high) is randomly drawn for each patient simulation from the distribution of iron overload data obtained from the UK chart review study (Table 1). Iron overload level at baseline impacts the risk of developing long-term iron overload complications.

Table 3 Patient baseline profiles for gender and age

Profile ID	Gender	Age category	Baseline age (years)	Adjusted share
1	Male	Paediatric (<12 years)	6	0.0%
2	Male	Adolescent (12-17 years)	15	15.2%
3	Male	Young adult (18-23 years)	21	20.7%
4	Male	Adult (≥24 years)	29.5	9.7%
5	Female	Paediatric (<12 years)	6	0.0%
6	Female	Adolescent (12-17 years)	15	18.1%
7	Female	Young adult (18-23 years)	21	24.7%
8	Female	Adult (≥24 years)	29.5	11.6%

Please note that profiles 1 and 5 have not been used in this economic analysis as beti-cel is not indicated for this age group, hence adjusted shares are set to 0%.

Patients' disease changes over time based on their response to treatment, the natural history of disease and aging. The outcome (LYs, QALYs and costs) depends on whether or not the patients receives treatment with beti-cel, become TI or TR with beti-cel treatment, on the baseline iron overload levels and the change in these levels (normalising for TI or reducing for TR patients).

Three complications are considered in the model: cardiac, liver and endocrine (diabetes, hypogonadism) complications. The complication rate applied in the model for each of these three types of complications depends on the level of iron overload. All complications have an impact on costs and quality of life (decrement). Only cardiac complications have a direct impact on mortality.
Patient mortality depends on age, the presence of a cardiac complication and dependence on transfusions. Excess mortality coefficients associated with transfusion-dependent and independent patients are applied.
A risk of infertility is taken into account in both arms of the model. This risk is associated with myeloablative treatment for patients treated with beti-cel and with hypogonadism, an endocrine complication of the disease, for those receiving SoC.
Ultimately, the conditions influence the timing of the occurrence of events (e.g. the level of iron overload determines the occurrence of a complication) and the value of the conditions may change following the occurrence of an event (e.g., the level of iron overload following beti-cel treatment).
As per ZIN's request, the applicant ran stability tests on the Dutch model, keeping in mind the Dutch decision relevant range for ICERs according to different levels of disease burden. For the Dutch beti-cel economic model, a stability analysis was run with a total of 20,000 profiles, with the output saved for every profile and plotted per step of 100 profiles. The applicant showed the results of the stability analysis graphically. And from that figure it can be seen, that the ICER appears to stabilize after approximately 2,500 profiles. Considering these Dutch stability test results and a manageable run time of the model, the base case analysis and the scenario analyses have now been conducted using 2,500 profiles. The PSA has been run with 600 profiles in order to keep a manageable run time. The applicant argues that in the PSA it is the objective to analyse uncertainty around several parameter inputs simultaneously, which analyses another type of uncertainty than testing robustness of ICER results with using increasing numbers of profiles ('profile stability').

2.3.3 Perspective

In accordance with the Dutch guideline for economic evaluations in health care, the model supports a cost-utility analysis (CUA) using a societal perspective. Indirect non-medical costs (travel, caregiver, productivity) and indirect medical costs (using the Practical Application to Include future Disease costs [PAID] method)[21] were considered. The Belgian scenario analysis is conducted using a payer perspective in accordance with Belgian Health Care Knowledge Centre (KCE) guidelines.[22]

2.3.4 Discounting

Costs were discounted at 4% and health effects at 1.5% according to the Dutch guidelines.[23]

2.4 Economic model inputs

2.4.1 Treatment effectiveness and long-term outcomes

Clinical outcomes used in the model include both main clinical trial outcomes as well as long-term transplant-related outcomes and complications of iron overload.

2.4.1.1 Transplant related outcomes

Beti-cel transplant related outcomes include transfusion status after transplant (transfusion independent (TI), transfusion reduced (TR)), infertility from myeloablative conditioning and iron normalisation post-transplant.

As already mentioned in section 2.2.4. the *main clinical outcome* evaluated in the HGB-204, HGB-205, HGB-207 and HGB-212 trials is TI defined as 12 months without any RBC transfusion while maintaining a weighted average Hb of ≥9 g/dL. In these trials 84.4% of the treated patients achieved TI (27/32 patients). For the five patients who did not achieve TI, TR was observed with a mean reduction in transfusion frequency of 74.75% from six months after infusion of beti-cel through to the last follow-up visit. In the long-term follow up study LTF-303 it was observed that the patients that achieved TI, maintained in the TI status (up to 71.8 months follow-up).[24] In the model TI patients are considered to be independent from transfusions beginning at 12 months and are assumed to remain TI for the remaining of their life. Patients who experience TR are assumed to remain TR for the rest of their life. In the model it is assumed that 84.4% of simulated patients achieve TI and 15.6% TR. In the transfusion-reduced patients, a 74.75% reduction in the number of transfusions is assumed in line with the observed data.[24]
Because the long-term effectiveness of beti-cel is still very uncertain, the applicant explored the impact of decreasing of treatment effect in TR patients in three scenario analyses with all TR patients relapsing to TD 5, 10 or 30 years after beti-cel transplant.
ZIN disagrees with the assumption that all TI patients remain TI for the remaining of their life. This is still very uncertain because a lack of long-term effectiveness data of beti-cel treatment. ZIN requests to add scenario analyses of decreasing effects in a small proportion of TI patients to explore the impact on the ICER or to assume in the base case analysis that a small proportion of the TI patients will decrease to the TR status in the model. The applicant argues that due to the mechanism of action of beti-cel (utilises an *ex-vivo* approach by adding functional copies of the β-globin gene into the patient's own cells) this corrects the underlying cause of the condition. As the cells used are the patient's own i.e. autologous, this approach eliminates major problems such as graft rejection. After one-time *ex vivo* treatment with beti-cel, modified stem cells can serve as a long-term reservoir for red blood cells that have the functional β-globin protein as mentioned by the applicant. From a clinical and/or scientific point of view, it might not be plausible that late secondary graft failure would occur after successful engraftment with beti-cel in an autologous-HSCT setting. The applicant does not agree with the request of ZIN to include an assumption on this in the base case because they emphasize that there is no evidence to support the idea that the therapeutic effect of beti-cel in patients that successfully engraft and achieve TI, may not be lifelong.
The Dutch clinical experts state that the long-term effectiveness as assumed by the applicant is not 100% certain. The data is not mature enough to draw hard conclusions. One result as can be seen in the study data is that "graft failure" was not seen and that transfusion reduced response (which can be seen as a type of graft failure) appeared shortly after the transplantation. If beti-cel can hinder the self-renewal of the hematopoietic stem cells is not known. Secondary graft failure of with beti-cel treated stem cells is not plausible, but cannot be excluded because of the limited experience and follow-up duration.

Myeloablative conditioning can cause infertility, because of the invasive nature of myeloablation, cryopreservation of spermatocytes or ovocytes is to be organised. Infertility in TDT patients can be caused by the disease itself (hypogonadotrophic hypogonadism),[25] from iron overload (gonadal toxicity)[26] or occur through myeloablative conditioning (step 4 of the beti-cel SCT procedure). In the model *infertility due to myeloablative conditioning and iron overload* are included as these will be different for patients treated with beti-cel or life-long blood transfusions.
The applicant performed a literature search to find data about infertility or gonadal function in thalassaemia patients post-transplant. Three studies[27-29] were identified in that search, one study performed in Italy[27], one in Thailand[28] and one in

France[29]. The applicant concludes that only the study by Poomthavorn et al.[28] from Thailand specifically studied infertility in stem-cell-transplanted, thalassaemic survivors, with infertility measured by gonadal dysfunction. It was reported that 48% of men and 77% of women were infertile in a population receiving a mixture of standard and reduced intensity myeloablative conditioning with busulfan chemotherapy. The applicant combined these data[28] with UK Hospital Episode Statistics (HES) data on infertility in the TDT population treated with blood transfusions[30] to calculate the incremental impact of the myeloablative conditioning step in the beti-cel treatment on infertility. The HES data indicated that 23.9% of male patients with TDT have testicular dysfunction and 19.5% of female patients have ovarian dysfunction.[30] To account for these 'background' infertility rates in TDT patients, the difference between these rates in TDT patients and the rates of infertility following myeloablative conditioning are applied in the model (e.g. females: 77%-19.5%=57%). In the model it is assumed that myeloablative conditioning with busulfan increases infertility by 24% in men and 57% in women. The data is based on a (not very recent) study from Thailand and UK data. The applicant validated these numbers with Dutch clinicians and they agreed to use these data due to absence of local data.

No physiologic mechanism for excess iron excretion exists in the body. Thus, as iron levels generally remain elevated following beti-cel transplantation[31-32], TDT patients need to continue iron excretion therapy for some time to normalise iron levels. Because the literature gives no clear information, Dutch and Belgian KOLs were asked about their experiences with duration of iron normalisation after allogeneic HSC transplantation. Dutch KOLs stated it would take 2 years for iron normalisation after allogeneic HSC transplantation which was also confirmed by the Belgian KOLs, and the same duration of 2 years can be assumed for iron normalisation after beti-cel transplantation. During this iron normalisation period, patients who achieve TI remain at risk of complications from iron overload. At the end of the normalisation period, all TI patients are assumed to achieve a normalised iron level. From that time point onwards, TI patients are no longer at risk of developing new iron overload complications. However, these patients might have developed iron overloading complications due to their iron load status at baseline and throughout the iron normalisation period as iron overload related complications are permanent once they develop. In the model a 2-year iron normalisation period (with related costs) is applied to all patients receiving beti-cel transplant regardless of age.[13-15]
ZIN wonders if the 2-years iron normalisation period is plausible or if this should be longer. The assumption on time to iron normalization has once more been validated with the Dutch clinical experts. They indicated that in clinical practice they use phlebotomy to reduce iron overload in the vast majority of patients, as this is the best and fastest way to remove iron. Based on their experience in patients transplanted for sickle cell disease, they once more confirmed that the time needed to get to acceptable iron levels is approximately 2 years. Since the individual response to iron chelation is variable, it sometimes takes longer, and sometimes it is faster. As in the Netherlands it seems that almost all patients (95%) will be treated with the fastest way of iron chelation (phlebotomy), it makes sense that the iron normalization period will be similar to the clinical experience as described by the clinical experts (2 years to iron normalization). However, since 5% of patients will receive iron chelation therapy, the applicant also ran a scenario analysis with an normalisation period of 3.0 years for all patients.
In the model, the distribution of iron chelation therapies in the iron normalisation period after beti-cel transplant, has been updated in all analyses to 95% of patients receiving phlebotomy, 4.9% receiving oral iron chelation, and 0.1% receiving a combination of oral and SC iron chelation therapies. In the initially submitted

analysis, this distribution was 50% phlebotomy, 49% oral therapies, and 1% combination of oral and SC iron chelation therapies.

Patients with substantial TR are expected to ultimately achieve reduced levels of iron during a 2-year normalisation period. To estimate the iron levels for TR patients after a 2-year iron normalisation period, it was assumed there would be no high iron levels and that relatively more patients would have low iron levels compared to moderate iron levels, resulting in the iron levels detailed in table 4. The UK chart review data were used and the midpoints for low, moderate and high iron levels were recalculated to low and moderate levels only, leading to the assumed percentages that are in the table. The Dutch clinical experts agreed that there is no reliable source for iron reduction in TR patients and confirmed that in general, the calculated approach is as good as any other for both TI and TR after 2 years of iron removal. If the patient is not TI, reduced iron levels are to be expected (but not to normal levels). But this is still an uncertain parameter in the CEA.

Table 4 Distribution of iron loading after iron normalisation therapy

Iron Normalisation at 2 Years Post-transplant	Distribution of Iron Loading			
	Serum Ferritin	**LIC**	**Myocardial T2***	
			LIC ≥15 mg/g (High)	**LIC <15 mg/g (Moderate / Low)**
Transfusion-independent Patients				
Normalised Iron	100%	100%	100%	100%
Low Iron	0%	0%	0%	0%
Moderate Iron	0%	0%	0%	0%
High Iron	0%	0%	0%	0%
Transfusion-reduced Patients				
Normalised Iron	0%	0%	0%	0%
Low Iron	47.5%	74.5%	92.5%	92.5%
Moderate Iron	52.5%	25.5%	7.5%	7.5%
High Iron	0%	0%	0%	0%

2.4.1.2 Complications of iron overload

Iron overload may result in complications in the heart, liver, and endocrine organs (diabetes mellitus, hypogonadism). The model assumes that transfusion-dependent patients treated with the comparative treatment blood transfusions in combination with iron chelation therapy will maintain a static distribution of iron levels over time. Furthermore, even with optimal treatment, TDT remains a life-shortening disease with iron-overload related cardiac complications being the most common cause of death.[33-34] Iron overload related complications are permanent once they develop. See table 5 for the complication rates that are used in the model.

