Model-Projected Long-Term Clinical Outcomes of Exagamglogene Autotemcel (Exa-cel) Gene-Edited Therapy in Patients With Transfusion-Dependent β-Thalassemia in the United Kingdom

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INTRODUCTION

- β-thalassemia is a rare hereditary hemoglobinopathy characterized by reduced or absent β-globin production[1-3]
  - The most severe form of the disease is transfusion-dependent β-thalassemia (TDT), wherein patients depend on regular red blood cell transfusions (RBCTs) for survival[1,2]
- The current standard of care (SOC) for patients with TDT includes RBCTs and iron chelation therapies (ICTs)
- Exagamglogene autotemcel (exa-cel) is a cellular product consisting of autologous CD34$^+$ hematopoietic stem and progenitor cells modified by nonviral, *ex vivo* CRISPR/Cas9 that reduces erythroid-specific expression of *BCL11A*, which leads to an increase in fetal hemoglobin (HbF) levels; an increase in HbF levels ameliorates the severity of β-thalassemia and therefore has the potential to eliminate RBCTs in patients with TDT[4,5]
- Exa-cel is an investigational, one-time, potentially curative gene-edited therapy being evaluated for patients with TDT[5]

OBJECTIVE

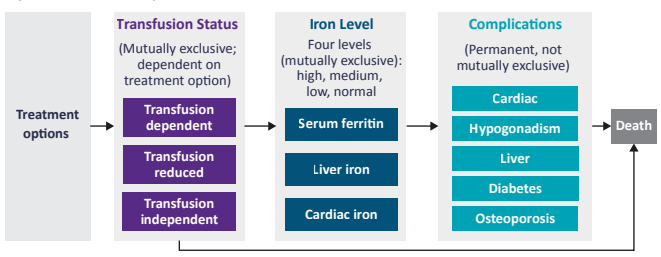
- To evaluate the long-term clinical outcomes for patients with TDT treated with exa-cel versus SOC in the United Kingdom

METHODS

Model Overview

- A Markov cohort model was developed to estimate the life expectancy and lifetime prevalence of clinical complications in patients with TDT treated with exa-cel versus SOC in the United Kingdom
- The model includes transfusion status (i.e., transfusion independent [TI], transfusion reduced [TR], and transfusion dependent [TD]) and death as health states; transfusion status is assumed to impact patients' iron levels (serum ferritin, liver iron, and cardiac iron), which consequently impact the development of TDT-related complications (**Figure 1**)
- At model start, all patients are assumed to be TD and to receive regular RBCTs and thus have non-normal iron levels
- Patients treated with SOC maintain the baseline transfusion status (TD), RBCT frequency, and non-normal iron levels throughout the model horizon
- The model has 3 phases for patients treated with exa-cel: a treatment phase, an iron-normalization/change phase, and a post-iron normalization phase (remainder of patients' lifetimes)
- Patients treated with exa-cel can achieve TI or TR at the end of the treatment phase
  - Patients who achieve TI or TR are assumed to remain in that health state for the remainder of the model horizon
- Patients' iron levels change based on changes in their transfusion status; the model assumes that the change in iron levels occurs at a constant rate over the duration of the iron normalization/change phase
  - Patients who achieve TI achieve iron normalization and are assumed to be at no further risk of developing TDT-related complications
  - Patients who achieve TR have reduced baseline iron levels (e.g., reduced from high to medium or medium to low) but do not achieve iron normalization
  - Patients who are TD remain at baseline iron levels
- Mortality risk is estimated based on transfusion status, the presence of complications, and the occurrence of other transplant-related events

Figure 1. Schematic of TDT Model Structure



TDT, transfusion-dependent β-thalassemia.