In the base case analysis, it is assumed that at baseline none of the patients has iron overloading complications (cardiac [heart failure, arrhythmias, pulmonary hypertension], liver [fibrosis, cirrhosis], endocrine [diabetes, hypogonadism]). Depending on the baseline iron load status, patients can be at risk of developing these complications from baseline (start of model) onwards moving forward in time, in the same manner as patients treated with SoC are at risk for these complications. However, a patient treated with beti-cel who achieves TI, is only at risk of developing these complications throughout the iron normalisation phase when patients still not yet have normalised iron levels in the model. Reason for this is that from the moment the iron levels in organs and blood are normalised the patient is

no longer at risk of developing these complications.
In the adjusted base case analysis, the applicant estimated that 36% of patients who received beti-cel transplant developed iron overload related complications compared to 97% of patients who were treated with SoC during their lives. The estimates of 36% of beti-cel patients and of 97% of SoC patients developing long term iron overload complications is in line with literature. In the light of the recent publications, the fact that there are no data available for the Netherlands, and because there is no reason to assume these rates will be different in the Netherlands, the Dutch clinical experts believe that these are clinically plausible assumptions.[2]

Table 5 Predicting complications of iron overload

	Annual Rate to Develop Complication		
Iron Loading	**Cardiac Complications**	**Liver Complications**	**Source:**
Low Iron	0.011	0.000	Angelucci et al.[36], 2016, Pepe et al., 2017[35]
Moderate Iron	0.019	0.000	
High Iron	0.065	0.083	
	Risk Equation for Other Complications		
Coefficient Names	**Diabetes Mellitus**	**Hypogonadism**	**Source:**
Intercept	-6.642	-2.921	Ang et al. 2014[37]
Myocardial T2	2.960	1.361	
Age	0.095	0.095	
Ferritin	2.695	1.065	
Duration of Follow-up	8 years	8 years	

Note: Liver Complications: assume all patients are Hepatitis C negative. Moderate/Low iron rate: annual rate = 0; High rate: Complication free survival is 0.5 at 100 months, annual rate = 0.0832.

To predict the cardiac complications of iron overload, the applicant uses the study by Pepe et al.[35] This study was selected by the applicant due to its recency, large sample size and extensive follow-up (57.91 ± 18.23 months), and the explicit provision of hazard ratios by myocardial T2*. The study reported that 2.2% (7/322) of patients with low iron (myocardial T2* >20 ms) had heart failure, compared to 3.9% (4/103) with moderate iron (myocardial T2* 10-20 ms) and 12.5% (7/56) with high iron (myocardial T2* <10 ms). The study also reported a mean time to heart failure onset of 24.81 months. The proportion of patients was therefore annualised, assuming a time point of 24.81 months at event, i.e. for high iron an annualised rate of 0.065 was derived [-ln(1-7/56)/(24.81/12)].

The applicant used the study by Angelucci et al.[36] reporting liver complication rates due to liver iron loading, in the model. This source provided complication rates stratified by iron levels and, presented data for patients with hepatitis C virus infection versus those without. It is expected that in the near future, liver complications will be close to those of patients without hepatitis C virus, and these rates were therefore used in the model base case (see table 5).

The risk for developing diabetes (DM) or hypogonadism (HG) is integrated in the model by means of calculations using risk equation coefficients, based on the study by Ang et al. (2014)[37], and parameter values for myocardial T2*, age and serum

ferritin. Ang et al. (2014) calculates odds ratios of occurrence of DM and (separately) HG associated with several risk factors, using multivariate logistic regression. For the risk equation used in the model, all ORs from the multivariate regressions with p < .05 (i.e., ORs associated with myocardial T2*, age, and serum ferritin) were transformed to linear coefficients by taking the natural log of the OR. Using the estimated coefficients and overall prevalence of diabetes mellitus (41%) and hypogonadism (67%), the intercepts were computed as follows.

- *Intercept for diabetes mellitus: LN(0.41) – SUM(2.960, 0.095, 2.695) = -6.642*
- *Intercept for hypogonadism: LN(0.67) – SUM(1.361, 0.095, 1.065) = -2.921*

The rates mentioned in table 5 have been validated for Dutch patients by clinical experts, who confirmed that there is no reason to assume these will be different as Dutch patients originate from the same geographic areas as those in the publications used.

2.4.1.3 Adverse events

In the pharmacotherapeutic report the following most frequent adverse events are mentioned: thrombocytopenia, anaemia, stomatitis, alopecia, nausea, vomitus and neutropenia. Of these frequent adverse events, the following were reported as grade 3 or 4 of severity: thrombocytopenia, anaemia and vomitus. No patient left the clinical study. No patient died in the studies.

Beti-cel drug related AEs of grade 3-4 severity and an observed incidence of ≥5% in both the completed trials (HGB-204, 205, 207) and ongoing beti-cel trial (HGB-212) are included in the CE analysis. According to these criteria, thrombocytopenia was the only AE related to beti-cel to be included in the model with a frequency of 2.2%. AEs specifically associated with the preparation phase for beti-cel administration are not included in this analysis as it is assumed that the cost impact of these AEs is captured by administration, hospitalisation and ongoing monitoring costs. Similarly, quality of life impact for these AEs is reflected in the utility decrement associated with transplantation.

The AE probabilities associated with iron chelation therapy are presented below in Table 6. For deferiprone and deferasirox, AE data was taken from the respective prescribing information.[38-39] For desferrioxamine, however, the prescribing information indicated that insufficient data was available to estimate rates of AEs. As such, AE data was obtained from a published systematic literature review[40] identified through a targeted literature review.

Table 6 Probability of adverse events with iron chelation therapy

	Probability		
Adverse event	**desferrioxamine Mesilate**	**deferasirox**	**deferiprone**
Arthralgia / myalgia	5%	0%	9%
Injection site reaction	17%	0%	0%
Neutropenia	0%	0%	7%
Nausea / vomiting	0%	10%	12%
Abdominal pain / discomfort	0%	19%	10%
Diarrhoea	0%	11%	0%
Alanine Aminotransferase increased	0%	0%	7%
Chromaturia	0%	0%	14%
Creatinine increased	0%	11%	0%
Rash	0%	8%	0%

Source: Fisher et al., 2013[40] (desferrioxamine mesilate); Prescribing Information[38-39] (deferasirox, deferiprone)

2.4.1.4 Mortality

In the model a distinction is made between mortality with and without cardiac disease. Even though other iron overload-related complications may impact survival also, the applicant assumed that cardiovascular complications have the largest impact (80% of the deaths in TDT is caused by cardiac disease).[9-11, 41-42]

Mortality risk over time in modelled patients without cardiac disease varies with patients' age using general population life table data. Life tables for the Netherlands were utilised in the base case.[43] Based on fit assessments using the sum of squared residuals distance measure and visual fit, the Gompertz model was selected as the most appropriate for the base case as it shows the least distance between the empirical and predicted survival curves up to the age of 50 years (when half of TDT patients are expected to have died[34]). The fit assessments have been conducted on UK lifetables (male, female; 2016-2018). The applicant assumes that the UK lifetables are very similar to Dutch lifetables and the Gompertz distribution will also provide the most appropriate fit to Dutch lifetables. As per ZINs request, the applicant conducted fit assessments based on Dutch lifetables and they provide the same result, with the Gompertz model being the most appropriate fit.

To determine the effect of beti-cel on mortality, a standardised mortality ratio (SMR) post-transplant was applied based on transfusion-dependent status. The SMR is a ratio of observed versus expected number of deaths that are utilised for a given set of confounding variables (for instance age and gender) and then standardised for the general population.[44] In table 7 the used mortality ratios are presented.
TI patients in the model are assumed to have survival similar to that of an age- and sex-matched general population informed by life tables for the Netherlands. A moderate impairment of survival (SMR = 1.25) for mortality without cardiac disease in the TI population, is included in the base case due to the potential mortality impact of myeloablative conditioning. This SMR is an assumed value without direct literature support as there is insufficient history of transplant in patients with thalassaemia to provide clinical evidence. In absence of a specific SMR for patients with TR, it was assumed that the mortality ratio without cardiac disease for these patients was the mid-point of transfusion-dependent (3.9) and transfusion-independent patients (1.25), resulting in an assumed SMR of 2.6. For mortality without cardiac disease in the TD population the SMR reported for transfusion-dependent (TD) patients without cardiac complications by Delea et al. (2007), was selected as this was consistent with another published range of parameters but was the only point estimate. Moreover, as both studies calibrate the non-cardiac mortality based on the rates of cardiac mortality, the applicant judged it is to be essential to keep the same source for cardiac mortality as the source study for non-cardiac mortality.

ZIN argues that the SMR of 3.9 in TD patients is based on very old data. The source in the model is Delea et al. (2007)[11] , and this publication is based on data reported by a US study, which estimated mortality from 257 TDT patients on desferrioxamine followed between 1965 and 1994 (Gabutti et al. 1996).
ZIN requested the applicant to add more recent data about mortality in these patients and to validate these ratios with Dutch clinical experts. The applicant consulted Dutch clinical experts about this issue and they stated that the management of iron overload in TDT patients has been substantially optimized during the past 5 decades. Deferoxamine (subcutaneous chelator) has been widely used since the 1970s, improving survival. Deferiprone (oral chelator) was introduced

in the mid 1980s. This was followed by the introduction of cardiac monitoring by MRI about 2 decades later (end of the millennium), which had a substantial impact on survival of TDT patients. The latest improvement was the once-daily oral chelator deferasirox in 2007. The clinical experts further mentioned that this means that the effects of deferasirox on mortality have not been included in the SMR calculation published by Delea et al. (2007) which resulted in a point estimate of 3.9. However, there have been no more publications on SMR in TDT since. Clinically it is plausible that once-daily iron chelation therapy will improve adherence to therapy, and results in better iron chelation, which would be expected to decrease iron loading and potentially also organ damage. So, in theory one could expect that the SMR may have declined, however the effect size is difficult to estimate.
The applicant therefore ran an additional scenario analysis to assess the impact on the ICER results using an SMR of 3.0 (and because the SMR for TR patients is calculated as the mid-point of TD and TI patients, this is adjusted to an SMR of 2.1 in this scenario).

Table 7 Mortality inputs without and with cardiac disease

Mortality without Cardiac Disease	*Standardised mortality ratio (SMR)*	*Source*
Transfusion-independent	*1.25*	*Assumption*
Transfusion-reduced	*2.6*	*Assumption*
Transfusion-dependent	*3.9*	*Delea et al., 2007*[11]
	Annual mortality rate	
Mortality with cardiac disease, regardless of TD status	*13%*	*Delea et al., 2007*[11]

In the HGB-204, -205, -207 and -212 trials, all patients had successful beti-cel engraftment. However, the model allows to run sensitivity analyses in which less than 100% of patients have successful engraftment. In case patients experience engraftment failure, the model applies a case fatality rate of 54% based on literature.[45]

Conclusions about effectiveness and long-term outcomes in the model:
-ZIN disagrees with the assumption that all TI patients remain TI for their remaining life. This is still very uncertain because the lack of long-term effectiveness data of beti-cel treatment. ZIN requests the applicant to add scenario analyses of decreasing effects in a small proportion of TI patients to explore the impact on the ICER and/or to assume in the base case analysis that a small proportion of the TI patients will decrease to the TR status in the model. The applicant explored the impact of decreasing from TR to TD status but did not analyse that for the decrease from TI to TR status. The applicant argues that due to the mechanism of action of beti-cel (utilises an *ex-vivo* approach by adding functional copies of the β-globin gene into the patient's own cells) this corrects the underlying cause of the condition and therefore the chance of secondary graft failure after successful beti-cel treatment seems negligible. The Dutch clinical experts state that the long-term effectiveness as assumed by the applicant is not 100% certain. They say that secondary graft failure of with beti-cel treated stem cells is not plausible, but cannot be excluded because of the limited experience and follow-up duration.
- Although the Dutch clinical experts agreed with the applicants assumption that of a 2-years duration of iron normalisation after beti-cel transplantation, this remains an uncertain parameter in the CE-model. The clinical experts stated that the duration of iron normalisation after beti-cel treatment depends among others on the type of iron chelation therapy. The duration will probably vary between 2 and 3 years. In

the base case analysis the 2-year duration is used (because the most of the patients are treated with phlebotomy) and in a scenario the 3-years duration is used.
- In the base case analysis the model estimated that 36% of the patients treated with beti-cel and 97% treated with standard of care, had iron overload related complications. The applicant checked the clinical plausibility of these percentages with Dutch clinicians and they agreed with these percentages. Although these are still uncertain parameters in the CEA.
- Uncertainty exists about the used SMR data in the model. These are based on assumptions because a lack of data or these are based on very old studies. Dutch clinical experts confirmed the lack of recent data, so this remains an uncertain parameter in the CEA.

2.4.2 Utilities

Given the incomplete utility dataset from the beti-cel trials and their ceiling effects, the applicant assumes that the EQ-5D data collected in the beti-cel trials may not accurately reflect the HRQoL of patients treated with beti-cel. Therefore the applicant performed a literature search for HRQoL data.[46] The studies found were not useful due to several limitations. Given the limitations regarding the beti-cel trial data and literature HRQoL data, the applicant conducted a vignette study[6] in the UK general population (see section 2.1.1.) to inform assumptions around the quality of life impact of TDT and beti-cel treatment. The UK vignette study was conducted to elicit utility values for health states related to treatment of TDT. Paediatric TDT patients could potentially be treated with allo-HSCT, all other patients are treated with SoC consisting of blood transfusions and iron chelation therapy. To be able to put the beti-cel utilities in context, the full spectrum of TDT treatment related health states were included in the vignette study, meaning also allo-HSCT treatment states like chronic GVHD.
In this study vignettes were developed to represent TDT with ongoing blood transfusions and iron chelation therapy (vignettes A1, A2), as well as the period of time for which patients undergo HSCT (autologous with beti-cel (B1) or allo-HSCT (B2, B3)). In addition, several post-transplant health states were evaluated (TI (C1), TR (C2), chronic GVHD (C3)) (see Figure 1). The vignettes were drafted based on published literature, clinician interviews, patient/caregiver interviews, and a pilot study. Utilities for these health states were then elicited in a TTO task with a 10-year time horizon for the five chronic health states (A1, A2, C1-C3) and a 1-year time horizon for the three path states (B1-B3).
A total of 207 general population (mean age: 43 years, 49.8% females) respondents completed the interviews, which were conducted in March 2018 in three locations in England. The resulting health state utilities derived from the vignette study are presented in Figure 1.

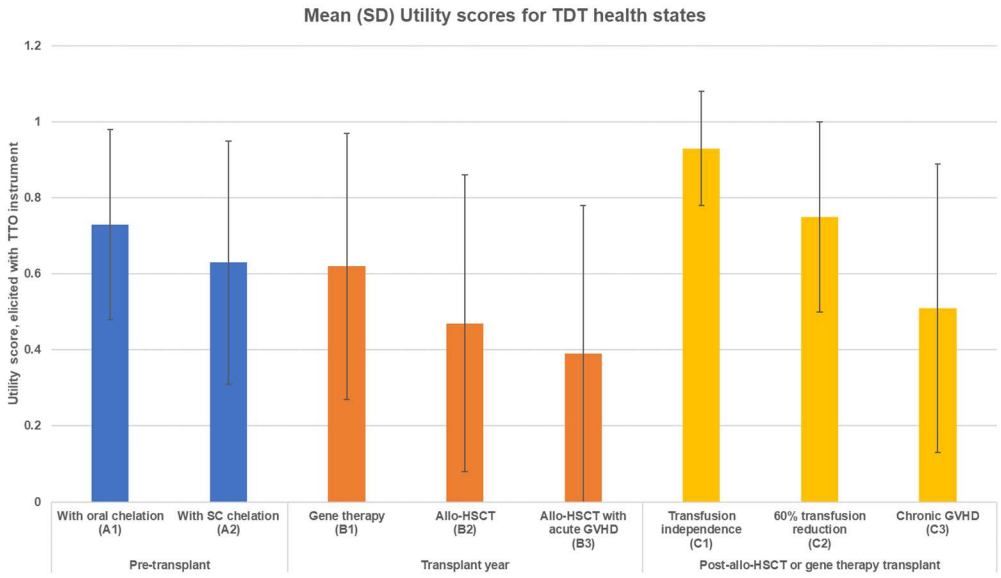

Figure 1 Utilities from Vignette study

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; GvHD, graft versus host disease; SC, subcutaneous; SD, standard deviation; TTO, time trade-off; TDT, transfusion-dependent thalassaemia

Table 8 gives an overview of all the disutilities that are used in the CE model.
The iron normalisation period following transplantation has impact on HRQoL and risk of complications for both patients who achieve TI and TR. During this period, patients who achieve TI experience a HRQoL impact associated with the mode of iron normalisation therapy provided. In addition, during the iron normalisation period patients remain at risk of complications from iron overload occurring while being on SoC before beti-cel transplant. At the end of the normalisation period, all TI patients are assumed to achieve a normalised iron level.[47]
The vignette study indicated a utility of 0.93 for TI patients (see Figure 1, C1). To calculate the disutility of TI the applicant used the UK general population norms instead of Dutch norms because the vignette study was conducted in the UK. The average age of patients in the vignette study was 43 years, who would be expected to have a utility of 0.9513 according to UK norms. So a lifelong disutility of 0.02 is applied in TI patients.

From the UK chart review study (see section 2.1.1.), the mean EQ-5D-3L utility score (valued using the Dutch value set) for adult patients (≥16 years, n=94) was 0.73 (SD=0.29). This value of 0.73 is used in the base case analysis. The UK chart review population had a median age of 24.1 years. The *disutility associated with transfusion-dependence* was calculated from the difference between the observed utility (0.73) in the UK chart review (patient median age of 24.1 years) and the mid-point of the general UK population age <30 years utility (0.939) and age 30-35 years utility (0.929). This resulted in *a disutility associated with transfusion-dependence (i.e. transfusion and iron chelation therapy)* of 0.20. Utility values from the UK vignette study related to TD status are used only in the scenario analysis (see table 8).
The utility decrement for *TR* is based on a linear assumption between TI (UK vignette study: 0.02) and TD (UK chart review: 0.20) based on the 74.75% transfusion reduction: 0.07.

Table 8 Utility decrements used in model

Transfusion status	Base case decrement	Source	Scenario analysis	Source
Beti-cel transplant related				
Pre-transplant	0	Assuming no disutility while waiting for treatment	N/A	N/A
Transplant	0.31	Vignette study (B1-C1: 0.62-0.93=-0.31)	N/A	N/A
Up to 1 year post-transplant	0.31	Vignette study (B1-C1: 0.62-0.93=-0.31)	N/A	N/A
Transfusion independent	0.02	Vignette study (0.95-0.93)	N/A	N/A
Beti-cel transplant related AEs				
Thrombocytopenia (duration 28 days)	0.108	Tolley et al. 2012[49]	N/A	N/A
Infertility (applied at age 15 to 50)	0.07	Busnelli et al., 2014; Scotland et al., 2011	N/A	N/A
Transfusion-dependent				
Transfusion reduced	0.07	Linear assumption between transfusion-independent and transfusion-dependent, utilising the 74.75% transfusion reduction	0.0755	Linear assumption between TI and TD from Vignette study
Transfusion dependent	0.20	Difference between utility from the UK Chart Review and the age-adjusted general population utility	0.22 (0.99*0.22 + (0.01*0.32)	Vignette study – weighted average of 0.22 (oral chelation) and 0.32 (sc chelation); with 99% of patients receiving oral chelation, and 1 % a combination of oral and SC
Long-term iron overload complications				
Cardiac complications	0.11	Karnon et al. 2012[9]	N/A	N/A
Liver complications	0.10	Assumed to be the same as endocrine complications	N/A	N/A
Endocrine complications (diabetes and hypogonadism)	0.10*	Karnon et al. 2012[9]	N/A	N/A

Abbreviations: AEs, adverse events; N/A, not applicable; SC, subcutaneous
**Weighted value based on the utilities of hypogonadism and diabetes*

In order to model the long-term utilities, and to account for age-related decrements in quality of life, utility values stratified by age group for the general population of the Netherlands were used. General population values for the Netherlands were age-corrected values of the EQ-5D index population norms reported in the study by Szende et al. (2014).[48]
ZIN asked the applicant why the utility values for the general population (based on Szende et al) in the model are not subdivided for the younger age categories. This is important especially because this disease concerns a younger patient population. The applicant mentioned that Szende et al. (2014) is used to inform utilities by age to account for decreasing utility due to aging. For the age category <30 years, the average (0.939) of the two age groups 18-24 years (value: 0.950) and 25-34 years (value: 0.927) is used. This means that for younger patients (12-24 years) a lower utility value is used than reported in the Szende et al. 2014 publication, and for older patients (24-29 years) a higher utility value is used. The applicant conducted scenario analyses on these assumptions. They evaluated scenarios where 100% of the treated population was of a starting given age group, so that the QALY impact of

using the age-category specific utility value for the relevant age group from the Szende et al paper could be estimated.

The applicant assumed that the quality of life impact of short-term AEs associated with beti-cel treatment would be reflected in the utility decrement associated with transplantation. Additionally, a *utility decrement is applied for thrombocytopenia* (0.108 per event, duration 28 days). The disutility for thrombocytopenia AE is derived from a UK study in chronic lymphocytic leukemia, as no Dutch or thalassemia-specific study was found in the literature.[49]
The myeloablative conditioning step required for transplantation can result in long-term AEs: *subfertility and infertility*. For these patients, a disutility associated with infertility (0.07, annual disutility) is applied in the model during their child-bearing years (15 to 50 years).[50-52]
The disutilities associated with *cardiac and endocrine complications* have been derived from published data.[9] The Karnon et al. (2012) study[9] reported a utility weight of 0.114 for cardiac complications, 0.133 for diabetes and 0.067 for hypogonadism. The utility value of endocrine complications was derived from the average of the utility values for diabetes and hypogonadism (0.10). In the absence of specific utilities for liver complications, these were assumed to be the same as endocrine complications.
The applicant assumed that, due to a lack of robust utility data, *caregivers* do not experience a decrease in their HRQoL, and hence no utility decrements were applied for caregivers.
The applicant argues that the used multiplicative combining rule in the model provides a more conservative estimate as it reduces the impact of multiple concurrent conditions relative to an additive approach. They argue that this is a conservative approach for beti-cel, because SoC consisting of blood transfusions with iron chelation therapy is associated with more concurrent conditions reducing utility.

<u>Conclusions about the utilities used in the model:</u>
Because a lack of Dutch data, only utilities from UK populations are used. ZIN was not convinced the utilities from the vignette study are representative for the Dutch TDT patient population because it is an *UK* population, they are not patients and the respondents seem rather old (mean age: 43 years) in comparison to the patient population ZIN is interested in (mean age in trials: 20.6 years and in UK chart review median age: 24.1 years). The applicant argues that in vignette studies it is standard practice to use a general public to elicit utility values for health states by means of time-trade-off (TTO). It is also standard practice to use a representative sample of the general public, so the mean age and male-female ratio should correspond with the general public rather than with the patient population. In absence of vignette study results using a representative sample of the Dutch general public, the health states descriptions from the vignette study have been validated with Dutch clinical experts. The Dutch clinical experts stated that the health states descriptions do not differ between the UK and the Netherlands[2].
Therefore the applicant thinks it is reasonable to assume similar results would have been obtained with a sample of respondents from the Dutch general public.
ZIN agrees with the used utilities because Dutch clinical experts indicated they expect the utilities to be similar between the UK and the Netherlands and no other information and data are available. The impact of variation in these utility values should be analyzed in sensitivity analyses.

2.4.3 Resource use and costs

The applicant states that all relevant cost items from a societal perspective have been included in the model. Costs sources include the Zorginstituut Nederland (ZIN) guidelines,[53] Nederlandse Zorgautoriteit website (NZA),[54] Z-index[55] and international literature. All costs have been indexed to 2020 price levels by means of the Centraal Bureau voor de Statistiek (CBS) Consumer Price Index (CPI).[56] For the year 2020, an average has been used up to September 2020.

2.4.3.1 Direct healthcare costs

Transplant-related costs

Beti-cel treatment costs include beti-cel acquisition costs and beti-cel transplant-related costs. Drug acquisition costs for beti-cel are €1,575,000 and are included as one-time costs in the model (at model entry, transplant phase). Beti-cel transplant-related costs include (table 9):

- beti-cel pre-transplant work-up costs (hypertransfusion of red blood cells, pre-treatment stage tests, mobilisation and apheresis of stem cells, patient conditioning (myeloablative chemotherapy)) and fertility cryopreservation before myeloablative conditioning therapy (pre-transplant phase)
- beti-cel administration costs (transplant procedure at hospital, transplant phase)
- beti-cel post-transplant monitoring costs (post-transplant phase) (see table 9)

The DBC code for the *pre-transplant work-up* for autologous SCT was used as a proxy for the beti-cel pre-transplant work-up costs. The Dutch KOLs indicated that patients undergo cryopreservation therapy for fertility preservation before myeloablative conditioning. For adult patients, they mentioned that only around 75% of male patients cryopreserve sperm, and even less female patients (around 40%) will undergo oocyte cryopreservation. In the base case analysis the applicant assumes all patients will undergo cryopreservation and thus incur the related cryopreservation costs. Costs are only applied for one cycle, as the report describes that within an oncological indication (as the myeloablative conditioning with busulfan chemotherapy) patients commonly need one cycle. Female patients incur costs for stimulation of egg cells, puncture, cryopreservation and storage, whereas male patients incur costs for cryopreservation and storage only. After indexing the costs to 2020 price levels, costs are €2,310.30 for female patients and €491.84 for male patients. A weighted average, based on 54.5% female patients, results in €1,482.90. In total, travel costs for five 2-way trips to a specialised hospital (€206.20) are incurred in the beti-cel pre-transplant phase. This is based on 1 visit for the cryopreservation procedure, 1 visit for the pre-transplant stage test, 2 visits for the mobilisation and apheresis procedure, and 1 visit for the patient conditioning procedure. This resulted in *total beti-cel pre-transplant costs* of €10,353 for children, and €10,773 for adults.

The cost of hospitalisation for *beti-cel administration* is €41,750 and includes the rate for beti-cel transplant administration, 37 nursing days and travel costs.

The DBC code for *post-transplant monitoring* of allo-HSCT was used as a proxy for the beti-cel post-transplant monitoring costs. These are annual costs and only applied in the first year post-transplant.