Data Sources and Model Inputs

- A cohort of patients with TDT was modeled from baseline. The cohort had a mean age of 21.8 years and required a mean of 17.2 RBCTs/year,[6] based on the characteristics of patients in the primary efficacy set enrolled in the CLIMB THAL-111 trial of exa-cel[5]
  - Patients were assumed to have no TDT-related complications at baseline
- Baseline iron levels were derived from published literature[7]
  - Serum ferritin: low (≤1,000 ng/mL): 23.0%; moderate (1,000–2,500 ng/mL): 38.8%; high (>2,500 ng/mL): 38.2%
  - Cardiac iron: low (>20 ms): 88.2%; moderate (10–20 ms): 11.8%; high (<10 ms): 0%
  - Liver iron: low (<7 mg/g): 60.5%; moderate (7–15 mg/g): 23.5%; high (≥15 mg/g): 16.0%
- Exa-cel clinical efficacy was informed by the published results of the CLIMB THAL-111 primary efficacy set (follow-up duration from 13.8 months to 43.7 months)[5]:
  - Ninety-three percent of patients treated with exa-cel were assumed to transition to the TI health state in the model, given that 25 of 27 patients in the primary efficacy set had stopped RBCTs at the time of the data cut
  - The remaining 7% of patients treated with exa-cel were assumed to achieve TR, with an average reduction in RBCTs of 87.6% from baseline, based on the clinical outcomes of the remaining 2 trial patients who had not yet stopped RBCTs at the time of the data cut
  - The duration of time to iron normalization/change was varied in the model from 2 to 5 years

Data Sources and Model Inputs (Continued)

- The risks of developing TDT-related complications, based on iron levels and transfusion status, were derived from published literature (**Table 1**)
  - Patients treated with exa-cel who achieve TI and normal iron levels are assumed to be at no further risk of developing complications

Table 1. Risks of Developing TDT-Related Complications

Complication	Risk of Developing Complication	Source
Cardiac complications	Annual risk by cardiac iron content level: • Low: 1.1% • Moderate: 1.9% • High: 4.0%	Pepe, et al.[8]
Liver complications	Annual risk by liver iron content level: • Low: 0.1% • Moderate: 0.1% • High: 8.5%	Data on file[6]; Angelucci, et al.[9]
Diabetes hypogonadism	Annual risk equation based on age, serum ferritin levels, and cardiac levels	Ang, et al.[10]
Osteoporosis	Age-specific monthly incidence rate in the general (non-TDT) population with an increased risk associated with TD (RR: 26.98) and TR (RR: 13.99)	Hippisley-Cox, et al.[11]; Data on file[6]

RR, rate ratio; TD, transfusion dependent; TDT, transfusion-dependent ß-thalassemia; TR, transfusion reduced.

- Transfusion status-dependent mortality was considered as standardized mortality ratios (SMRs) applied to the age- and gender-specific mortality rates in the general population of the United Kingdom:
  - Consistent with other economic analyses,[12] patients who were TD were assumed to have a 3.9-fold increased risk of mortality versus the general population[13]
  - Patients who achieved TI were assumed to have a 25% increased risk of mortality versus the general population to account for the impact of previous TDT and use of myeloablative conditioning as part of the exa-cel treatment process
  - Patients who were TR were assumed to have a 2.6-fold increased risk of mortality, estimated as the mid-point of TI and TD
  - Patients who developed cardiac complications had an increased annual mortality risk of 13%,[12,14] and patients with diabetes were assumed to have a 1.5-fold increased risk of mortality[15]

Model Outcomes

- The following outcomes were projected by the model:
  - Mean life expectancy
  - Mean number of RBCTs
  - Proportion of patients developing complications
- All outcomes were undiscounted

Scenario Analyses

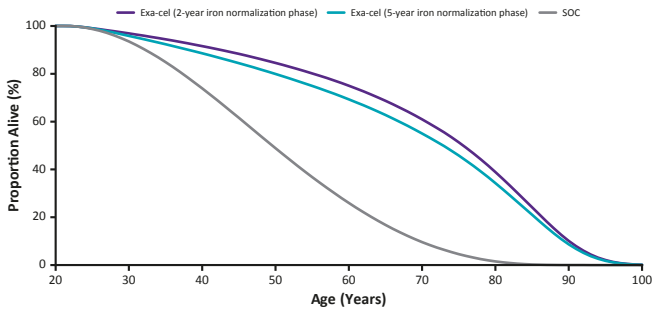
- Model parameters were varied to examine the impact of alternative inputs on clinical outcomes, including:
  - A cohort with a mean age of 12 years, based on the minimum requirements for CLIMB THAL-111 trial eligibility
  - The risk of mortality among patients with cardiac complications was assumed to be an SMR of 106.6, based on an alternative source[11] (base case: annual mortality risk of 13%)

RESULTS

Base Case Results

- Over the lifetime horizon, patients treated with exa-cel had a substantial increase in survival of 17.8 to 20.5 years compared to SOC, when varying time to iron normalization/change from 5 to 2 years, respectively (**Figure 2**)
  - The mean predicted survival (i.e., age at death) of patients treated with exa-cel was 68.2 to 70.8 years versus 50.3 years in patients treated with SOC