Post beti-cel transplantation, patients receive and thus incur costs for iron chelation therapy and iron chelation therapy monitoring during a 2-year period called the iron normalisation phase (table 10). Patients receive either iron chelation therapy consisting of phlebotomy (unit cost: €720, NZa 028999015) every 4 weeks or oral iron chelation therapy or a combination of oral and SC iron chelation therapy. The distribution of type or iron chelation therapy is based on Dutch KOL input.[13-14]

Table 9 Overview of beti-cel transplant-related costs

Transplant phase	Total costs	Source
Pre-transplant work-up + cryopreservation		
<18 years	€10,353	€8,664.33 (DBC-code 979003040) and €1,482.90 (the costs of cryopreservation therapy, DBC-codes 140228 – 0773404 'stimulating egg cells at outpatient clinic' and 140226 – 0773302 'Puncture at outpatient clinic'[57] and €206.20 (travel costs five 2-way trips to a specialised hospital)
≥18 years	€10,733	€9,044.20 (DBC-code 979003011, which also includes a maximum of 5 nursing days) and €1,482.90 (cryopreservation costs) and €206.20 (travel costs five 2-way trips to a specialised hospital)
Transplant administration		
<18 years	€41,750	€16,053.40 (NZA declaration code 97003003 – transplantation of own stem cells) and €25,655 (37 nursing days * €693.38[53]: based on clinical trial experience) and €41.24 (travel costs)
≥18 years	€41,750	
Post-transplant monitoring		
Monitoring costs, year 1	€8,948	€8,700.35 (DBC-code 97003008) and €247.44 (six times travel costs for a 2-way trip to a specialised hospital)
Total costs for beti-cel transplant		
<18 years	**€61,051**	
≥18 years	**€61,431**	

Note: The above presented costs include travel costs.

Table 10 Iron normalisation phase: iron chelation therapy and monitoring costs

Type of therapy	Iron chelation – oral	Iron chelation – oral + SC	Phlebotomy	Weighted average cost
Proportion of patients	49%	1%	50%	-
Age < 18 years	€20,013	€64,118	€9,360	€15,127
Age ≥ 18 years	€26,265	€99,014	€9,360	€18,540

SC: subcutaneous

Blood transfusions and iron chelation therapy costs

Standard of care consists of blood transfusions, iron chelation therapy and monitoring.

Table 11 presents a summary of the calculated total annual treatment costs of blood transfusion, iron chelation drug acquisition, iron chelation administration and iron chelation monitoring for transfusion-reduced and transfusion-dependent patients. In its dossier the applicant gives all the details regarding resource use and unit costs they used to estimate the costs as mentioned in table 11.

Table 11 Total annual blood transfusion an iron chelation therapy cost incl. monitoring costs

Type of Chelation Therapy	Subcutaneous	Oral
Transfusion-reduced patients		
Age < 18	€32,467	€18,566
Age ≥ 18	€48,380	€24,344
Transfusion-dependent patients		
Age < 18	€54,733	€30,641
Age ≥ 18	€89,678	€43,194

To obtain costs of initial and subsequent units of blood transfusion, costs for a packed red blood cell (pRBC), laboratory testing and outpatient visit were combined. An overview of associated unit costs is given in Table 12 below.
Annual blood transfusion costs for TR and TD patients were calculated per age category (age <18 years versus age ≥18 years) by multiplying the blood transfusion unit costs and the frequency of transfusions per year. For adolescent and adult patients, a mean frequency of 15 transfusions per year and an interval of 3-4 weeks between transfusions for TD patients was obtained from Dutch KOL input. For TR patients a reduction of transfusion by 74.75% is assumed based on the observed mean reduction in the HGB-204, 205,207 and 212 trials. In table 12 the calculated annual blood transfusion costs are shown.

Table 12 Unit costs for blood transfusion and chelation therapy and annual costs

Component	**Mean unit cost**	**Assumptions and source**
Total costs, 1st unit	€428.50	ZIN Costing Manual and NZA tariffs
Total costs, subsequent unit	€280.04	
Patient Age	**Calculated Annual Blood Transfusion Cost: Transfusion-dependent (€)**	**Calculated Annual Blood Transfusion Cost: Transfusion-reduced (€)**
Age < 18	€10,628	€2,684
Age ≥ 18	€16,929	€4,275
	Calculated Annual Iron chelation (DFX oral) Cost: Transfusion-dependent (€)	**Calculated Annual Iron chelation (DFX oral) Cost: Transfusion-reduced (€)**
Age < 18	€19,668	€15,297
Age ≥ 18	€26,223	€19,668

DFX, Deferasirox
Source: Dutch KOLs input.[13-14, 58-59] A mean frequency of 15 transfusions per year
Unit costs: Z-index[55] (2020)

To derive the cost of iron chelation therapy, the distribution of oral iron chelation therapy was based on Dutch KOL input (table 2). The SmPC was utilised to obtain the dose regimens of each chelator.
As can be seen from table 2, the most used iron chelation therapy (98% of the

patients) is oral *deferasirox (DFX)*. We focus on this therapy here because almost all the patients use this in the Netherlands. For DFX the dose range of the film-coated tablet is 14-21 mg/kg per day, therefore a midpoint dose of 17.5 mg/kg is assumed by the applicant for TD patients. The minimum dose (14 mg/kg) is assumed for TR patients.[13] The unit cost of DFX 90mg 30 film-coated tablets pack is €179.49, resulting in a cost of €5.98 per 90 mg tablet. Calculated annual drug acquisition are presented in table 12.
Resource use associated with the *monitoring of iron chelation therapy* was taken from the guidelines from Guy's and St. Thomas' NHS Foundation Trust,[60] which was validated with Dutch KOLs and costed with Dutch unit costs. Total annual monitoring costs (weighted average for adults and adolescents) for oral DFX are estimated at €1,139.

Beti-cel and iron chelation AE management costs
The model makes a distinction between acute AE costs (due to thrombocytopenia associated with beti-cel) and AE costs (due to iron chelation treatment).
As described in section 2.4.1.3., thrombocytopenia is the only AE related to beti-cel to be included in the model. AEs specifically associated with the preparation phase for beti-cel administration are not included in this PE evaluation as the applicant assumed that the cost impact of these AEs is captured by administration, hospitalisation and ongoing monitoring costs.
Total costs of managing thrombocytopenia are €3,156, and thrombocytopenia occurred in 2.2% of patients treated with beti-cel in the beti-cel trials. The costs are included as one-time costs in the model. It is included as one-time costs per simulated patient on beti-cel; 0.022 * €3,156 = €69.43 per simulated patient on beti-cel.The cost for managing thrombocytopenia (€3,132) was taken from Bouwmans et al. 2009,[61] a retrospective cohort study in the Netherlands. Travel costs of €23.60 were added assuming 4 times a 2-way travel to regional hospital for platelet infusions.
Costs applied to the *AEs associated with iron chelation therapy* are listed by the applicant and concern: injection site reaction, nausea/vomiting and rash (a general practitioner (GP) phone triage is assumed), arthralgia/myalgia, neutropenia, abdominal pain/discomfort, increased alanine aminotransferase, diarrhoea and increased creatinine (a consultation with a GP is assumed), chromaturia (no medical care was required). Management costs for AE due to iron chelation therapy are included as costs per AE as for all AEs it is assumed these could be managed with only a GP phone triage or consultation, and no short or long-term use of medication. So, if a patient experiences an AE like abdominal pain, one-time costs for managing this AE are applied. However, patients are at annual risk of developing these AEs, hence a patient can experience a specific AE like abdominal pain more than once during their lifetime. The GP unit costs are based on the ZIN costing manual.

Long-term iron overload complication management costs
The cost of managing iron overload complications was informed from published international literature and Dutch reference costs. Cardiac and other complications including diabetes and hypogonadism were taken from a lifetime cost-utility analysis[9] of DFX in beta-thalassaemia patients with chronic iron overload. Cost related to managing cardiac complications in the first year is €7,812 and €4,023 in the following years. The NZA declaration code 110801002 - hospitalisation with a maximum of 5 nursing days in case of a disease of the liver was used to quantify the annual cost of care for liver complications. The cost of care managing liver complications is €2,705. For complications including diabetes and hypogonadism the cost of care is €3,362 (Karnon et al. 2012).[9] No travel costs are included in these complication costs, because it is unclear how many outpatient and inpatient visits are needed per complication.

Indirect medical costs due to life years gained, using PAID tool
In a scenario analysis, estimates for indirect medical costs due to life years gained (costs for health care expenditures unrelated to transfusion-dependent thalassaemia) were based on the PAID tool.[21,23] For the total indirect medical costs' estimate, all diseases were included with the exception of 'Diseases of blood and blood-forming organs'. Annual estimates, both for the last year of life and other years of life, were inflated to 2020.

2.4.3.2 Direct non-medical costs: patient and family costs

Travel costs
Travel and parking costs have been considered by accounting for a two-way trip to the hospital. The travel costs for a two-way trip to the hospital (€0.19 per km based on the ZiN guidelines) are multiplied by the average distance to the hospital (two times 7.0 km for a return trip) when it concerned a visit to a regional hospital.[53] For all visits related to the transplant procedure taking place in a specialised centre, the average distance was assumed to be 100km. Parking costs, included once for every visit, were €3.24 (indexed to 2020). As a result, a two-way trip amounts to €5.90 for a regional hospital and €41.24 for a specialised centre. Travel costs are incurred for each hospital visit in every step of the beti-cel transplant phase (100 km each), blood transfusions (7 km each) and blood transfusion and iron chelation therapy monitoring (7 km each).

Caregiver burden
Caregiver costs are included to reflect the time (and costs) spent by caregiver to care for TDT patients.
The applicant consulted the Dutch clinical experts about this and they said that the general process in the period after transplant, based on transplantations for malignant indications such as relapsed lymphoma or multiple myeloma, is the following: when patients who receive beti-cel transplant are discharged from the hospital, they will go home for recovery. At home they will need day-to-day care during the first 4 weeks (adolescents) or 8 weeks (adults) and thereafter homecare for another 3 months. After this period, patients will no longer require homecare, however, they will stay at home for about 1-2 months. In addition, adolescent patients require a caregiver to bring them to the hospital and support them during the monitoring visits which also includes phlebotomy during the entire iron normalization period.

Adolescents:
Day-to-day care: 4 weeks times 4 hours per day = 4*7*4 = 112 hours
Homecare: 3 months times 2 hours per week = (52/4)*2 = 26 hours
Monitoring and phlebotomy care during iron normalization period:
For all adolescent patients, Dutch clinical experts state that it takes about 4 hours for a caregiver to bring the adolescent patient to the hospital and to support them during the monitoring and phlebotomy procedures. Monitoring visits including phlebotomy are scheduled every 4 weeks during the iron normalization period. During the iron normalization period, 95% of patients are on phlebotomy and 5% are on oral chelation/oral+SC. Phlebotomy takes only about 15 minutes and is scheduled alongside monitoring which takes around 4 hours. To simplify calculations, the 4 hours can be applied to patients on phlebotomy (95%) and to patients on oral chelation (without or with SC) (5%) which only need monitoring hours. Every 4 weeks times 4 hours for 2 years = (104 weeks (=2 years) / 4 weeks)*4 hours = 104 hours. Total: 112 + 26 + 104 = 242 hours. Applying the informal care hour rate of €15.12 results in ***€3,659.04*** *for adolescent TI patients.*

TR patients receive SoC but less units of blood per blood transfusion (but the same frequency of blood transfusions as for TD patients on SoC). Informal care for SoC, and thus also TR patients, was estimated by Dutch clinical expert in treating adolescent TDT patients to be 561.25 hours per year. *Adolescent TR (and SoC) patients* receive this informal care for a period of 3 years, as their baseline age is 15 years, and they receive this care until the age of 18 years. A period of 3 years, with 561.25 hours per year and an informal care cost rate per hour of €15.12 gives a total of discounted costs of **€24,492.20.**
Compared to SoC patients, TR patients differ in that they underwent beti-cel transplant, and hence face a recovery period. During this recovery period they need 112 hours of day-to-day care and 26 hours of homecare similar to TI patients, which results in a total additional of 112 + 26 = 138 hours of informal care.
138 hours times €15.12 (hour rate) = €2,086.56. *Adolescent TR patients* incur a total of informal care costs of = €24,492.20 + €2,086.56 = **€26,578.76**

For *adolescent SoC patients* the model applies 561.25 hours per year*[24], with annual costs of €8,486 euro for a maximum of 3 years, as their baseline age is 15 years, and they receive this care until the age of 18 years. Adolescent SoC patients incur a total of informal care costs of = **€24,492.20**

Adults:
Day-to-day care: 8 weeks times 4 hours per day = 8*7*4 = 224 hours
Homecare: 3 months times 2 hours per week = (52/4)*2 = 26 hours
Dutch clinicians stated adult patients do receive monitoring and phlebotomies during the iron normalization period, however, they do not need a caregiver to bring them to the hospital and support them during the monitoring and phlebotomy procedures.
Total: 224 + 26 = 250 hours. Applying the informal care hour rate of €15.12 results in **€3,780.00** *for adult TI patients and TR patients.*

Scenario analysis > 3 years iron normalization period
In this scenario analysis, informal care costs will only go up for adolescent TI patients, as it will take 1 additional year for monitoring and phlebotomies.
Every 4 weeks times 4 hours results for an additional year results in an additional 52 hours. Applying the informal care hour rate of €15.12 results in **€786.24 euros** for 1 additional year of iron normalization for adolescent TI patients.

2.4.3.3 Indirect non-medical costs: productivity loss

Patients aged 12 year and older are included in the model. In the Netherlands, employment rates are assessed from the age of 16.[62] Table 13 gives an overview of inputs used to calculate productivity losses. The number of hours worked per week and costs per hour are based on numbers available for the general Dutch population. It is assumed that patients who were treated with beti-cel or SoC are equally productive and as productive as the general Dutch population. Productivity loss is based only on life expectancy, meaning the productivity of patients who die before retirement age is lost. Productivity loss of patients who are alive but may have reduced capacity to work is not included. The productivity losses were calculated using the friction cost method, so costs are only applied during a friction period of 12 weeks for those patients who die before retirement age. This means costs are only calculated for a maximum of 12 weeks.

Table 13 Productivity losses inputs

Input	**Value (2020)**
Friction period*	12 weeks (ZIN cost manual)[53]
Start of working age	16 years
Retirement age	67 years[63]
Productivity costs per hour[188]	
Men	€40.93
Women	€34.13
Weighted average	€37.23
Hours worked per week[198]	
Men	42
Women	30
Weighted average	35
Weeks worked per year	48**
Annual value of productivity (weighted average)	**€63,359**

**The friction period is determined as follows: Friction period = 365/(total amount of filled vacancies per year/total amount of open vacancies a year) + 4 weeks (28 days).[53]*
***Minimum of 4 holiday weeks applied.[64]*

Conclusions about resource use and costs:
ZIN agrees with the resource use and costs as used in the CE-model.

2.4.4 Applicants modelassumptions

Table 14 provides a list of assumptions that apply to the model.

Table 14 Model assumptions by the applicant

Variable	***Assumed value***	***Justification by the applicant***
Baseline characteristics of patients	Age, gender and bodyweight of the patient population is based on patients enrolled in the clinical trials (HGB-204, 205, 207 and 212) that were evaluable for TI.	Average body weight data from a UK chart review study (adolescent: 40 kg; adult: 64 kg), has been validated as an alternative source by Dutch KOLs and was assumed by Dutch KOLs to better represent the body weight of Dutch adult patients. In the model, average body weight is used to calculate iron chelation dosing and related iron chelation drug acquisition costs. Lower bodyweight corresponds to lower doses, and hence lower iron chelation drug costs.
Baseline iron distribution	Based on the UK chart review	In the absence of published literature and readily-available datasets for the Netherlands, data of the medical chart review conducted by the applicant was used.
Iron overload-related complications at baseline	Assumed to be nil in all patients.	A review of medical history data indicated none of the patients had liver complications or diabetes, but two had some element of cardiac complications and two had hypogonadism. However, the severity of the complications were not sufficient enough to prevent the patient being enrolled in the study, so it was assumed that all patients had zero iron overload complications at model baseline.
Time to iron	2 years	Experience by Dutch KOL with allogeneic

normalisation in patients that become TI		HSCT indicates that a period of up to 2 years is required for iron normalisation following successful transplantation. Dutch KOL state iron overload is only seen in adult patients.
Iron levels in transfusion-reduced patients	No patients with high or normalised iron, and more patients with low iron compared to transfusion-reduced patients	Patients with substantial transfusion-reduction are expected to ultimately achieve reduced levels of iron. It is expected that the inflection point for what is considered 'substantial' is when transfusion frequency is 60% reduced, on the basis that the patients' ongoing chelation regimen can in essence 'catch up' on the existing iron stores and start reducing iron versus, for some patients, just maintaining iron at an existing level (e.g. given varying levels of patient adherence to chelator regimens).
Adverse events of beti-cel	One-off costs for adverse events were applied for adverse events directly related to beti-cel itself.	The overall adverse event profile for subjects participating in beti-cel trials reflects the consequences of underlying TDT, anticipated effects of the study procedures involved in preparation for beti-cel administration, such as mobilisation with G-CSF and/or plerixafor, apheresis and conditioning with busulfan and beti-cel administration itself. Adverse events related to beti-cel administration directly are taken into account in the model.
Transfusion-free mortality	SMR 1.25	An assumed moderate impairment of survival is included to capture the potential mortality impact of myeloablative conditioning. This is likely to be a conservative assumption as it applies for the patients' entire lifetime. The likelihood of this assumption being conservative is further highlighted when considering that the assumed value is consistent with SMR values reported for patients with Type 2 diabetes[65].
Infertility disutility	Applied between the ages of 15 and 50 to both men and women, and not affected by fertility treatment	Whilst a 10-year duration has been applied in another evaluation[51], this 10 year duration was considered to not reflect the child-bearing age of women. Therefore, a disutility of 0.07 was applied over the ages of 15 to 50, to reflect the childbearing age used by Statistics Netherlands.[52] To be conservative, the model does not consider a change in utility if infertile patients receive effective treatment for infertility, and does not consider costs of infertility treatment.
Caregiver disutility	Assumed no utility decrement for caregivers.	Conservative assumption.
Productivity loss	TDT patients on SoC and	In absence of Dutch data, it was assumed

	patients treated with beti-cel are assumed equally productive and as productive as the general population.	equal to the general Dutch population.
Standard error	If no standard error is available for the point estimate, the standard error is assumed to be 10% of the mean	This allows deterministic and probabilistic sensitivity analyses.

2.5 Validation

To ensure that the model was scientifically and clinically valid, the following steps were taken by the applicant:

- Throughout the model development process, the applicant has been seeking input from health economic advisors and KOLs regarding the model structure and assumptions through advisory boards.[66]
- The final draft of the economic model was validated by an external agency (FIECON).
- A questionnaire was sent out to two Dutch KOLs and two Belgian KOLs to validate clinical, resource use and cost inputs, model assumptions and discuss the anticipated positioning of beti-cel in TDT. This was further discussed in separate teleconferences.
- During the consultation process of the concept reports, Dutch clinical experts were approached again by both the applicant and ZIN. This was done to validate some UK data for the Dutch situation.

2.6 Sensitivity and scenario analyses

Table 15 presents the economic model parameter values, range/confidence intervals and probability distributions applied in probabilistic analyses and deterministic sensitivity analyses, and sources.

Table 15 Summary of parameters applied in the economic model

Parameter	Mean (base case)	Lower	Upper	PSA	Source
Patient age distribution					
12-17 years	10%	100%	0%	Not included	HGB-204, -205, -207, -212
18-23 years	61.3%	0%	0%		
24-29 years	8.2%	0%	Older adult: 30-39 years: 100%		
30-34 years	20.5%	0%	100%		
35-39 years	0%	0%	0%		
40-44 years	0%	0%	0%		
45-50 years	0%	0%	0%		
Adolescent	15 years	12 years	17 years	Not included	Calculated
Young adult	21 years	18 years	23 years		
Older adult	29.5 years	24 years	34 years		
Patient characteristics					
Sex (%	54.5%	0%	100%	Beta,	HGB-204, -

female)				assume SE 20% mean	205, -207, -212
Weight*, adolescent	44.9 kg	40 kg	49 kg	Normal, assume SE 20% mean	HGB-204, -205, -207, -212
Weight*, adult	56.9 kg	51.2 kg	62.6 kg		
Time to assess iron levels post-transplant (duration iron normalisation period)					
TI patients	2.0 years	1.0 years	3.0 years	Normal, assume SE 20% mean	Dutch and Belgian KOLs
TR patients	2.0 years	1.0 years	3.0 years		
Efficacy and mortality inputs					
Engraftment success: beti-cel	100%	93%‡	100%	Not included	HGB-204, -205, -207, -212; ‡: *allo-HSCT*[67]
Engraftment failure case-fatality rate	54%	0%	100%	Beta, assume SE 20% mean	Sabloff et al. 2011
Transplant success: beti-cel	84.4%	78%	90%	Beta, assume SE 20% of (1-mean)	HGB-204, -205, -207, -212
If transplant failure, % reduced transfusions, by genotype*	100%	0%	100%	Not included	Assumption
Relapse after beti-cel transplant – TI patients	0%	Not included		Not included	HGB-204, -205, -207, -212
Relapse after beti-cel transplant – TR patients to TD patients	0%	Scenario: relapse at 5 years, 10 years, 15 years		Not included	HGB-204, -205, -207, -212
TDT excess mortality at baseline	3.9	1.1	3.91	Lognormal	Delea et al. 2007
TDT excess mortality post-transplant, by transfusion status*					
TI patients	1.25	1	1.5	Lognormal, assume SE 20% of (mean-1)	Assumption
TR patients	2.60	1.1	3.91		Assumption
TD patients	3.90	1.1	3.91		Delea et al. 2007
Cardiac mortality rate	13%	0%	20%	Lognormal, assume SE 20% mean	Kremastinos et al. 2001 (source used in Delea et al. 2007)
Infertility risk from myeloablative conditioning					
Beti-cel, males	24%	15%	34%	Beta, assume SE	Jobanputra et al. 2020
Beti-cel,	57%	34%	78%		

females				20% of mean	
SoC, males	0%	0%	0%		Assumption
SoC, females	0%	0%	0%		
Childbearing years	15-50 years	Not included		Not included	CBS
Acute AE beti-cel, thrombocytopenia	2.2%	Not included		Not included	SmPC beti-cel (Zynteglo)
Patients with normalised iron load at risk of complications	0%	Not included		Beta, assume SE 20% of mean	Assumption
Cardiac complication rates, by iron overload*					
Normalised	0.0000	0.0000	0.0000	Lognormal, assume SE 20% of mean	Angelucci et al. 2002
Low	0.0112	0.0022	0.0113		
Medium	0.0190	0.0038	0.0191		
High	0.0646	0.0129	0.0662		
Liver complication rates, by iron overload*					
Normalised	0.0000	0.0000	0.0000	Lognormal, assume SE 20% of mean	Angelucci et al. 2002
Low	0.0000	0.0000	0.0000		
Medium	0.0000	0.0000	0.0000		
High	0.0832	0.0805	0.0859		
DM risk equation intercept	-6.6416	-5.9775	-7.3058	Not included	Ang et al. 2014
HG risk equation intercept	-2.9215	-2.6293	-3.2136	Not included	Ang et al. 2014
Distribution of iron chelation therapy					
Oral: deferasirox (DFX)	98%	Not included		Not included	Dutch KOLs
Oral: deferiprone (DFP)	1%				
Oral + SC: DFP + desferrioxamine (DFO)	1%				
Annual risk of AEs with iron chelation therapy (DFO / DFX / DFP)					
Arthralgia / myalgia	5% / 0% / 9%	Varied as part of AE costs per transfusion		Assume SE 20% of mean	DFO: Fisher et al. 2013 DFX / DFP: SmPCs
Injection site reaction	17% / 0% / 0%				
Neutropenia	0% / 0% / 7%				
Nausea / vomiting	0% / 10% / 12%				
Abdominal pain / discomfort	0% / 19% / 10%				
Diarrhea	0% / 11% / 0%				

Alanine aminotransferase increased	0% / 0% / 7%			
Chromaturia	0% / 0% / 14%			
Creatinine increased	0% / 11% / 0%			
Rash	0% / 8% / 0%			
Annual cost of monitoring iron chelation therapy, DFO / DFX	1,139	737-1,627 770 – 1,699	Gamma, assume SE 20% of mean	NZa
Annual cost of monitoring iron chelation therapy, DFP	1,189			
Cost of managing AEs of iron chelation therapy				
Arthralgia / myalgia	35.64	23.06 – 50.91 11.88 – 26.23	Gamma, assume SE 20% of mean	NZa
Injection site reaction	18.36	23.06 – 50.91		
Neutropenia	35.64	11.88 – 26.23		
Nausea / vomiting	18.36	23.06 – 50.91		
Abdominal pain / discomfort	35.64	23.06 – 50.91		
Alanine aminotransferase increased	35.64	23.06 – 50.91 23.06 – 50.91		
Chromaturia	0			
Diarrhea	35.64	11.88 – 26.23		
Creatinine increased	35.64			
Rash	18.36			
Iron load complication costs				
Cardiac, Year 1	7,812	5,055 – 11,158 2,603 – 5747	Gamma, assume SE 20% of mean	Karnon et al. 2012
Cardiac, Year 2+	4,023	1,751 – 3,864		DBC
Liver, Year 1, Year 2+	2,705	2,176 – 4,802		DBC
Endocrine (diabetes and hypogonadism), Year 1, Year 2+	3,362			Karnon et al. 2012
Annual productivity loss	63,359	Not included	Gamma, assume SE 20% of mean	ZIN Cost manual
Annual caregiver costs, TD and	8,486	5,492 – 12,121	Gamma, assume SE 20% of	CBS

TR, Age <18 years				mean	
Utility inputs					
Utilities by age*	<34 years: 0.9385 to 85+ years: 0.8300	<34 years: 0.877 to 85+ years: 0.7685	<34 years: 1 to 85* years: 0.8915	Gamma, assume SE 20% of mean	Szende et al. 2014
Disutility by transfusion status*, TI	-0.0200	-0.0129	-0.0286	Gamma, assume SE 20% of mean	UK Vignette study
Disutility by transfusion status*, TR	-0.0714	-0.0462	-0.1020		Linear assumption
Disutility by transfusion status*, TD	-0.2036	-0.1317	-0.2908		UK chart review, Dutch value set
Disutility of infertility	-0.0700	-0.0453	-0.0999	Gamma, assume SE 20% of mean	Busnelli et al., 2014; Scotland et al., 2011
Disutility of cardiac complications	-0.1100	-0.0712	-0.1571	Gamma, assume SE 20% of mean	Karnon et al. 2012
Disutility of liver complications	-0.1000	-0.0647	-0.1428		Karnon et al. 2012
Disutility of other iron complications	-0.1000	-0.0647	-0.1428		Karnon et al. 2012
Disutility of acute transplant AE: thrombocytopenia (duration: 28 days)	-0.0007	-0.0005	-0.0011	Gamma, assume SE 20% of mean	Tolley et al. 2012

2.6.1 Univariate sensitivity analyses

For the sensitivity analyses, each parameter was assigned a certain distribution, with the mean of the distribution typically equal to the point estimate. The standard error (SE) of the distributions was set according to any distributional information provided in the original source, or if no distributional information is available, the SE was assumed to be 20% of the mean estimate.