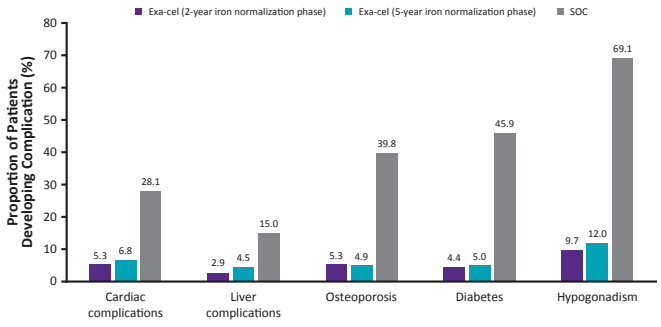
Figure 2. Projected Survival for Patients with TDT



exa-cel, exagamglogene autotemcel; SOC, standard of care; TDT, transfusion-dependent ß-thalassemia.

- Patients treated with exa-cel received ~465 fewer RBCTs over the lifetime horizon compared to SOC (exa-cel: ~25 vs SOC: 491)
- Further, the lifetime burden of complications of TDT was projected to be substantially lower in patients treated with exa-cel versus SOC (**Figure 3**)

Figure 3. Proportion of Patients Developing TDT-Related Complications

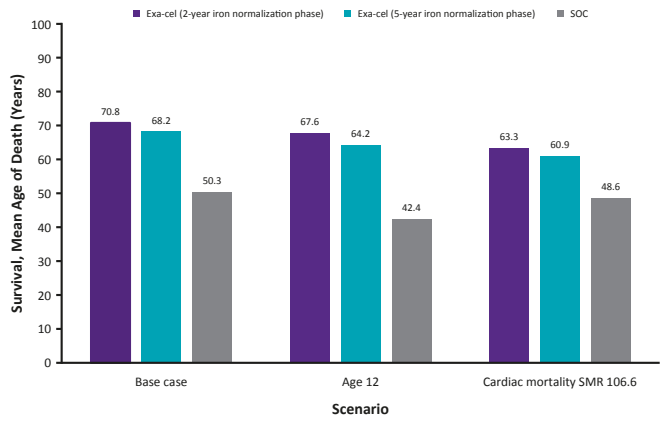


exa-cel, exagamglogene autotemcel; SOC, standard of care; TDT, transfusion-dependent β-thalassemia.

Scenario Analyses Results

- Patients treated with exa-cel had an increase in survival ranging from 12.3 to 25.2 years compared to SOC across the various scenarios analyzed (**Figure 4**)
  - Exa-cel resulted in an avoidance of up to 498 RBCTs over a lifetime when initiated in patients aged 12 years and assuming a 2-year iron normalization/change period

Figure 4. Scenario Analyses Results



exa-cel, exagamglogene autotemcel; SMR, standardized mortality ratio; SOC, standard of care.

LIMITATIONS

- Healthcare decision analytic models based solely on transfusions and iron levels could oversimplify the complexity of TDT pathophysiology, given the impact of anemia and ineffective erythropoiesis
- Model transition probabilities were based on published literature using historical data on patients with TDT from the United Kingdom and Europe; additional contemporary United Kingdom–specific transition probabilities could reduce uncertainty
- As a simplifying assumption, the modeled cohort receiving SOC was assumed to maintain initial iron levels and frequency of RBCTs throughout the lifetime horizon
- The model did not estimate the impact of newer chronic TDT therapies (i.e., luspatercept) on projected outcomes, as the use of these therapies is limited; previous literature suggests that including these therapies as part of SOC treatment provides modest improvements in clinical outcomes in patients with TDT[16]
- Lifetime clinical efficacy inputs for exa-cel were based on up to 43.7 months of clinical data; however, given the mechanism of action of exa-cel, treatment durability is expected to be lifelong
- The base case assumption that the iron normalization/change period lasts 2 to 5 years was based on clinical opinion and was consistent with previous TDT health technology assessment assumptions[12,17]

CONCLUSIONS

- Model projections suggest that treatment with exa-cel could substantially improve survival, lower the prevalence of TDT-related complications, and reduce disease burden over a lifetime in patients with TDT compared to treatment with SOC

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AUTHOR DISCLOSURES

CU, SJ, NL, DF, JH, and AL are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company. HF and HY are employees of Analysis Group, Inc., and may hold stock or stock options in the company.

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