For costs and resource use estimates, a gamma distribution was fitted to prevent values less than zero. Treatment costs remained fixed.
The analysis involved varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. Each parameter was allocated a 'low' value and a 'high' value, where the low value is the lower bound of the 95% confidence interval (CI) and the high value is the upper bound of the 95% CI. By varying the value of each parameter one at a time, the sensitivity of the model results to that parameter can be estimated.

2.6.2 Probabilistic sensitivity analyses (PSA)

The PSA involves drawing values for each model parameter from its individual uncertainty distribution, performed for each parameter simultaneously. This constitutes one 'simulation'. In total, 1,000 simulations were performed, which gave a distribution of incremental results, and consequently, an idea of the overall uncertainty surrounding the cost-effectiveness results.

ZIN notices that some essential parameters were not included in the PSA:

- engraftment success beti-cel (base-case 100%, DSA 93% (allo-HSCT)-100%);
- if transplant failure, % reduced transfusions, by genotype (base-case 100%, DSA 0%-100%);
- relapse after beti-cel transplant – TI patients (base-case 0%, no DSA);
- relapse after beti-cel transplant – TR patients to TD patients (base-case 0%, scenario's 5, 10, 15 years).

By excluding these important parameters the uncertainty in the model may be inadequately captured. These parameters all concern the lifelong effectiveness of beti-cel as assumed by the applicant.

2.6.3 Scenarioanalyses

Scenario analyses provide insight into model parameters and their relationship with key model outcomes. They also test the rigor and strength of model assumptions. Table 16 presents the scenarios that were analysed.

Table 16 Scenario analyses

Parameter	Base case	Scenario description
Value based (VB) payment	No VB model for risk sharing	Periodic payments if transfusion free*
Outcomes-based rebate	No VB model for risk sharing	80% Rebate if not transfusion free at T=25 months (with T=0 at beti-cel infusion)
Discounting	4.0% costs 1.5% effects	The discount rates associated with costs and outcomes are varied between 0 and 1.5%
Demographic characteristics (age, gender distributions)	Derived from clinical studies HGB-204, 205, 207 and 212 Age distribution: 12-17: 10% 18-23: 61.3% 24-29: 8.2% 30-34: 20.5% 35-39: 0% 40-44: 0% 45-50: 0% 54.5% female	Based on HES data Age distribution: 12-17: 28.0% 18-23: 12.0% 24-29: 14.0% 30-34: 17.0% 35-39: 12.0% 40-44: 12.0% 45-50: 5.0% 47.0% female
Age	Patients ≥12 to 50 years	-Only patients aged 12 to 17 years treated with beti-cel -Only patients aged 18 to 34 treated with beti-cel
Body weight	Derived from clinical studies HGB-204, 205, 207 and 212 Adolescents: 44.9 kg	Derived from UK chart review Adolescents: 40.0 kg

	Adults: 56.9 kg	Adults: 64.0 kg
Extinction of treatment in TR patients	TR patients remain TR for the rest of their lives	Three scenarios: -All TR patients relapse to TD at 5 years after beti-cel transplant -All TR patients relapse to TD at 10 years after beti-cel transplant -All TR patients relapse to TD at 30 years after beti-cel transplant
Mortality Transfusion-independent	SMR 1.25	Remove assumed impairment of survival due to myeloablative conditioning: set SMR 1.00
Mortality Transfusion reduced	SMR 2.6	Remove survival impairment: set SMR to 1.00
Mortality Transfusion-dependent	SMR 3.9	Remove survival impairment: set SMR to 1.00
Utility values	Based on vignette study -Decrement TI: 0.02 Based on UK chart review -Decrement TD: 0.20 -Decrement TR: 0.07	Based on vignette study: -Decrement TD: 0.22 -Decrement TR: 0.08
Indirect medical costs PAID	No indirect medical costs due to LYs gained.	Indirect medical costs due to LYs gained calculated using the PAID tool taken into account.
Belgian inputs	Dutch resource use, costs and lifetables	Belgian resource use, costs and lifetables
Belgian inputs + VBP	N/A	Belgian resource use, costs and lifetables; apply VBP with 80% rebate if not TI at T=25 months (with T=0 at beti-cel transplantation)

**Please find a detailed description of VB payment and outcomes-based payment models in the budgetimpact analysis report.*

3 Results pharmaco-economic evaluation

3.1 Burden of disease

The burden of disease (BoD) is calculated based on the lost life years and quality of life caused by the disease under evaluation. To estimate the BoD, the iMTA Disease Burden Calculator was used by the applicant.[68] The tool can be used to calculate the 'proportional shortfall' of a condition. The tool is populated with life expectancy data for the general healthy Dutch population taken from CBS for the year 2013.[43] Besides that, Dutch-specific EQ-5D-3L utility data is based on Hejink *et al.* (2011).[69]

Table 17: BoD calculation transfusion-dependent B-thalassaemia (TDT).	
QALE of patients with TDT who do not have a β^0/β^0 genotype who receive SoC (blood transfusions in combination with iron chelation therapy).	24.71
QALE of the general Dutch population with the same age and gender distribution as the patients with TDT who do not have a β^0/β^0 genotype as included in the beti-cel trials.	52.52
Absolute QALY loss (fair innings)	27.81
Proportional shortfall	**0.53**

The BoD estimates for the population of patients with non-β^0/β^0 TDT justify a reference value (threshold) of €50,000 per QALY gained. When investigating the uncertainty around the BoD by use of the SE of the discounted QALYs based on the PSA, the iMTA Disease Burden Calculator provided a 100% likelihood that the applicable maximum WTP threshold is €50,000 per QALY gained.

The applicant refers to a recent article (Nur E., Buddingh E.P., Smiers F.J., 2016)[70] published in the Dutch Journal for Haematology, Dutch haematologists specialised in treating TDT patients and the applicant emphasizes that TDT is one of the most devastating hereditary haemoglobinopathies, accounting for high morbidity and mortality in the affected population due to lifelong iron overloading even with optimal SoC. The applicant therefore believes that the above calculation underestimates the actual BoD for TDT patients. ZIN disagrees with the applicants statement that the BoD estimation of 0.53 is an underestimation because the SMR of 3.9 in the SoC patients is based on very old data. Because of improvements in the SoC in the last decades it can be expected that a lower SMR should be assumed and thus a longer life expectancy for patients with SoC. In that case the BoD will be even lower than 0.53. So ZIN thinks the BoD estimate of 0.53 for TDT patients is reasonable.

3.2 Incremental and total effects

Table 18 presents the results in discounted and undiscounted life-years gained and QALYs gained of treatment with beti-cel versus standard of care as estimated by the applicant. Taking into account a discount rate of 1.5% for effects, the total discounted life years is estimated at 36.3 years for beti-cel compared to 27.8 years for SoC. This results in an incremental LY gain of 8.5 years and a discounted incremental gain of 11.8 QALYs due to treatment with beti-cel.

Table 18 Discounted 1.5% and undiscounted incremental and total effects

	Discount rate 1.5%		
	Beti-cel	**SoC**	**Incremental**
Life-years	36.3	27.8	8.5

QALYs	30.3	18.6	11.7
	Undiscounted		
	Beti-cel	**SoC**	**Incremental**
Life-years	54.1	37.5	16.6
QALYs	45.1	24.7	20.4

QALYs: quality-adjusted life years; SoC: Standard of care

3.3 Incremental and total costs

	Discount rate 4%		
	Beti-cel	**SoC**	**Incremental**
Transplant cost			
Pre-transplant	€ 10,700	€ 0	€ 10,700
Hospitalisation cost	€ 41,750	€ 0	€ 1,620,750
Beti-cel up-front cost (drug acquisition)	€ 1,579,000	€ 0	
Transplant-Related event cost			
Acute AEs	€ 69	€ 0	€ 69
Post-transplant monitoring	€ 8,025	€ 0	€ 8,025
Iron chelation during iron normalisation period cost	€ 14,880	€ 0	€ 14,880
Transfusion-Dependent cost	€ 78,110	€ 820,352	- € 742,242
Oral chelation therapy	€ 77,879	€ 800,536	
SC chelation therapy	€ 0	€ 0	
Oral + SC chelation therapy	€ 231	€ 19,816	
Transfusion-Dependent AE cost	€ 54	€ 339	- € 285
Iron overloading Complication cost			
Cardiac: Year 1	€ 188	€ 730	- € 542
Cardiac: Years 2+	€ 1,094	€ 4,135	- € 3,041
Liver: all years	€ 1,130	€ 4,960	- € 3,830
Other*: all years	€ 18,213	€ 40,082	- € 21,869
Indirect cost			
Indirect cost of treatment**	€ 0	€ 0	€ 0
Indirect cost of caregiving	€ 341	€ 2,164	- € 1,822
Value of productivity loss	€ 1,202	€ 3,385	- € 2,183
Total direct cost	**€ 1,752,770**	**€ 870,594**	**€ 882,176**
Total indirect cost	**€ 1,543**	**€ 5,548**	**- € 4,005**
Total cost	**€ 1,754,313**	**€ 876,142**	**€ 878,171**

Table 19 presents the per patient discounted costs by cost category for beti-cel and SoC as estimated by the applicant. This table shows that beti-cel results in overall lifetime costs of €1,754,313 compared to overall lifetime costs of €876,142 for SoC. Beti-cel is associated with an incremental cost of €878,171 compared to SoC.

Table 19 Discounted 4% incremental and total costs

	Discount rate 4%		
	Beti-cel	**SoC**	**Incremental**
Transplant cost			
Pre-transplant	€ 10,700	€ 0	€ 10,700
Hospitalisation cost	€ 41,750	€ 0	€ 1,620,750
Beti-cel up-front cost (drug acquisition)	€ 1,579,000	€ 0	

Transplant-Related event cost			
Acute AEs	€ 69	€ 0	€ 69
Post-transplant monitoring	€ 8,025	€ 0	€ 8,025
Iron chelation during iron normalisation period cost	€ 14,880	€ 0	€ 14,880
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Iron overloading Complication cost			
Cardiac: Year 1	€ 188	€ 730	- € 542
Cardiac: Years 2+	€ 1,094	€ 4,135	- € 3,041
Liver: all years	€ 1,130	€ 4,960	- € 3,830
Other*: all years	€ 18,213	€ 40,082	- € 21,869
Indirect cost			
Indirect cost of treatment**	€ 0	€ 0	€ 0
Indirect cost of caregiving	€ 341	€ 2,164	- € 1,822
Value of productivity loss	€ 1,202	€ 3,385	- € 2,183
Total direct cost	**€ 1,752,770**	**€ 870,594**	**€ 882,176**
Total indirect cost	**€ 1,543**	**€ 5,548**	**- € 4,005**
Total cost	**€ 1,754,313**	**€ 876,142**	**€ 878,171**

AE: adverse event; SC: sub-cutaneous; SoC: standard of care
**Other iron overloading complications include diabetes and hypogonadism.*
***Travel costs have been included, but were added to treatment events (e.g. pre-transplant beti-cel work-up visit at the hospital), and hence treatment costs presented in this table include travel costs as well.*

3.4 Incremental costeffectiveness ratios

The applicant concludes that treatment with beti-cel results in additional discounted costs of €878,171 compared to SoC and that it generates additional LYs and QALYs (discounted) of 8.5 and 11.8 respectively. This results in an ICER of €103,266 per LY gained and €75,871 per QALY gained compared to SoC over a lifetime time horizon (as presented in Table 20).

Table 20 Discounted and undiscounted outcomes

	ICER
Discounted	
Incremental cost per LY gained (discounted)	€ 103,247
Incremental cost per patient QALY gained (discounted)	€ 75,871
Undiscounted	
Incremental cost per LY gained (undiscounted)	€ 7,097
Incremental cost per patient QALY gained (undiscounted)	€ 5,864

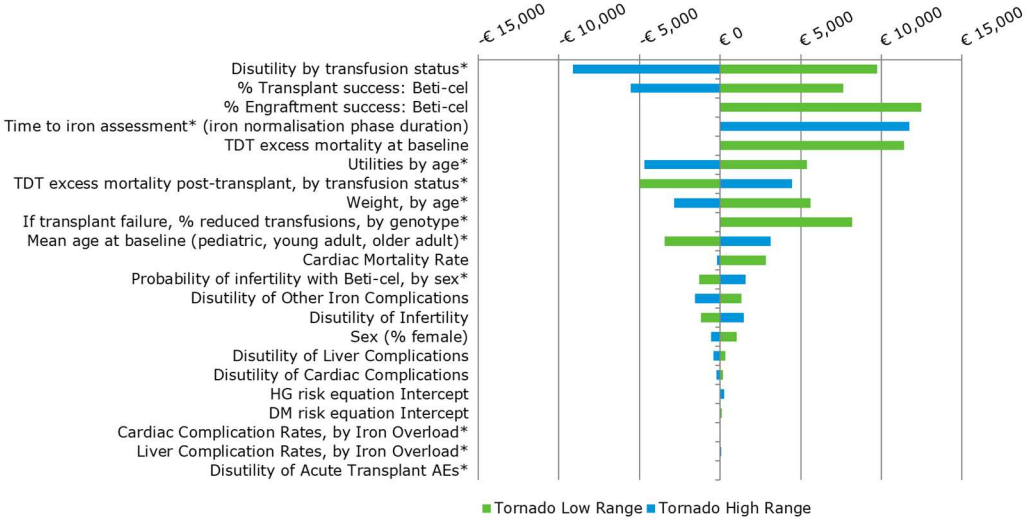
ICER: incremental cost-effectiveness ratio; LY: life-years; QALYs: quality-adjusted life years

3.5 Sensitivity analyses

3.5.1 Univariate sensitivity analyses

Figure 3 presents the parameters that have been varied in the DSA by the applicant and which have an impact on the ICER results for beti-cel compared to SoC. The

base case value, lower value and higher value of these parameters and impact on incremental costs, incremental QALYs and ICER are presented in Table 1 in the appendix.



Figuur 3: ***Tornado diagram ICER-QALY change to base case (beti-cel versus SoC) as reported by the applicant***

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; SoC, standard of care; TDT, transfusion-dependent thalassemia

**Multiple related parameters varied in one scenario*

As can be seen from figure 3 the ICER results substantially change when the following input parameters are varied to lower or upper DSA values: disutility by transfusion status, % transplant success of beti-cel, % engraftment success of beti-cel, iron normalisation phase duration, TDT excess mortality at baseline and post-transplant, utilities by age and % reduced transfusions if transplant failure. These parameters have the most impact on the ICER, and as can be seen in table 1 in the appendix, changing these parameters can increase the ICER by €7,625 to €12,476 separately. This can change the ICER to approximately €85,000 per QALY if only the %engraftment success of beti-cel is lowered from 100% to 93% (based on engraftment failure with allo-HSCT). Summing up all the changes would make the ICER even higher and then it could even reach the €100,000 per QALY.

Lowering the *TDT excess mortality rate* from 3.9 to 1.1 has a substantial effect on the incremental costs. Beti-cel patients who achieve TI at 12 months after beti-cel transplant no longer experience TDT excess mortality, whereas SoC patients are TD for lifetime and face TDT excess mortality. When the rate is set to 1.1 (lower DSA value), the incremental costs decrease by €60,178 and the incremental QALY value decreases by 2.35 compared to base case. This can be explained by the fact that at a lower TDT excess mortality rate, SoC patients live longer compared to base case, and thereby incur more costs and gain more QALYs. So lowering the TDT excess mortality rate with 2.8 increases the ICER by €11,389.

The base case percentage *beti-cel transplant success* is set at 84.4% based on the beti-cel clinical trial data. When the percentage is set to 78% (lower DSA value), the incremental costs increase with €31,610 as compared to base case. When a lower percentage of patients have a successful transplant and not achieve TI, there are more TR patients after transplant, resulting in more additional blood transfusions and iron chelation therapy costs or caregiver costs. So by lowering the beti-cel transplant success with only 6.4% already increases the ICER with €7,625.

In the base case *the iron normalisation phase duration for TI and TR* patients is set on 2 years. If this duration increases to 3 years this results in €43,225 more costs

for the beti-cel patients and 1.16 less QALYs. The ICER will increase to €84,000 per QALY.

3.5.2 *Probabilistic sensitivity analyses (PSA)*

Figure 4 presents the incremental discounted costs and QALYs outcomes associatedwith beti-cel and SoC, in a cost-effectiveness plane. The spread of the points horizontally illustrates the uncertainty in cost results, and the spread of the points vertically demonstrates the uncertainty in the QALY results. The probabilistic ICER as estimated by the applicant is €80,952 per QALY gained (95% CI: € 59,090 - € 112,767) for the comparison beti-cel compared to SoC, which is some higher than the deterministic ICER of €75,871 per QALY gained.

The uncertainty associated with each treatment, in terms of the probability that each treatment is cost-effective, is presented over the range of WTP values in the form of a CEAC in figure 5. The applicant concludes on the basis of this figure that the probability that beti-cel is cost-effective at a WTP of €50,000 per QALY gained is 0%. At a WTP threshold of €80,000 per QALY gained, this probability increases to 47%.
But as mentioned before the applicant excluded some of the important parameters which the DSA indicates had an impact, and therefore it would seem that the PSA does not fully capture the uncertainty. The parameters that were excluded are the ones the applicant believes are not clinical plausible to change, because of the working mechanism of gene therapies like beti-cel. Therefore ZIN concludes that the probabilistic ICER might be an underestimation.

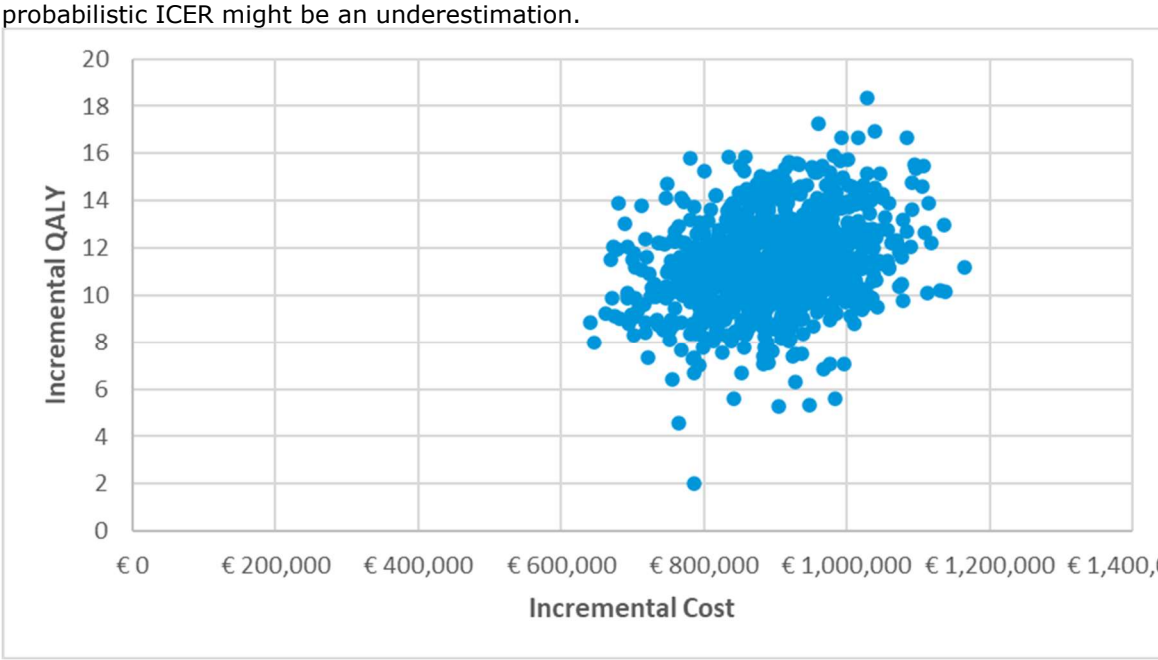


Figure 4 Incremental cost-effectiveness plane, incremental costs and effects of betibeglogene autotemcel compared to Soc (bloodtransfusions and iron chelation): PSA of 1,000 simulations.

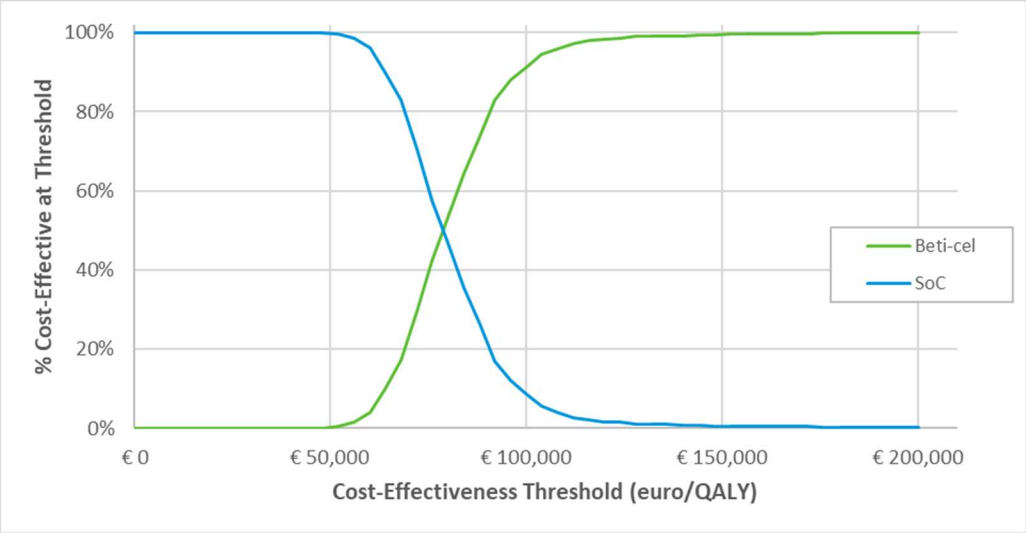


Figure 5: "Cost effectiveness acceptability curve" (CEAC) of betibeglogene autotemcel compared to SoC (bloodtransfusions and iron chelation)(based on a PSA of 1,000 simulations).

3.5.3 *Scenarioanalyses*

In table 21 a set of exploratory scenario analyses is presented as conducted by the applicant to provide insight into assumptions made for model parameters and their relationship with key model outcomes.

The applicant shows that a scenario which uses a *VBPoT model*, results in spreading payments for beti-cel over 5 years based on treatment success decreases incremental costs, with no change in incremental LYs or QALYs. Applying the VBPoT model results in an ICER of €47,225/QALY, which is lower than the base case ICER (€75,871/QALY). The decrease in the ICER can be solely explained by a decrease in beti-cel drug acquisition costs as a result of the VBPoT model.

Similar to the VBPoT scenario, an *outcomes-based rebate model* with a 80% rebate for patients who do not achieve TI or remain TI (at T=24 months), results in a decrease in incremental costs, with no change in incremental LYs or QALYs. The resulting ICER is estimated by the applicant at €60,089/QALY.

In the scenario as done in the original base-case submission, where demographic characteristics (age, gender distribution) are based on UK HES data, there is an increase in incremental costs, and a decrease in incremental LYs and QALYs. This can be explained mainly by the difference in age distribution, where the HES patient pool is older, and also includes patients above the age of 35 years compared to the beti-cel trials population. As mentioned above, patients treated with beti-cel accrue less iron loading complications costs, caregiving costs and productivity loss costs over lifetime due to their freedom of blood transfusions compared to patients on SoC. With older patients (HES patient pool) the remaining lifetime shortens which decreases these cost-savings. As a consequence, the ICER substantially increases to €84,804 per QALY in this scenario. The percentage of TDT patients above 35 years of age will probably be very low. Because beti-cel is an intensive treatment for which a reasonable health condition is needed. Older patients mostly have developed iron overloading complications already.

In the original submitted scenario's the applicant analysed the impact of extinction of treatment effect in TR patients in three scenario analyses, with all TR patients relapsing to TD 5, 10 or 30 years after beti-cel transplant. In the adjusted submission, after consultation, the applicant excluded the 5 years scenario. They argue that since no relapse has been observed for TR patients during the first 5

years after treatment with beti-cel, and there is also no signal for decreasing effect, the applicant believes this is an unrealistic scenario after all. For that reason, with the new base case only scenario analyses have been performed with the assumption that TR patients relapse to TD 10 or 30 years after beti-cel transplant.
Results of the scenarios of all TR patients relapsing to TD status at 10 or 30 years are provided in table 21. In the scenario, with all TR patients relapsing to TD status within 10 years after transplant, annual treatment costs increase for the modelled beti-cel population, and the ICERs increase to €113,013/LYG and €82,659/QALY.
When setting all SMRs to 1.00, this has, as expected, an impact on incremental LYs and QALYs. In the base case, a SMR of 3.9 is applied for TD and of 1.25 for TI. This larger SMR value for TD patients together with a higher risk of death due to cardiac disease in TD patients, leads to 8.6 incremental LYs in the base case. By eliminating the difference in SMR value for TD and TI patients, incremental LYs and QALYs lower to 5.6 and 10.1, respectively. As setting all SMRs to 1.00 this scenario has impact on costs per QALY gained , €81,123/QALY.
Another uncertain parameter in this CEA is the duration of iron normalisation after beti-cel transplantation. In the base-case analysis a duration of 2 years is assumed. In a scenario with a 3-year normalisation period resulted in a discounted ICER of €80,413/QALY.

Table 21 Results scenario analyses – discounted

	Incremental costs	**Incremental LYs**	**Incremental QALYs**	**ICER (cost/LYG)**	**ICER (cost/QALY)**
Base case	€ 889,667	8.6	11.7	€ 103,247	€ 75,871
Scenarios:					
Base case (undiscounted results)	€ 118,260	16.7	20.2	€ 7,097	€ 5,864
Risk sharing: (VBPoT model)	€ 553,763	8.6	11.7	€ 64,265	€ 47,225
Outcomes-based rebate model: 80% rebate at T=25 months if not transfusion-free at T=19 to T=24 months	€ 704,612	8.6	11.7	€ 81,771	€ 60,089
Discount rates 1.5% (for costs and effects*)	€ 513,676	8.6	11.7	€ 59,613	€ 43,806
Age 12 to 17 years	€ 873,356	9.1	12.7	€ 95,478	€ 68,922
Age 18 to 34	€ 892,080	8.6	11.6	€ 104,308	€ 76,857
Body weight UK chart review	€ 855,296	8.6	11.7	€ 99,258	€ 72,940
TR patients relapse to TD at 5 years; Not applicable anymore, as per clinical trial results**	NA	NA	NA	NA	NA
TR patients relapse to TD at 10 years	€ 909,545	8.0	11.0	€ 113,013	€ 82,659
TR patients relapse to TD at 30 years	€ 886,727	8.0	11.2	€ 110,918	€ 79,116
SMRs set to 1.00	€ 822,794	5.6	10.1	€ 146,792	€ 81,232
Utility values based on UK vignette study (for TD and TR)	€ 889,667	8.6	12.1	€ 103,247	€ 73,608
Indirect medical costs based on PAID tool	€ 908,510	8.6	11.7	€ 105,434	€ 77,478
Iron normalization period of 3.0 years (instead of 2.0 years in	€ 903,552	8.3	11.2	€ 108,231	€ 80,413

base case)					
TD patients to have SMR of 3.0 (instead of 3.9 in base case); adjusted SMR TR of 2.1 (midpoint of TD (3.0) and TI (1.25))	€ 873,332	7.8	11.2	€ 112,277	€ 77,811

NA: not applicable; PAID: Practical Application to Include future Disease costs; SMR: standardised mortality ratio; TD: transfusion-dependent; TR: transfusion-reduced; UK: United Kingdom; VBPRoT: value based pricing rebate over time
**In the base case a discount rate of 1.5% is applied to effects as well.*
***As per clinical trial results, described above in the response with question 31, no relapse has been observed for TR patients during the first 5 years after treatment with beti-cel, and there is also no signal for decreasing effect (see also response to question 15), bluebird bio believes this is an unrealistic scenario after all. For that reason, with the new base case only scenario analyses have been performed with the assumption that TR patients relapse to TD 10 or 30 years after beti-cel transplant.*

3.5.3.1 Belgian scenario results

To estimate the CE of beti-cel compared to SoC for the Belgian setting a scenario analysis was conducted by the applicant. All resource use and cost inputs and lifetables used for this scenario analysis are presented in tables in an Appendix of the submission dossier. For the Belgian scenario, model settings that differed from base case were the perspective and discount rate for costs. In accordance with the Belgian Health Care Knowledge Centre (KCE) guidelines, a payer perspective and a 3% discount rate for costs were used.
The results show comparable LYGs (8.64 vs 8.67 (Netherlands)) and QALYs (11.91 vs 11.7 (Netherlands)).
Regarding costs, total costs for beti-cel are comparable as well (€1,754,900 vs €1,754,313 (Netherlands)) and for SoC higher (€951,880 vs €876,142 (Netherlands)) compared to Dutch base case, resulting in lower incremental costs (€803,020 vs €889,667 (Netherlands)). These results can be explained as follows:

- SoC in Belgium is higher due to higher drug acquisition costs for oral iron chelation therapy and higher annual iron chelation therapy monitoring costs:
  - Annual acquisition oral iron chelation therapy: €25,697 (adolescents) – €34,262 (adults) vs €19,668 - €26,223 (Netherlands)
  - Annual monitoring: €2,411 vs €1,139 (Netherlands).

As a result, the ICER as estimated by the applicant is slightly lower for Belgium, namely €92,952 per LY gained and €67,428 per QALY gained.

4 Discussion and Conclusions

In the cost-effectiveness analysis the applicant concludes that patients treated with beti-cel gain 11.7 additional QALYs over lifetime compared to SoC. One-time treatment with beti-cel leads to additional discounted costs of €889,667 compared to SoC, resulting in an ICER of €75,871 per QALY gained for the Netherlands and €67,428 per QALY gained for Belgium.

ZIN concludes (after being advised by the WAR and BeNeLuXa partners) that betibeglogene autotemcel in the treatment of transfusion-dependent B-thalassaemia (TDT) is not a cost-effective treatment. The ICER as presented by the applicant might be too low due to some very optimistic assumptions about the lifelong effectiveness of beti-cel, which is still very uncertain due to lack of long term effectiveness data. In addition to that, in the CE-model the applicant is very pessimistic about the overall survival of transfusion-dependent (TD) patients. There are several aspects in the applicants cost-effectiveness analysis (model structure and input data) that are still very uncertain due to lack of proper data or due to limitations in sensitivity analyses.

Model inputs treatment effectiveness:

- ZIN disagrees with the assumption that all TI patients remain TI for their remaining life. This is still very uncertain because of the lack of long-term effectiveness data of beti-cel treatment. ZIN requested the applicant to add scenario analyses of decreasing effects in TI patients to explore the impact on the ICER and/or to assume in the base case analysis that a small proportion of the TI patients will decrease to the TR status in the model. The applicant explored the impact of decreasing from TR to TD status but did not analyse that for the decrease from TI to TR status. The applicant argues that due to the mechanism of action of beti-cel (utilises an ex-vivo approach by adding functional copies of the β-globin gene into the patient's own cells) this corrects the underlying cause of the condition and therefore the chance of secondary graft failure after successful beti-cel treatment seems negligible. The Dutch clinical experts state that the long-term effectiveness as assumed by the applicant is not 100% certain. They say that secondary graft failure of with beti-cel treated stem cells is not plausible, but cannot be excluded because of the limited experience and short follow-up duration.
- Although the Dutch clinical experts agreed with the applicants assumption of a 2-years duration of iron normalisation after beti-cel transplantation, this remains a very uncertain issue in the CE-model. The clinical experts stated that the duration of iron normalisation after beti-cel treatment depends among others on the type of iron chelation therapy. The duration will probably vary between 2 and 3 years. In the base case analysis the 2-year duration is used (because the most of the patients are treated with phlebotomy) and in a scenario the 3-years duration is used.
- In the adjusted base case analysis the model estimated that 36% of the patients treated with beti-cel and 97% treated with standard of care, had iron overload related complications. The applicant checked the clinical plausibility of these percentages with Dutch clinicians and they agreed with these percentages. Although these are still uncertain parameters in the CEA because it is unknown what the long term complications will be after beti-cel treatment.
- Uncertainty also exists about the used SMR data of TD patients in the model. These are based on assumptions because a lack of data or these are based on very old studies. Dutch clinical experts confirmed the lack of recent data. ZIN

thinks that the used SMR for the TD patients (3.9) might be too high, because standard of care for TDT patients improved a lot during the last decades. Because old data is used (1964-1994) those improvements are not included in the model now, so this might result in a too optimistic cost-effectiveness of beti-cel compared to standard of care.

Model inputs utilities:

- Because of a lack of Dutch data, only utilities from UK populations are used. Dutch clinical experts stated that the health states descriptions do not differ between the UK and the Netherlands. ZIN agrees with the used utilities because no other information and data are available. The impact of variation in these utility values was analysed in sensitivity analyses.

Sensitivity analyses:

ZIN notices (after reviewing by Beneluxa partners) that some essential parameters were not included in the PSA. They all concern short and long term effectiveness parameters (e.g. engraftment success of beti-cel; transplant failure, % reduced transfusions; relapse after beti-cel transplant in TI patients and TR patients). By excluding these important parameters the uncertainty in the model may be inadequately captured.

Overall, ZIN concludes that beti-cel is not a cost-effective treatment for TDT patients compared to standard of care (lifelong blood transfusions and iron chelation therapy) at a for this disease WTP value of €50.000 per QALY. There is a lot of uncertainty about the long-term effectiveness of beti-cel, the duration of iron normalisation after beti-cel, the mortality rate for transfusion-dependent patients and the possibility of adverse events in medium-to-long term. Because of these uncertainties the cost-effectiveness estimates are likely to be too optimistic, because it is assumed that after beti-cel treatment, bloodtransfusions (and iron chelation therapy) are not needed anymore for the rest of a patient's life. Related to that patients treated with beti-cel develop less iron overload complications and are assumed to live much longer. When we assume the applicants (too optimistic) deterministic ICER of €75,871 per QALY the price of beti-cel should decrease with approximately 20% to drop below the WTP value of €50.000 per QALY.

5 Literature

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Appendix

Table 1 Parameter impact on incremental costs, QALYs and ICER as compared to the original base case

			Incremental costs	**Incremental QALYs**	**ICER (cost/QALY)**
Base case			**€878,171**	**11.8**	**€ 75,871 /QALY**
Parameter	**Mean (base case)**	**DSA value (lower, upper)**	**Incremental costs as compared to base case**	**Incremental QALYs as compared to base case**	**Change in ICER as compared to base case**
Cardiac mortality rate	13%	0%	- € 101,815	-1.80	€ 2,819
		20%	€ 13,083	0.21	- € 188
% Transplant success: beti-cel	84.4%	78%	€ 31,610	-0.75	€ 7,625
		90%	- € 24,893	0.63	- € 5,550
TDT excess mortality at baseline	3.9	1.1	- € 60,178	-2.35	€ 11,389
		3.91	€ 157	0.01	- € 20
Weight, by age*	Adolescent: 44.9 kg Adult: 56.9 kg	Adolescent: 40 kg Adult: 51.2 kg	€ 67,424	0.00	€ 5,598
		Adolescent: 49 kg Adult: 62.6 kg	- € 34,377	0.00	- € 2,854
Time to iron assessment* (iron normalisation phase duration) for TI and TR patients	2 years	1 years	€ 14,868	-0.37	- € 3,566
		3 years	€ 43,225	-1.16	€ 11,743
Mean age at baseline (adolescent, young adult, older adult)*	Adolescent: 15 years Young adult: 21 years Older adult: 29.5 years	Adolescent: 12 years Young adult: 18 years Old adult: 24 years	- € 12,271	0.42	- € 3,427
		Adolescent: 17 years Young adult: 23 years Old adult: 34 years	€ 12,652	-0.33	€ 3,141
Sex (% female)	54.5%	0%	€ 10,523	-0.02	€ 1,011
		100%	- € 9,181	-0.04	- € 545
If transplant failure, % reduced transfusions, by genotype*	100%	0%	€ 48,678	-0.62	€ 8,182
		100%**	€ 0**	0.00**	-
TDT excess mortality	TI: 1.25	TI: 1	€ 3,257	0.94	- € 5,003

post-transplant, by transfusion status*	TR: 2.60 TD: 3.90	TR, TD: 1.1			
		TI: 1.50 TR, TD: 3.91	- € 1,970	-0.72	€ 4,448
% Engraftment success: beti-cel	100%	93%‡	€ 6,661	-1.69	€ 12,476
		100%**	€ 0**	0.00**	-
Cardiac complication rates, by iron overload*	Iron level Normalised: 0.0000 Low: 0.0112 Medium: 0.0190 High: 0.0646	Iron level Normalised: 0.0000 Low: 0.0022 Medium: 0.0038 High: 0.0129	- € 415	-0.01	€ 34
		Iron level Normalised: 0.0000 Low: 0.0113 Medium: 0.0191 High: 0.0662	€ 404	0.01	- € 35
Disutility of cardiac complications	-0.1100	-0.0712	-	-0.03	€ 196
		-0.1571	-	0.04	- € 236
DM risk equation intercept	-6.6416	-5.9775	€ 21	-0.02	€ 119
		-7.3058	€ 34	0.01	- € 55
HG risk equation intercept	-2.9215	-2.6293	- € 692	0.00	- € 47
		-3.2136	€ 1,255	0.03	€ 263
Liver complication rates, by iron overload*	Iron level Normalised: 0.0 Low: 0.0 Medium: 0.0 High: 0.0832	Iron level Normalised: 0.0 Low: 0.0 Medium: 0.0 High: 0.0805	€ 76	0.0	€ 23
		Iron level Normalised: 0.0 Low: 0.0 Medium: 0.0 High: 0.0859	€ 122	-0.01	€ 62
Disutility of liver complications	-0.1000	-0.0647	-	-0.05	332
		-0.1428	-	0.07	- € 399
Disutility by transfusion status*	-0.02	-0.0129	-	-1.43	€ 9,746
		-0.0286	-	1.73	- € 9,122
Utilities by age*	<34 years: 0.9385 to 85+ years: 0.8300	<34 years: 0.877 to 85+ years: 0.7685	-	-0.83	€ 5,392
		<34 years:	-	0.83	- €4,695

		1 to 85* years: 0.8915			
Probability of infertility with beti-cel, by sex*	Male: 24% Female: 57%	Male: 15% Female: 34%	-	0.22	- € 1,305
		Male: 34% Female: 78%	-	-0.25	€ 1,567
Disutility of infertility	-0.0700	-0.0453	-	0.20	- € 1,171
		-0.0999	-	-0.24	€ 1,475
Disutility of other iron complications	-0.1000	-0.0647	-	-0.22	€ 1,322
		-0.1428	-	0.26	- €1,534
Disutility of acute transplant AEs*	-0.0007	-0.0005	-	0.00	-
		-0.0011	-	0.00	-

DM, diabetes mellitus; DSA, deterministic sensitivity analysis; LB, lower bound; UB, upper bound

**multiple related parameters varied in one scenario*

***DSA value equal to base case value, hence no change in incremental costs.*

ǂBased on engraftment failure with allo-HSCT.